Biotherapy Journal Review

Volume 2, Number 3; Summer 2016












BioTherapeutics, Education & Research Foundation

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The BTER Foundation's

Biotherapy Journal Review

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From the Editor's Desk:

This month, we have selected to review pivotal studies from the literature on maggot therapy, helminthic therapy, phage therapy, and probiotics. While most of these studies offer important findings that will move their respective fields forward, the helminthic therapy study did not identify any statistically significant benefits in multiple sclerosis patients treated with *Trichuris suis* ova therapy. This "negative study" hit many in the helminthic therapy community very hard, and stifled much of the enthusiasm of helminthic therapy researchers and patients alike.

We are reviewing the study here because we believe that protocols that do not work can be as educational – and can potentially advance the field – as much as protocols that do work. In the words of Johnny Cash, ". . . build on failure. . . . use it as a stepping stone." The authors discussed several explanations for their findings; the reviewer notes a few possible explanations as well. Perhaps the reader has additional thoughts . . . about this article, or about the Biotherapy Journal Review in general. If so, visit our website and comment. Or send us your comments and submissions in a letter to the editor at editor@bterfoundation.org. We are here for you, so tell us what you think, and what you want.

Indeed, while I have your attention, let me share my excitement over our upcoming issue dedicated to biotherapy with mammals! Not only will we be reviewing some interesting work in the fields of service animals, hippotherapy and olfactory detection, but we will also be featuring some original artwork between the sections. So be sure to take a close look at the coming issues, and to share with us YOUR reviews, manuscripts, artwork, or announcements.

As always, this issue is brought to you by the generous support of BTER Foundation members and donors, along with the contributions of its authors and reviewers. Thank you, all.



Ronald A. Sherman, MD, MSc, DTM&H
Director, BTER Foundation

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Section I: Journal Reviews

The BTER Foundation's

Biotherapy Journal Review

Volume 2, Number 3; Summer 2016

Title: Methods for external disinfection of blow fly (Diptera: Calliphoridae) eggs prior to use in wound debridement therapy.
Authors: Brundage AL, Crippen TL, Tomberlin JK.
Reviewer: Mr. Frank Stadler, BSc Hon, doctoral candidate
To view the article review, visit page 6

Title: Effect of the probiotic strain *Bifidobacterium animalis subsp. lactis*, BB-12®, on defecation frequency in healthy subjects with low defecation frequency and abdominal discomfort: a randomised, double-blind, placebo-controlled, parallel-group trial.
Authors: Eskesen D, Jespersen L, Michelsen B, Whorwell PJ, Müller-Lissner S, Morberg CM.
Reviewer: Ronald Sherman, MD
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Title: Bacteriophage treatment of intransigent diabetic toe ulcers: a case series.
Authors: Fish R, Kutter E, Wheat G, Blasdel B, Kutateladze M, Kuhl S.
Reviewer: Ronald Sherman, MD
To view the article review, visit page 14

Title: Trichuris suis ova therapy in relapsing multiple sclerosis is safe but without signals of beneficial effect.
Authors: Voldsgaard A, Bager P, Garde E, Åkeson P, Leffers AM, Madsen CG, Kapel C, Roepstorff A, Thamsborg SM, Melbye M, Siebner H, Søndergaard HB, Sellebjerg F, Sørensen PS.
Reviewer: Ronald Sherman, MD
To view the article review, visit page 18

Maggot Debridement Therapy Reviews

Journal Citation

Brundage AL, Crippen TL, Tomberlin JK. **Methods for external disinfection of blow fly (Diptera: Calliphoridae) eggs prior to use in wound debridement therapy.** Wound Repair Regen. 2016;24(2):384-93.

Published Abstract

Maggot debridement therapy (MDT) is the use of the larval stage of flies (i.e., Calliphoridae) to remove necrotic tissue and disinfect wounds. Effective MDT requires aseptic technique to prevent the unintentional introduction of pathogenic bacteria into a wound to be debrided; yet the external surface of Calliphoridae eggs is often heavily contaminated with bacteria. Studies of external disinfection of dipteran eggs have been reported, but neither their efficacy nor effect on egg viability has been adequately assessed. The present study evaluated the efficacy of ten disinfection techniques involving immersion, rinse, or a combination of both in formalin, Lysol, formaldehyde, bleach, ethanol, Sporgon, or benzalkonium chloride. All techniques resulted in significant decreases in culturable, aerobic bacterial load on *Lucilia cuprina* eggs. For *L. cuprina*, a 10 minute 3% Lysol immersion was the most efficacious, disinfecting 96.67% of egg samples, while resulting in 31.84% egg mortality. The 5% formalin immersion was least efficacious, disinfecting only 3.33% of *L. cuprina* egg samples, while resulting in 33.51% egg mortality. A formaldehyde immersion, one of the most commonly used disinfection techniques, was moderately effective, disinfecting 66.7% of egg samples, while resulting in 40.16% egg mortality. For *Chrysomya rufifacies* and *Cochliomyia macellaria* egg samples, the 10 minute 3% Lysol immersion disinfected 100% of the samples, and for *Lucilia sericata*, 80% of egg samples, while resulting in 33.97%, 7.34%, and 36.96% egg mortality, respectively. H_2CO disinfected 16.67% of *Ch. rufifacies*, 26.67% of *C. macellaria*, and 56.67% of *L. sericata* egg samples, while resulting in 21.98%, 10.18%, and 32.19% egg mortality, respectively. Due to its high disinfection efficacy and relatively low egg mortality, a 10 minutes 3% Lysol immersion is recommended for sterilizing Calliphoridae eggs prior to rearing of larvae for use in MDT.

Context (briefly, why and how the research was carried out)

The authors point out that while a number of papers outline various sterilization protocols and reagents for fly eggs in medical maggot production, there has been insufficient evaluation or validation of the efficacy of sterilization methods, not only regarding the sterility of the eggs but also regarding egg survival. In this study ten sterilization treatments were tested on eggs from *Lucilia cuprina*. *Cochliomyia macellaria*, *Chrysomya rufifacies* and *Lucilia sericata* were exposed to two treatments, H2CO and 10 minutes soak in Lysol.

Main experimental treatments to determine sterilization efficacy and eclosion rate included:
Immersion (for 5 minutes unless otherwise stated) in

a) 5% formalin,
b) 10% formalin,
c) 3% Lysol,
d) 3% Lysol for 10 minutes
e) 5% H_2CO
f) 5% NaOCl followed by 5% H_2CO.

Rinsed in

g) 10 cc 70% EtOH
h) 30 cc 1% NaOCl

Combination of

i) 10 minutes immersion in ADBAC followed by rinse in 10 cc 70% EtOH
j) Immersion in 95% EtOH then evaporation for 5 minutes followed by immersion in SporGon®.

Other experiments included

- Effect of agitation on sterilization efficiency and eclosion
- The testing of immersion tolerance for medical fly eggs,
- Identification of baseline contamination of unsterilized eggs,
- Chorion visualization to determine chorion damage

It is important to introduce here the polycarbonate filter system that was used to hold the eggs during sterilization treatments (Figure 1) because it is relevant to the discussion below.



EW-29550-40
Polycarbonate Filter Holder, 13 mm
http://www.coleparmer.com/Product/Polycarbonate_Filter_Holder_13_mm_12_pk/EW-29550-40 (Accessed, 21 August 2016)

Findings

With regard to the sterilization efficacy experiments, please refer to the abstract for detailed results. Overall, the authors conclude from their findings that a 10 minute 3%

Lysol immersion provides the best sterilization and eclosion results for Calliphorid eggs. Immersion tolerance results are somewhat intriguing and will be discussed below in more detail. In summary, *Ch. Rufifacies* and *C. macellaria* exhibited high eclosion rates of above 88%. *L. cuprina* was the most sensitive to length of immersion with a statistically significant drop in eclosion rate for longer immersion times. However, even at 10 minutes eclosion was still high (76.3% +- 7.1). The most surprising result was that for *L. sericata*. Eclosion was below 50% and not significantly different between the treatments. Even eggs that were not immersed had very low eclosion of (47.3%).

Discussion (looking at author's conclusions and your own thoughts)

First up, the authors are to be congratulated for contributing experimental data to the discussion of sterilization efficacy in maggot debridement therapy. Confidence in the quality and sterility of medical maggots is key to making this treatment more popular and more widely available.

This brief review will mainly focus on 1) validity and comparability of test outcomes of this study with the wider literature and medical maggot production practice, 2) the unusually low eclosion rate of *L. sericata* in the immersion experiment compared with the additional sterilization experiment conducted with *L. sericata*, and 3) general relevance of findings for medical maggot production and maggot debridement therapy.

Validity and comparability of sterilization efficacy testing

The authors conducted sterility testing using reagents that have been used by researchers and medial maggot producers as published in the literature as far back as the early 20th century. It is important to note that sterility testing was not conducted using the same methodology as described in the respective literature or practiced in commercial laboratories. To the reviewer's knowledge, there has been no report of the use of a polycarbonate filter holder (Fig 1) for egg sterilization in MDT.

Independent of the chemical reagents used there is a clear difference in the protocols, procedures for sterilization described in this paper compared to the literature and practice. First, in many labs sterilization is conducted in open vessels such as beakers or larger test tubes and greater volumes of sterilization reagent are used to treat and rinse the eggs. The polycarbonate filter holder appears to only hold a volume of 2.5 mL for immersion. This does not allow for sufficiently generous washing of eggs. Moreover, when the sterilization reagent and rinse are pushed through the filter, the eggs may be pressed against the filter paper preventing proper circumferential removal of bacteria from the chorion. Second, deagglutination in practice involves usually both mechanical separation of eggs and surfactant treatment with NaOCl or sodium sulfite. Only treatments f) and h) used this approach with NaOCl and with higher sterilization rates. Third, the most used species for MDT is *L. sericata* and to a lesser degree *L. cuprina*. It should therefore be a priority to thoroughly test sterilization methods on these two species. The authors argue for preferential use of *L. cuprina* on the basis of its sensitivity to immersion. It appears to the reviewer that for the study to have practical use, both *L.*

sericata and *L. cuprina* should have been tested in equal measure or preference should have been given to *L. sericata*.

In short, while this study compares the respective sterilization options on a level playing field with the same albeit new methodology, it does not replicate and evaluate sterilization procedures reported in the literature. This is somewhat problematic because the poor sterilization outcomes reported in this study for many of the commonly used reagents implies inefficient and perhaps even inadequate sterilization of medial maggots used for MDT. However, this is unlikely because any commercial producer faced with such poor sterilization outcomes would rapidly improve the methodology in order to avoid costly waste of resources due to rejection of production batches. Moreover, it must be stressed and made explicit to the uninitiated reader that best practice medical maggot production does include sterility testing of maggots before application in MDT. This ensures that contaminated batches if they should occur are discarded and not used in treatment.

To conclude, this study is invaluable as it establishes the superiority of Lysol as a disinfection reagent under given experimental conditions. The problem, however, is the widely differing experimental methods employed here and elsewhere and the limitations this imposes on generalizability of findings. In fact, it appears to the reviewer that the objectives of this research have been achieved only in part.

Low eclosion rates for L. sericata

The authors report very poor eclosion rates (<50%) for *L. sericata* in the immersion experiment compared to the other species tested, even for those maggots not immersed in water. This appears highly unusual particularly when considering that in the sterilization experiment, eclosion rates of around 70% were noted for *L. sericata*.

Relevance and implication of this study

The reviewer would like to emphasize that quality control in best practice medical production ensures that no contaminated medical maggots reach the patient. The outcomes of this study are likely the consequence of methodological differences and the different equipment used compared to sterilization protocols described in the literature. Nevertheless, the authors have clearly established that under their experimental conditions, Lysol is the best sterilization reagent.

With regard to egg mortality due to sterilization, it should be noted that there is probably an overproduction and surplus of eggs in commercial production meaning that higher mortality rates can probably be tolerated in favor of high sterility. After all, only successfully eclosed larvae are packaged and used for MDT. Higher egg mortality would only be a problem if eggs instead of larvae were packaged and dispatched for MDT treatment.

-Reviewed by Mr. Frank Stadler, BSc Hon, doctoral candidate

Probiotics and Bacteriotherapy Reviews

Journal Citation:

Eskesen D, Jespersen L, Michelsen B, Whorwell PJ, Müller-Lissner S, Morberg CM. **Effect of the probiotic strain *Bifidobacterium animalis subsp. lactis*, BB-12®, on defecation frequency in healthy subjects with low defecation frequency and abdominal discomfort: a randomised, double-blind, placebo-controlled, parallel-group trial.** *Br J Nutr*. 2015;114(10):1638-46.

Published Abstract

The aim of the present study was to investigate the effect of Bifidobacterium animalis subsp. lactis, BB-12®, on two primary end points - defecation frequency and gastrointestinal (GI) well-being - in healthy adults with low defecation frequency and abdominal discomfort. A total of 1248 subjects were included in a randomised, double-blind, placebo-controlled trial. After a 2-week run-in period, subjects were randomised to 1 or 10 billion colony-forming units/d of the probiotic strain BB-12® or a matching placebo capsule once daily for 4 weeks. Subjects completed a diary on bowel habits, relief of abdominal discomfort and symptoms. GI well-being, defined as global relief of abdominal discomfort, did not show significant differences. The OR for having a defecation frequency above baseline for ≥50% of the time was 1·31 (95% CI 0·98, 1·75), P=0·071, for probiotic treatment overall. Tightening the criteria for being a responder to an increase of ≥1 d/week for ≥50 % of the time resulted in an OR of 1·55 (95% CI 1·22, 1·96), P=0·0003, for treatment overall. A treatment effect on average defecation frequency was found (P=0·0065), with the frequency being significantly higher compared with placebo at all weeks for probiotic treatment overall (all P<0·05). Effects on defecation frequency were similar for the two doses tested, suggesting that a ceiling effect was reached with the one billion dose. Overall, 4 weeks' supplementation with the probiotic strain BB-12® resulted in a clinically relevant benefit on defecation frequency. The results suggest that consumption of BB-12® improves the GI health of individuals whose symptoms are not sufficiently severe to consult a doctor (ISRCTN18128385).

Context

Gastrointestinal (GI) microbiota are now recognized to play an integral role in such functional bowel disorders as irritable bowel syndrome (IBS) and constipation. Therefore, it is reasonable to investigate whether administered microbes (probiotics) could alleviate the symptoms of functional bowel disorders or even the mild symptoms in otherwise “normal” individuals.

In prior studies, the administration of *Bifidobacterium animalis* subsp. *lactis* (BB-12®) has already been shown to improve abdominal distress and defecation irregularity in certain patient groups.

In this study, the authors "set out with the primary objective to investigate the effect of the probiotic strain BB-12® in different dosages on defecation frequency and global relief in healthy subjects with low defecation frequency and abdominal discomfort. The secondary objective was to investigate the effect on abdominal pain and bloating. As little is known about healthy populations with minor GI complaints, we also wanted to explore whether certain subgroups were more likely to benefit from treatment with the probiotic strain BB-12®

The study was designed as a randomized, double-blind, placebo-controlled, multicenter clinical trial, conducted in two parts: a 2-week baseline ("run-in period") followed by a 4 week intervention period. The intervention consisted of administering 1 capsule of BB-12® to subjects each day, in doses of either 1 or 10 billion colony-forming units (CFU) per capsule. The control group received identical placebo capsules. Subjects were allowed to continue all other medications and their normal activities, except excessive physical exercise or the consumption of probiotics or fermented dairy products.

Subjects were recruited voluntarily if they were between 18 – 70 years old, with a low defecation frequency (defined as 2 - 4 days/week) and complaints of general abdominal discomfort. Subjects were excluded if they had a history or diagnosis of specific GI disease such as IBS, prior complicated GI surgery, depressive disorder, or the use of oral antibiotics within the preceding 4 weeks. The use of drugs or large doses of vitamins and minerals or food or herbal supplements, even for digestive symptoms, was permitted as long as the substance and dose was stable.

After enrollment and randomization, subjects began the 6 week study, completing a daily and weekly diary assess study outcomes, their symptoms, their self-assessment of any changes over the past week, and their compliance with the study regimen. Subjects also completed questionnaires regarding their physical activity and adverse events.

Primary end points were defecation frequency and GI well-being. Responders were defined as subjects with an average weekly defecation frequency above baseline for at least 50% of the time (at least 2 weeks of the 4-week intervention period); GI well-being responders were defined as subjects who achieved "relief" for at least 50% of the time. Secondary end points were symptom severity scores for abdominal pain and bloating. Data was analyzed with rigorous standard statistical methodology. Before completion of the study, data was submitted for two interim analyses.

Findings

A total of 1248 subjects were randomized into the study and analyzed in the intent-to-treat analysis. Attrition was less than 1%. The characteristics of the three study groups

were similar at Baseline. Subject compliance with study protocol was reported as 100%. The low dose (1 million CFU) arm of the study was closed early, as the result of the interim analysis.

The odds ratio (OR) – which can be likened to statistical probability – for having a defecation frequency above baseline for ≥50% of the time was 1·31 (95% CI 0·98, 1·75), P=0·071, for probiotic treatment overall. However, when looking only at those subjects who increased their bowel frequency by at least ≥1 day/week for ≥50% of the time, there was a significant difference between subjects who received the probiotic supplements and those who did not: OR of 1·55 (95% CI 1·22, 1·96), P=0·0003. Defecation frequency increased for subjects in all three treatment groups, though it increased more for those in the probiotics arms than in the control arm (P=0·0065). Defecation frequency increased most for those subjects whose baseline frequency was ≥3 day/week. No dosage-related difference was seen with defecation frequency nor with any other finding of benefit or harm.

There were no statistically significant differences in symptoms of GI well-being between the three treatment groups. Abdominal pain and bloating decreased by about 40% for subjects in all treatment groups during the study period (no significant difference between different interventions). Stool consistency became softer for subjects in all study groups, though maybe more so for those in the one billion group (P= 0·056).

While 337 adverse events were reported in 233 subjects (18·7 %), all but 17 events in 14 subjects were considered unrelated to the study. Most of these were GI related, and there was no difference between the number or severity of adverse event and the treatment group.

Discussion

The authors are to be commended for executing a rigorous scientific study, complete with randomization and controls, a baseline observational period, extensive statistical analyses (including intent-to-treat analysis and intermediate analysis), and a large enrollment of over 1,200 subjects. Their study demonstrated a clear increase in defecation frequency in patients with baseline stooling of only 3 – 4 days per week, if they received the daily BB-12® probiotic supplement (either 1 billion or 10 billion CFU dose). Although the probiotic was not definitely associated with increased defecation frequency for those with baseline stooling of ≤3 days / week (since most patients increased their defecation frequency during the study, regardless of treatment group), those who increased their frequency by at least one more day per week, for at least 2 weeks out of the 4-week intervention period, were more likely to have received the probiotic than not. Why were the benefits less visible in subjects with lower defecation frequency? This could be a result of a difference in severity, or even a difference in etiology. Clearly the subject population was not a uniform group, even though the distribution among the three treatment arms appears to have been homogeneous. Then again, one can always blame probability – a reality whose effects are minimized only by studying larger and larger sample sizes.

It is interesting that there was no dose effect seen with the BB-12®. This suggests that the benefits of this organisms are reached at some minimal level of consumption (presumably ≤ 1 million CFU / day). Higher doses were associated with no greater benefits and no greater harms.

The authors claim that "the results suggest that consumption of BB-12® improves the GI health of individuals whose symptoms are not sufficiently severe to consult a doctor." But I would temper that statement because – while there were clearly benefits in defecation frequency for many of the subjects – increased defecation frequency should not be interpreted as improved GI health overall. Indeed, all other measurements of GI health, such as symptoms of abdominal discomfort, stool consistency, etc., improved in subjects from all intervention groups, with no clear statistically significant association with the probiotics intervention arms.

Still, the study demonstrated BB-12® to be safe, with no more adverse events than those seen in the placebo-controlled arm. The results suggest that it is reasonable for individuals with infrequent defecation and GI symptoms who have no specific etiology identified and/or who have not felt their symptoms warranted consulting a doctor might benefit from a trial of BB-12®, and have little to lose from doing so.

-Reviewed by Ronald Sherman, MD



Phage Therapy Reviews

Journal Citation

Fish R, Kutter E, Wheat G, Blasdel B, Kutateladze M, Kuhl S. **Bacteriophage treatment of intransigent diabetic toe ulcers: a case series. *J Wound Care*.** 2016;25 Suppl 7:S27-33.

Published Abstract

Objective: Diabetic foot ulcer (DFU) infections are a growing public health problem, with increasing prevalence, poor response to antibiotics and bacterial resistance to traditional antimicrobials leading to increased morbidity and mortality. Bacteriophages (phages), the viruses that target specific bacteria, are one option for addressing bacterial infections, especially where antibiotics fail. Of particular value is a class of virulent staphylococcal phages that hit almost all Staphylococcus aureus, including most methicillin-resistant Staphylococcus aureus (MRSA) strains. Here we report a continuous case series assessing the effectiveness of treating infected and poorly vascularised toe ulcers with exposed bone, after failure of recommended antibiotic therapy, using topically applied Staphylococcus aureus-specific phage. ***Method***: This was a compassionate-use case series of nine patients with diabetes and poorly perfused toe ulcers containing culture-proven Staphylococcus aureus infected bone and soft tissue, who had responded poorly to recommended antibiotic therapy. Six representative cases are presented here. The only generally accepted other option in each case was toe amputation. Exposed portions of the infected phalanges were removed in three cases and left in place in two cases. One case presented as a micro-clot induced gangrene following vascular stenting. In this case, phage were used to prevent infection. The phage used was a commercially available fully sequenced preparation of staphylococcal phage Sb-1. Phage solution was applied topically to the ulcerations once weekly, following standard good wound care. The amount of phage solution applied varied from 0.1 to 0.5 cc depending on volume and area of the ulceration. ***Results***: All infections responded to the phage applications and the ulcers healed in an average of seven weeks with infected bone debridement. One ulcer, where vascularity was extremely poor and bone was not removed to preserve hallux function, required 18 weeks of treatment. In the case of the toe with the micro-clot gangrene, the toe was salvaged and healed in seven weeks without complications. ***Conclusion***: Topical application of a staph mono-phage preparation can be used successfully to treat infected toe ulcerations with bone involvement, despite very poor vascularity and failure of antibiotic treatment. The success within this small series provides the groundwork for controlled clinical trials of staph phage for diabetic foot infections.

Context

This research – an exploration of the utility of bacteriophage to treat infected diabetic foot ulcers – was carried out to address several significant problems currently plaguing our society. Diabetes is on the rise, and so are the complications, not the least of which are foot ulcers that do not heal, and often result in amputations. While antibiotics are not a simple fix for infected diabetic foot ulcers, even under the best of circumstances, the fact that more and more bacteria are becoming resistant to our antibiotics have made the antibiotics less useful. Some organisms, such as methicillin-resistant *Staphylococcus* aureus (MRSA) are now susceptible only to the most toxic of antibiotics, if they are susceptible to any at all.

Bacteriophages are viruses that parasitize only specific bacteria. They do not infect other cells or other animals, and they die out when their host bacteria have been destroyed. The therapeutic use of bacteriophage died out, too, in most of the world, with the antibiotic era. Use and research continued only in a few centers, predominantly in Eastern Europe.

The past couple decades have seen a renewed interest in using bacteriophage to control pathogenic bacteria, but large-scale, controlled, prospective trials are still quite rare.

It is in this context that this project was undertaken: an analysis of the experience of treating diabetic foot ulcers at a hospital-based wound clinic with a 10^7 - 10^8 phage/ml solution of a commercial preparation of staphylococcal phage Sb-1 (Eliava Sb-1). Staphylococcal phage Sb-1 was first isolated in 1977 at the Eliava Institute (Tbilisi, Republic of Georgia) and is a relative of the phages already approved by the U.S. Food and Drug Administration (FDA) for eliminating *Listeria monocytogenes* in some prepared foods. In fact, a closely related phage can be found in another phage product (Staphage Lysate produced by Delmont Laboratories in Philadelphia) which is already legally marketed for use in animals in the U.S. as an immune stimulant against *Staphylococcus* infections.

Patients were considered eligible for the compassionate use of this investigational product if they failed to respond to conventional wound care and antibiotic therapy, with amputation being the only remaining routine option. The authors briefly described their treatment protocol as follows:

> "Treatment involved standard wound care, including weekly soft tissue debridement if necessary. The softened, exposed and obviously infected bone was debrided in three cases and left in place in two cases where bone debridement would have led to a less favorable functional and cosmetic result. For experimental treatment, the phage preparation was dripped into the wound cavity; gauze packing was placed over the wound and soaked with the phage preparation (0.1 to 0.5cc, depending on ulcer volume), covered with petroleum gauze and wrapped with dry

gauze. The patient was instructed to leave the treatment in place for 48 hours before removing it and replacing the treatment with moist dressings. This protocol was repeated weekly until the ulcer became too small to pack."

Findings

A total of nine patients were treated over two years, all with vascular insufficiency, four with osteomyelitis and bone. MRSA was found in one of the wounds, methicillin-susceptible *S aureus* (MSSA) in all of the others. Eight of the wounds were clinically infected; one was gangrenous at considered to be "at high risk" of infection. All 9 infections responded to treatment; all nine wounds healed in an average of seven weeks (range: 4 - 18 weeks). There were no adverse events observed during treatment or follow-up.

Discussion

The authors concluded that "Topical application of a staph mono-phage preparation can be used successfully to treat infected toe ulcerations with bone involvement, despite very poor vascularity and failure of antibiotic treatment. The success within this small series provides the groundwork for controlled clinical trials of staph phage for diabetic foot infections." Both conclusions are valid.

It is worth noting that phage Sb-1 was not the only treatment administered. Subjects received the gamut of good wound care, including frequent debridement and antibiotics, where indicated. But standard of care treatments like these had been attempted all along, and these subjects failed to respond, as defined by the compassionate use protocol. We must assume that they would have gone on to receive an amputation, had they not been allowed to try phage therapy.

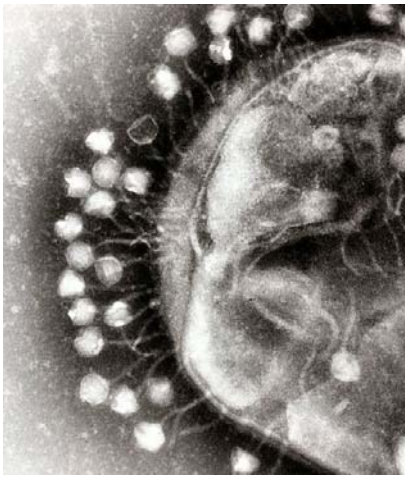
The authors have contributed not only to the literature of phage therapy, but also to our understanding of wound infections in general. This study has demonstrated that even though most wounds are colonized and often infected by multiple organisms, a treatment aimed at a single microbe was still associated with successful treatment of the infected wound. This gives us much food for thought, not only as we begin to design the much-needed and highly justified clinical trials of phage therapy, but also as we re-consider how we currently treat diabetic foot ulcers with broad-spectrum antibiotics in order to kill multiple organisms, despite the commonly seen risks of killing beneficial microbes in the gut (the gastrointestinal biome) and further selecting for microbes with even greater antimicrobial resistance.

Some readers may ask: why did the subjects not receive maggot therapy? How can they be described as having no commercially available treatment options if they had not been considered for maggot therapy? At least in the biotherapy community, this is a valid question. The answer is quite simple: medicinal maggots are NOT currently approved for managing infection, even if they are approved for debridement in

general. Could maggot therapy have been used successfully, either with or instead of phage therapy? While there is data to suggest that this is the case, and although many people may use maggot therapy in tough cases like this, there are no clinical trials to support it. And here we get to the crux of the matter: it is only through well-designed controlled studies – preferably randomized prospective studies, but at least controlled – that we can say with confidence that intervention A is significantly responsible for outcome B. The authors know that they have not proven that phage therapy was the deciding factor, but they hope (and I hope) that their experience and analysis contributes significantly to the body of evidence that we now have to support some good prospective clinical trials of phage therapy.

The authors have contributed not only by providing additional justification for clinical trials, but they have also identified some of the impediments that have blocked clinical trials from having already been done, and they have provided guidance to help overcome some of those impediments. Clinical trials are expensive, and are generally sponsored only by those organizations that believe they can adequately benefit from such a large investment. The authors propose that public money could kick-start some studies, or be combined with corporate money to sponsor such studies. Another obstacle to moving forwards with clinical trials is that there are many different phages and many different ways to combine them into a useful product; and many different infections that could likely benefit. Where do we start? By demonstrating the benefits of a pure strain of naturally occurring phage, they convincingly argue that perhaps we should start with clinical trials of pure, naturally occurring, inexpensive phage, and let the results of those trials generate private support to develop the more expensive – but more lucrative – modified and mixed phage products. This is another approach that may help move us forwards with conducting the clinical trials that are needed before phage therapy can become a reality for the rest of us.

-Reviewed by Ronald Sherman, MD



Helminthic Therapy Reviews

Journal Citation

Voldsgaard A, Bager P, Garde E, Åkeson P, Leffers AM, Madsen CG, Kapel C, Roepstorff A, Thamsborg SM, Melbye M, Siebner H, Søndergaard HB, Sellebjerg F, Sørensen PS. ***Trichuris suis* ova therapy in relapsing multiple sclerosis is safe but without signals of beneficial effect.** Mult Scler. 2015;21(13):1723-9.

Published Abstract

BACKGROUND: An observational study has suggested that relapsing-remitting multiple sclerosis patients with helminth infections have lower disease activity and progression than uninfected multiple sclerosis patients. **OBJECTIVE:** To evaluate the safety and efficacy on MRI activity of treatment with TSO in relapsing MS. **METHODS:** The study was an open-label, magnetic resonance imaging assessor-blinded, baseline-to-treatment study including ten patients with relapsing forms of multiple sclerosis. Median (range) age was 41 (24-55) years, disease duration 9 (4-34) years, Expanded Disability Status Scale score 2.5 (1-5.0), and number of relapses within the last two years 3 (2-5). Four patients received no disease modifying therapy, while six patients received IFN-β. After an observational period of 8 weeks, patients received 2500 ova from the helminth *Trichuris suis* orally every second week for 12 weeks. Patients were followed with serial magnetic resonance imaging, neurological examinations, laboratory safety tests and expression of immunological biomarker genes. **RESULTS:** Treatment with *Trichuris suis* orally was well-tolerated apart from some gastrointestinal symptoms. Magnetic resonance imaging revealed 6 new or enlarged T2 lesions in the run-in period, 7 lesions in the early period and 21 lesions in the late treatment period. Two patients suffered a relapse before treatment and two during treatment. Eight patients developed eosinophilia. The expression of cytokines and transcription factors did not change. **CONCLUSIONS:** In a small group of relapsing multiple sclerosis patients, oral therapy was well tolerated but without beneficial effect.

Context

Multiple sclerosis (MS) is a debilitating neurological disease which progressively leads to the disappearance of myelin around motor nerve cells, thereby slowing the conduction along those pathways. The result is a progressive weakness or paralysis which may wax and wane over time, but ultimately progresses in severity. MS is much more prevalent in regions of the world with well-developed sanitation, but rare in countries with high rates of helminth carriage. This has led many to believe that helminth exposure may protect against the development of MS, and may even be able to slow the progression of this disease.

T. suis, the porcine whipworm, is a helminth naturally infecting pigs. It can transiently colonize humans, but generally cannot survive long in the human gut, and has not been observed to cause human disease. In small, unblinded trials, treatment with *T. suis* ova (TSO) was found to be safe and effective in active in treating inflammatory bowel disease.

While there are some anecdotal reports of MS patients whose symptoms improved with the administration of helminths (helminthic therapy), there has been little in the way of published studies. Correale and colleagues followed 12 patients with MS and various helminth infections for an average of 4.5 years and noted fewer exacerbations, less disease progression and less disease activity on magnetic resonance imaging (MRI) than 12 matched uninfected controls (1). Helminth-infected individuals also had less pro-inflammatory cytokines than non-infected subjects (2).

In 2021, Fleming and colleagues (3) published a Phase 1 trial of 5 treatment-naive relapsing-remitting multiple sclerosis subjects who were given 2500 TSO orally every 2 weeks for 3 months in a baseline versus treatment control exploratory trial. The treatments were well tolerated, MRI lesions decreased, and favorable changes is cytokine levels (increases in IL-4 and IL-10) were measured. The same year, Benzel and colleagues (4) published their studies of 4 MS patients treated with TSO for 6 months. These researchers demonstrated a slight decrease in interleukin (IL)-2, a temporary increase of IL-4, and a mild eosinophily, all suggesting that TSO therapy had a moderate beneficial immunomodulatory impact in MS.

Given these encouraging results, the authors of the present study "conducted a 20-week phase IIa baseline-to-treatment trial to evaluate the safety and efficacy of treatment with TSO in relapsing MS." Their study design was a prospective randomized pilot study of safety and efficacy, with baseline-to-treatment comparisons of clinical findings and blindly assessed MRIs. The 6-week baseline or run-in period was followed by an early (6-week) and late (6 week) treatment periods, with assessments at the beginning and end of each 6-week interval. The intervention (treatment) consisted of an aqueous suspension 2500 TSO per treatment (15 ml) administered in the outpatient clinic every two weeks (total of 6 doses over the 12 weeks of treatment).

Subjects were recruited from among those with relapsing forms of MS for more than a year, at the outpatient clinic at the Danish Multiple Sclerosis Center in Copenhagen. Subjects needed to be between 19 and 55 years old, with an Expanded Disability Status Scale score $\leqslant$ 5.5, no or unchanged IFN-β therapy for the previous three months, at least two documented relapses during the prior 2 years (at least one of which was within the prior 1 year), and MRI results meeting the Barkhof criteria for MS. Subjects were excluded if they received steroids in the previous month, received previous treatment with cyclophosphamide, mitoxantrone or other intensive immunosuppression, received total body irradiation or any experimental therapy, received treatment with azathioprine or any immunomodulatory drug apart from IFN-β within 6 months prior to enrolment, stayed in tropical areas during the preceding 3 months or had a history of current pregnancy or breastfeeding, cardiac diseases, malignant hypertension, diabetes mellitus, renal insufficiency, concurrent systemic infections with hepatitis B or C

virus or HIV, or any medical or psychiatric condition that could interfere with the subject's participation in the study protocol.

Primary endpoints of efficacy were the number of new or enlarging lesions on T2-weighted MRI scans performed at baseline and every 6 weeks. Secondary endpoints were the number of gadolinium enhancing lesions in T1-weighted MRI scans and the number of documented relapses. Standard safety parameters were monitored to assess overall safety. Blood samples were obtained at baseline and after 6 and 12 weeks of therapy for the analysis of cytokine gene expression. MRI and immunological results were analyzed using the non-parametrical chi-square contingency table and Friedman tests with post hoc Kruskal–Wallis tests corrected for multiple comparisons yielding a level of statistical significance at $p = 0.025$. Safety data was assessed using descriptive statistics.

Findings

Ten subjects were enrolled in the study.

The total number of new and/or enlarged T2 lesions was 6 lesions in the pre-treatment scans, 7 lesions in the early treatment period, and 21 lesions in the later treatment period ($p = 0.034$). The number of patients with new and/or enlarged T2 lesions was three in the pre-treatment period, two in the early, and eight in the later treatment period. Two patients experienced a relapse during the baseline period; two patients experienced relapses in the late treatment period.

It should be noted that, of the 10 subjects enrolled, Six were treated with IFN-β during the study; four patients did not receive any immunomodulating drugs. Four patients missed one MRI scan (no. 2) and one patient missed two scans (no. 2 and 4) due to renovation of the MRI scanner. Due to technical problems with a too-short interval between injection of gadolinium contrast and the T1-weighted MRI scan, the count of the number of contrast-enhancing lesions was unreliable and had to be omitted.

No serious adverse events were reported during the study. Four subjects complained of abdominal discomfort or pain, mostly mild, lasting from days to several weeks. Two patients reported flatulence and one of these patients also had diarrhea. Except for eosinophilia, all other blood parameters showed no significant changes.

For the whole patient group, the blood eosinophil count was significantly higher at 6 weeks ($p = 0.02$) and twelve weeks ($p = 0.01$) than at baseline. No significant difference was found in the level of gene expression for any of the cytokines tested: Th1 cytokines and transcription factors *IFNG*, *TBX21*, *HLX1* or *EOMES*; the Th2 transcription factor *GATA3*; the Th17 transcription factor *RORC*; regulatory cytokines and the transcription factor *FOXP3*, *IL10* and *TGFB1*; the antigen-presenting cell cytokines *IL1B*, *IL12A*, *IL12B*, *IL23A*, *IL27* and *EBI3*; the tumor necrosis factor superfamily molecules *TNF*, *LTA*, *LTB* and *TRAIL*; or the matrix metalloproteinase *MMP9*, *TIMP1* or *SPP1* molecule.

Discussion

This study is not new (it was published in 2015), but it is the latest helminthic therapy clinical trial to be published, and it is an important contribution on several levels.

The authors successfully demonstrated with this small but rigorous study that TSO is a relatively safe modality, having found no serious adverse events after 12 weeks of use. This is consistent with earlier studies of TSO – in MS patients and non-MS patients – where mild GI complaints are the only side effects attributable to TSO.

However, the authors did not demonstrate any clinical benefit of TSO for these 10 MS subjects. Therefore, the authors concluded that "treatment with TSO is safe and well tolerated, but was without any trend towards a positive effect on disease activity when administered to patients with relapsing MS. Hence, we found it unjustified to embark on the planned double-blind, placebo-controlled phase II study."

The authors should be congratulated for having published their work, and the publisher congratulated for printing it, since often studies that fail to prove the desired hypothesis do not see the light of day. The reason? As a result of these findings, some have described this study as a "failure," or worse yet, they have described helminthic therapy as a failure, at least as a possible treatment for MS. I prefer the interpretation of Thomas Edison, who is reported to have said: "I have not failed. I've just found 10,000 ways that won't work." Voldsgaard and colleagues may have proved that this treatment did not work, but what treatment will work? What comes next? A different dose or frequency of administration? A different helminth? A different subset of MS patients, or a different target illness altogether?

The authors go through this very process of examination when reviewing their findings. They clearly gave it the same careful thought when designing the project. Prior research with TSO for MS and other disorders used the same dose. Perhaps there was a difference in the method of preparation of the reagents. Perhaps some of the TSO was less viable than normal, or prepared in a different way (which would explain not only why there was no clinical benefit, but also why there was no significant change in immunological cytokines). While MS is probably a heterogeneous disease, and as such, patients should not all be expected to respond to any treatment in the same way, reviewing the subject profiles did not allow me to identify any characteristic that might select a subset of potential responders for the next clinical trial.

What? Another clinical trial? Didn't the authors state that they found it "unjustified to embark on the planned double-blind, placebo-controlled phase II study." Yes, they did, but that was a large, expensive trial. But I hope they or someone else will be willing to try another small clinical trial of helminthic therapy for MS again. After all, if these researchers identified a significant improvement, we would not accept that as the final verdict, but rather would want to repeat the study, likely with additional twists, to make sure that the results were really valid and reproducible. So why not follow this study with another small, relatively inexpensive study – but with a different helminthic product, or a

different treatment regimen – to test whether or not helminthic therapy really does not benefit MS. After all, the more we learn what does not work, the closer we get to finding out what does work.

-Reviewed by Ronald Sherman, MD

ADDITIONAL REFERENCES

1) Correale J and Farez M. Association between parasite infections and immune responses in multiple sclerosis. *Ann Neurol* 2007; 61: 97–108.

2) Correale J and Farez M. Helminth-infections associated with multiple sclerosis induce regulatory B cells. *Ann Neurol* 2008; 64: 187–199.

3) Fleming JO, Isaak A, Fabry Z, et al. Probiotic helminth administration in relapsing–remitting
multiple sclerosis: A phase 1 study. *Multiple Sclerosis* 2011; 17(6): 743–754.

4) Benzel F, Erdur H, Rosche B, et al. Immune monitoring of *Trichuris suis* egg therapy in multiple
sclerosis patients. *J Helminthology* 2012; 86(3): 339–347.



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Section II: Biotherapy Citations for Summer 2016

A. Apitherapy and Bee Venom Therapy

Fratellone, P. M., Tsimis, F., and Fratellone, G. Apitherapy Products for Medicinal Use. J.Altern.Complement Med. 7-27-2016

ABSTRACT: For the past 10 years, beekeeping has increased due to a growing awareness of the disappearance of bees since Colony Collapse Disorder. Most of the disappearance of honey bees can be attributed to the use of pesticides. Apitherapy is the science and art of maintaining health with the use of products from the honeybee hive: honey, bee pollen, propolis, royal jelly, and bee venom. We have been beekeeping for the last 10 years. We use every product from the beehive for both personal and patient use.

Xian, P. F., Chen, Y., Yang, L., Liu, G. T., Peng, P., and Wang, S. X. [Effect of bee venom injection on TrkA and TRPV1 expression in the dorsal root ganglion of rats with collagen-induced arthritis]. Nan.Fang Yi.Ke.Da.Xue.Xue.Bao. 2016; 36(6):838-841

ABSTRACT: *OBJECTIVE*: To investigate the therapeutic effect of acupoint injection of bee venom on collagen-induced arthritis (CIA) in rats and explore the mechanism of bee venom therapy in the treatment of rheumatoid arthritis. *METHODS*: Fifteen male Wistar rats were randomly divided into bee venom treatment group (BV group), CIA model group, and control group. In the former two groups, CIA was induced by injections of collagen II+IFA (0.2 mL) via the tail vein, and in the control group, normal saline was injected instead. The rats in BV group received daily injection of 0.1 mL (3 mg/mL) bee venom for 7 consecutive days. All the rats were assessed for paw thickness and arthritis index from days 14 to 21, and the pain threshold was determined on day 21. The expressions of TRPV1 and TrkA in the dorsal root ganglion at the level of L4-6 were detected using immunohistochemistry and Western blotting, respectively. *RESULTS*: The rats in CIA model group started to show paw swelling on day 10, and by day 14, all the rats in this group showed typical signs of CIA. In BV group, the rats receiving been venom therapy for 7 days showed a significantly smaller paw thickness and a low arthritis index than those in the model group. The pain threshold was the highest in the control group and the lowest in the model group. TRPV1-positive cells and TrkA expression in the dorsal root ganglion was significantly reduced in BV group as compared with that in the model group. *CONCLUSION*: s Injection of bee venom can decrease expression of TRPV1 and TrkA in the dorsal root ganglion to produce anti-inflammatory and analgesic effects, suggesting the potential value of bee venom in the treatment of rheumatoid arthritis.

B. Helminthic Therapy

Liu, J., Morey, R. A., Wilson, J. K., and Parker, W. Practices and outcomes of self-treatment with helminths based on physicians' observations. J.Helminthol. 5-31-2016; 1-11

ABSTRACT: The successful use of helminths as therapeutic agents to resolve inflammatory disease was first recorded 40 years ago. Subsequent work in animal models and in humans has demonstrated that the organisms might effectively treat a wide range of inflammatory diseases, including allergies, autoimmune disorders and inflammation-associated neuropsychiatric disorders. However, available information regarding the therapeutic uses and effects of helminths in humans is limited. This study probes the practices and experiences of individuals 'self-treating' with helminths through the eyes of their physicians. Five physicians monitoring more than 700 self-treating patients were interviewed. The results strongly support previous indications that helminth therapy can effectively treat a wide range of allergies, autoimmune conditions and neuropsychiatric disorders, such as major depression and anxiety disorders. Approximately 57% of the self-treating patients observed by physicians in the study had autism. Physicians reported that the majority of patients with autism and inflammation-associated co-morbidities responded favourably to therapy with either of the two most popular organisms currently used by self-treaters, Hymenolepis diminuta and Trichuris suis. However, approximately 1% of paediatric patients experienced severe gastrointestinal pains with the use of H. diminuta, although the symptoms were resolved with an anti-helminthic drug. Further, exposure to helminths apparently did not affect the impaired comprehension of social situations that is the hallmark of autism. These observations point toward potential starting points for clinical trials, and provide further support for the importance of such trials and for concerted efforts aimed at probing the potential of helminths, and perhaps other biologicals, for therapeutic use.

Maizels, R. M. Parasitic helminth infections and the control of human allergic and autoimmune disorders. Clin.Microbiol.Infect. 2016; 22(6):481-486

ABSTRACT: The profile of global health today presents a striking reciprocal distribution between parasitic diseases in many of the world's lower-income countries, and ever-increasing levels of inflammatory disorders such as allergy, autoimmunity and inflammatory bowel diseases in the more affluent societies. Attention is particularly focused on helminth worm parasites, which are associated with protection from allergy and inflammation in both epidemiologic and laboratory settings. One mechanistic explanation of this is that helminths drive the regulatory arm of the immune system, abrogating the ability of the host to expel the parasites, while also dampening reactivity to many bystander specificities. Interest has therefore heightened into whether helminth parasites, or their products, hold therapeutic potential for immunologic disorders of the developed world. In this narrative review, progress across a range of trials is discussed, together with prospects for isolating individual molecular mediators from helminths that may offer defined new therapies for inflammatory conditions.

Zakeri, A., Borji, H., and Haghparast, A. Interaction between Helminths and Toll-Like Receptors: Possibilities and Potentials for Asthma Therapy. Int.Rev.Immunol. 4-27-2016

ABSTRACT: Toll-like receptors (TLRs) are essential components of the innate immune system. They play an important role in the pathogenesis of allergic diseases, especially asthma. Since TLRs significantly orchestrate innate and adaptive immune response, their manipulation has widely been considered as a potential approach to control asthma symptoms. It is well established that helminths have immunoregulatory effects on host immune responses, especially innate immunity. They release bioactive molecules such as excretory-secretory (ES) products manipulating TLRs expression and signaling. Thus, given the promising results derived from preclinical studies, harnessing helminth-derived molecules affecting TLRs can be considered as a potential biological therapy for allergic diseases. Prospectively, the data that are available at present suggest that, in the near future, it is possible that helminth antigens will offer new therapeutic strategies and druggable targets for fighting allergic diseases. This review describes the interactions between helminths and TLRs and discusses the potential possibilities for asthma therapy. In this opinion paper, the authors aimed to review the updated literatures on the interplay between helminths, TLRs, and asthma with a view to proposing helminth-based asthma therapy.

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C. Ichthyotherapy

No New Publications for Summer 2016.



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D. Leech Therapy

Herlin, C., Bertheuil, N., Bekara, F., Boissiere, F., Sinna, R., and Chaput, B. Leech therapy in flap salvage: Systematic review and practical recommendations. Ann.Chir Plast.Esthet. 7-14-2016

ABSTRACT: *INTRODUCTION*: Medicinal leeches have been part of the therapeutic armamenterium of plastic surgeons for more than 50 years. While their use in hand surgery is a matter of course, their use in salvage of flaps with venous congestion remains facultative depending on teams. *MATERIALS AND METHODS*: We conducted a systematic review of leech therapy for flap salvage between 1960 and 2015, analyzing 121 articles and subsequently taking into consideration 41 studies. In parallel, we collected data from 43 patients for whom leach therapy had recently been applied in treatment of venous insufficiency in pedicled or free flaps after revision surgery had failed to improve flap vascularization, or in cases where flap revision was not appropriate. The data collected pertained to relevant indications, treatment procedure, efficacy, adjuvant therapies, side effects and complications. *RESULTS*: For this indication, the success rate of leech therapy ranged from 65 to 85% (83.7% in our series) according to the situations encountered. Optimal frequency of application ranged from 2 to 8hours, while average overall duration ranged from 4 to 10 days. The number of leeches to be applied can be determined depending on volume of the flap. In 50% of the cases reported in the literature, the patients required transfusion. Antibiotic prophylaxis against Aeromonas is highly advisable. A ciprofloxacin and trimethoprim-sulfametoxazole combination currently appears as the most relevant prophylactic antibiotherapy. *CONCLUSION*: Hirudotherapy is a reliable treatment in cases of patent venous insufficiency of pedicled or free flaps (or when revision surgery is not recommended). Even though the relevant literature is highly heterogeneous, we have attempted to put forward a specific protocol bringing together dosage, delivery route, frequency of administration and appropriate prophylactic antibiotherapy. An algorithm for treatment and management of venous congestion and a practical information sheet have been placed at the disposal of plastic surgery teams.

Reynolds, A. and OBoyle, C. Nurses' experiences of leech therapy in plastic and reconstructive surgery. Br.J.Nurs. 7-14-2016; 25(13):729-733

ABSTRACT: The aim of this study was to explore nurses' experience of using leech therapy. Leech therapy is useful in promoting revascularisation of skin grafts. Nurse disquiet in their role as leech therapists has been noted. This study explored the experience of Irish nurses. A qualitative design with an interview schedule was used to learn about emotional and practical clinical experiences. Interviews were carried out with seven nurses working with leeches in reconstructive surgery in 2013. These interviews were coded and explored for themes. Results revealed that many nurses feel aversion to the use of leeches. This may be associated with the use of a parasitic organism as treatment in conflict with the nurse's role in cross infection. It was also found that management of a nurse's own and patient's emotional responses is required. In conclusion, preparation for the role of leech therapy beyond the purely practical is necessary, and should explore affective responses of the practitioner and patients.

Uzun, G., Ozdemir, A., Yildiz, S., and Tanyuksel, M. To suck or not to suck: medicinal leech therapy for lower extremity wounds in patients with peripheral arterial disease. Int.Wound.J. 2016; 13(3):429-430

No Abstract Available.



E. Mammals- Service & Therapeutic Animals

Brand, S., Colledge, F., Beeler, N., Puhse, U., Kalak, N., Sadeghi, Bahmani D., Mikoteit, T., Holsboer-Trachsler, E., and Gerber, M. The current state of physical activity and exercise programs in German-speaking, Swiss psychiatric hospitals: results from a brief online survey. Neuropsychiatr.Dis.Treat. 2016; 12:1309-1317

ABSTRACT: *BACKGROUND*: Physical activity and exercise programs (PAEPs) are an important factor in increasing and maintaining physical and mental health. This holds particularly true for patients with psychiatric disorders undergoing treatment in a psychiatric hospital. To understand whether the benefits reported in the literature are mirrored in current treatment modalities, the aim of the present study was to assess the current state of PAEPs in psychiatric hospitals in the German-speaking part of Switzerland. *METHODS*: All psychiatric hospitals (N=55) in the German-speaking part of Switzerland were contacted in spring 2014. Staff responsible for PAEPs were asked to complete an online questionnaire covering questions related to PAEPs such as type, frequency, staff training, treatment rationale, importance of PAEPs within the treatment strategy, and possible avenues to increase PAEPs. *RESULTS*: Staff members of 48 different psychiatric hospitals completed the survey. Hospitals provided the following therapeutic treatments: relaxation techniques (100%), sports therapy (97%), activity-related psychotherapeutic interventions (95%), physiotherapy (85%), body therapies (59%), far-east techniques (57%), and hippotherapy (22%). Frequencies ranged from once/week to five times/week. Approximately 25% of patients participated in the PAEPs. Interventions were offered irrespective of psychiatric disorders. PAEP providers wanted and needed more vocational training. *CONCLUSION*: All participating psychiatric hospitals offer a broad variety of PAEPs in their treatment curricula. However, the majority of inpatients do not participate in PAEPs. Furthermore, those who do participate cannot continue to do so following discharge. PAEP providers need specific extended vocational trainings and believe that the potential of PA should be improved.

Breitenbuecher, C., Belanger, J. M., Levy, K., Mundell, P., Fates, V., Gershony, L., Famula, T. R., and Oberbauer, A. M. Protein expression and genetic variability of canine Can f 1 in golden and Labrador retriever service dogs. Canine.Genet.Epidemiol. 2016; 3:3

ABSTRACT: *BACKGROUND*: Valued for trainability in diverse tasks, dogs are the primary service animal used to assist individuals with disabilities. Despite their utility, many people in need of service dogs are sensitive to the primary dog allergen, Can f 1, encoded by the Lipocalin 1 gene (LCN1). Several organizations specifically breed service dogs to meet special needs and would like to reduce allergenic potential if possible. In this study, we evaluated the expression of Can f 1 protein and the inherent variability of LCN1 in two breeds used extensively as service dogs. Saliva samples from equal numbers of male and female Labrador retrievers (n = 12), golden retrievers (n = 12), and Labrador-golden crosses (n = 12) were collected 1 h after the morning meal. Can f 1 protein concentrations in the saliva were measured by ELISA, and the LCN1 5' and 3' UTRs and exons sequenced. *RESULTS*: There was no sex effect ($p > 0.2$) nor time-of-day effect; however, Can f 1 protein levels varied by breed with Labrador retrievers being lower than golden retrievers (3.18 +/- 0.51 and 5.35 +/- 0.52 mug/ml, respectively, $p < 0.0075$), and the Labrador-golden crosses having intermediate levels (3.77 +/- 0.48 mug/ml). Although several novel SNPs were identified in LCN1, there were no significant breed-specific sequence differences in the gene and no association of LCN1 genotypes with Can f 1

expression. *CONCLUSIONS*: As service dogs, Labrador retrievers likely have lower allergenic potential and, though there were no DNA sequence differences identified, classical genetic selection on the estimated breeding values associated with salivary Can f 1 expression may further reduce that potential.

Erdman, E. A. and Pierce, S. R. Use of Hippotherapy With a Boy After Traumatic Brain Injury: A Case Study. Pediatr.Phys.Ther. 2016; 28(1):109-116

ABSTRACT: *PURPOSE*: The purpose of this case report was to describe the use of hippotherapy with a boy who sustained a brain injury. *KEY POINTS*: A 13-year-old boy, 6 months after traumatic brain injury received 12 physical therapy sessions, which included hippotherapy. Improvements were noted in balance, strength, gross motor skills, gait speed, functional mobility, and reported participation. *SUMMARY*: Hippotherapy used with a 13-year-old boy after traumatic brain injury may have had a positive effect in the body structure, activity, and participation domains.

Hardin, P., Brown, J., and Wright, M. E. Prevention of transmitted infections in a pet therapy program: An exemplar. Am.J.Infect.Control. 7-1-2016; 44(7):846-850

ABSTRACT: The focus of the patient experience in health care delivery has afforded the opportunity to integrate pet therapy as a part of patient care. The purpose of this article is to present the implementation of a pet therapy program that includes guidelines for the prevention of transmitted infections. Consideration of infection prevention strategies has resulted in a 16-year program with no documented incidences of transmitted infections, averaging 20,000 pet therapy interactions per year.

Hsieh, Y. L., Yang, C. C., Sun, S. H., Chan, S. Y., Wang, T. H., and Luo, H. J. Effects of hippotherapy on body functions, activities and participation in children with cerebral palsy based on ICF-CY assessments. Disabil.Rehabil. 7-20-2016; 1-11

ABSTRACT: *PURPOSE*: To evaluate the effects of hippotherapy on body functions, activities, and participation in children with CP of various functional levels by using the International Classification of Functioning, Disability and Health-Children and Youth (ICF-CY) checklist. *METHODS*: Fourteen children with cerebral palsy (CP) (3-8 years of age) were recruited for a 36-week study composed of baseline, intervention, and withdrawal phases (12 weeks for each phase, ABA design). Hippotherapy was implemented for 30 min once weekly for 12 consecutive weeks during the intervention phase. Body Functions (b) and Activities and Participation (d) components of the ICF-CY checklist were used as outcome measures at the initial interview and at the end of each phase. *RESULTS*: Over the 12 weeks of hippotherapy, significant improvements in ICF-CY qualifiers were found in neuromusculoskeletal and movement-related functions (b7), mobility (d4) and major life areas (d8) and, in particular, mobility of joint functions (b710), muscle tone functions (b735), involuntary movement reaction functions (b755), involuntary movement functions (b765), and play (d811) (all $p < 0.05$) when compared with baseline. *CONCLUSION*: This study demonstrated the beneficial effects of hippotherapy on body functions, activities, and participation in children with CP. Implications for Rehabilitation ICF-CY provides a comprehensive overview of functioning and disability and constitutes a universal language for identifying the benefits of hippotherapy in areas of functioning and disability in children with CP. In children with CP, hippotherapy encourages a more

complementary approach that extends beyond their impairments and limitations in body functions, activities, and participation. The effect of hippotherapy was distinct from GMFCS levels and the majority of improvements were present in children with GMFCS levels I-III.

Jang, C. H., Joo, M. C., Noh, S. E., Lee, S. Y., Lee, D. B., Lee, S. H., Kim, H. K., and Park, H. I. Effects of Hippotherapy on Psychosocial Aspects in Children With Cerebral Palsy and Their Caregivers: A Pilot Study. Ann.Rehabil.Med. 2016; 40(2):230-236

ABSTRACT: *OBJECTIVE*: To investigate the effects of hippotherapy on psychosocial and emotional parameters in children with cerebral palsy (CP) and their caregivers. *METHODS*: Eight children with CP were recruited (three males and five females; mean age, 7.3 years; Gross Motor Function Classification System levels 1-3). Hippotherapy sessions were conducted for 30 minutes once weekly for 10 consecutive weeks in an indoor riding arena. The Gross Motor Function Measure (GMFM), Pediatric Balance Scale (PBS), and the Korean version of the Modified Barthel Index were evaluated. All children were evaluated by the Children's Depression Inventory, Trait Anxiety Inventory for Children, State Anxiety Inventory for Children, Rosenberg Self Esteem Scale, and the Korean-Satisfaction with Life Scale (K-SWLS). Their caregivers were evaluated with the Beck Depression Inventory, the Beck Anxiety Inventory, and the K-SWLS. We assessed children and their caregivers with the same parameters immediately after hippotherapy. *RESULTS*: Significant improvements on the GMFM, dimension E in the GMFM, and the PBS were observed after hippotherapy compared with the baseline assessment ($p<0.05$). However, no improvements were detected in the psychosocial or emotional parameters in children with CP or their caregivers. None of the participants showed any adverse effects or accidents during the 10 weeks hippotherapy program. *CONCLUSIONS*: Hippotherapy was safe and effectively improved gross motor and balance domains in children with CP. However, no improvements were observed in psychosocial or emotional parameters.

Pham, C. and Bitonte, R. Hippotherapy: Remuneration issues impair the offering of this therapeutic strategy at Southern California rehabilitation centers. NeuroRehabilitation. 4-6-2016; 38(4):411-417

ABSTRACT: *BACKGROUND*: Hippotherapy is the use of equine movement in physical, occupational, or speech therapy in order to obtain functional improvements in patients. Studies show improvement in motor function and sensory processing for patients with a variety of neuromuscular disabilities, developmental disorders, or skeletal impairments as a result of using hippotherapy. *OBJECTIVE*: The primary objective of this study is to identify the pervasiveness of hippotherapy in Southern California, and any factors that impair its utilization. *METHODS*: One hundred and fifty-two rehabilitation centers in the Southern California counties of Los Angeles, San Diego, Orange, Riverside, San Bernardino, San Diego, San Luis Obispo, Santa Barbara, Ventura, and Kern County were identified, and surveyed to ascertain if hippotherapy is utilized, and if not, why not. *RESULTS*: Through a review of forty facilities that responded to our inquiry, our study indicates that the majority of rehabilitation centers are familiar with hippotherapy, however, only seven have reported that hippotherapy is indeed available as an option in therapy at their centers. *CONCLUSION*: It is concluded that hippotherapy, used in a broad based array of physical and sensory disorders, is limited in its ability to be utilized, primarily due to remuneration issues.

Reubens, R. and Silkwood-Sherer, D. J. Intervention for an Adolescent With Cerebral Palsy During Period of Accelerated Growth. Pediatr.Phys.Ther. 2016; 28(1):117-125

ABSTRACT: *PURPOSE*: The purpose of this case report was to describe changes in body functions and structures, activities, and participation after a biweekly 10-week program of home physical therapy and hippotherapy using a weighted compressor belt. *PARTICIPANT*: A 13-year-old boy with spastic diplegic cerebral palsy, Gross Motor Function Classification System level II, was referred because of accelerated growth and functional impairments that limited daily activities. *OUTCOME MEASURES*: The Modified Ashworth Scale, passive range of motion, 1-Minute Walk Test, Timed Up and Down Stairs, Pediatric Balance Scale, Pediatric Evaluation of Disability Inventory Computer Adaptive Test, and Dimensions of Mastery Questionnaire 17 were examined at baseline, 5, and 10 weeks. *OUTCOMES*: Data at 5 and 10 weeks demonstrated positive changes in passive range of motion, balance, strength, functional activities, and motivation, with additional improvements in endurance and speed after 10 weeks. *CLINICAL IMPLICATIONS*: This report reveals enhanced body functions and structures and activities and improved participation and motivation.

Sicurella, T. and Fitzsimmons, V. Robotic pet therapy in long-term care. Nursing. 2016; 46(6):55-57

No Abstract Available.

Stace, L. B. Welcoming max: Increasing pediatric provider knowledge of service dogs. Complement Ther.Clin.Pract. 2016; 24:57-66

ABSTRACT: Service dogs have been used in the adult population for decades. Recently, there has been a diversification in types of service dogs, specifically for the pediatric population. Although guide dogs and mobility dogs are accepted in society, autism assistance dogs, seizure alert and response dogs and diabetic alert dogs are relatively new. As pediatric service dogs attract more attention, pediatric providers need to be prepared to answer parental inquires regarding service dog use. The pediatric provider is well equipped to identify children who could benefit from a service dog intervention and should be able to make a referral to a reputable service dog provider. This article presents guidance on appropriate patient selection, making a service dog referral, and risks and benefits involved. Pediatric providers are ideally positioned to be leaders in implementing this evolving new assistive technology that can help to alleviate pediatric disabilities for both the patient and family.

Stapleton, M. Effectiveness of Animal Assisted Therapy after brain injury: A bridge to improved outcomes in CRT. NeuroRehabilitation. 6-18-2016; 39(1):135-140

ABSTRACT: *BACKGROUND*: Animal Assisted Therapy (AAT) has been widely used as a complementary therapy in mental health treatment especially to remediate social skill deficits. The goal of AAT is to improve social, emotional, and cognitive functioning. OBJECTIVE: The purpose of this article is to draw upon the literature on AAT and explore specific applications to cognitive rehabilitation therapy (CRT) and social skills training. *METHODS*: This study provides a systematic review of most of the available literature on

ATT and assesses that potential uses of ATT for brain injury rehabilitation. *RESULTS*: Although the efficacy of AAT is not currently well documented by rigorous research, (Kazin, 2010) anecdotal evidence suggests that brain injury survivors may benefit from the combination of AAT and cognitive rehabilitation techniques. *CONCLUSIONS*: Acquired Brain Injury (ABI) survivors with cognitive impairments can benefit from AAT as part of a comprehensive and holistic rehabilitation treatment plan.

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F. Maggot Debridement Therapy

Diaz-Roa, A., Gaona, M. A., Segura, N. A., Ramirez-Hernandez, A., Cortes-Vecino, J. A., Patarroyo, M. A., and Bello, F. Evaluating Sarconesiopsis magellanica blowfly-derived larval therapy and comparing it to Lucilia sericata-derived therapy in an animal model. Acta Trop. 2016; 154:34-41

ABSTRACT: Larval therapy is used as alternative treatment for hard-to-heal chronic and infected wounds. Lucilia sericata is the most used blowfly species. However, it has been shown recently that Sarconesiopsis magellanica larval excretions and secretions have potent antibacterial activity; this blowfly belongs to the Calliphoridae family. The present work has dealt with evaluating larval therapy using S. magellanica on wounds induced in diabetic rabbits and its action was compared to the effect induced by L. sericata. Twelve New Zealand White rabbits (Oryctolagus cuniculus) were used; they were divided into 4 groups, the first two being treated with larval therapy derived from both aforementioned necrophagous blowflies, an antibiotic was used in the third and the fourth was used as control. All the animals were wounded on the back and infected with Pseudomonas aeruginosa and Staphylococcus aureus. Samples of the secretion from each animal's infected wound were taken and sown on blood agar. The colony forming units were then counted. The PUSH scale was used for the macroscopic evaluation of the wounds. Bacterial control was encountered 48h post-treatment in the treatments involving larval therapy and to a lesser extent with the antibiotic. Likewise, wound debridement was quicker and more efficient with larval therapy compared to the antibiotic group; however, wound closing time was 23 days in all treatments. The group treated with S. magellanica larvae had relatively quicker evolution until the proliferation phase and the start of maturation, even though there were no significant differences between both blowfly species evaluated here regarding treatments by the end of the treatment period. The present study has validated the diabetic rabbit model for inducing chronic wounds regarding larval therapy and has likewise confirmed the effectiveness of S. magellanica-derived larval therapy as an alternative for curing and healing wounds.

Elraiyah, T., Domecq, J. P., Prutsky, G., Tsapas, A., Nabhan, M., Frykberg, R. G., Hasan, R., Firwana, B., Prokop, L. J., and Murad, M. H. A systematic review and meta-analysis of debridement methods for chronic diabetic foot ulcers. J.Vasc.Surg. 2016; 63(2 Suppl):37S-45S

ABSTRACT: *BACKGROUND*: Several methods of debridement of diabetic foot ulcers are currently used. The relative efficacy of these methods is not well established. *METHODS*: This systematic review and meta-analysis was conducted to find the best available evidence for the effect of debridement on diabetic foot wound outcomes. We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus through October 2011 for randomized controlled studies (RCTs) and observational comparative studies. *RESULTS*: We identified 11 RCTs and three nonrandomized studies reporting on 800 patients. The risk of bias was moderate overall. Meta-analysis of three RCTs showed that autolytic debridement significantly increased the healing rate (relative risk [RR], 1.89; 95% confidence interval [CI] 1.35-2.64). Meta-analysis of four studies (one RCT) showed that larval debridement reduced amputation (RR, 0.43; 95% CI, 0.21-0.88) but did not increase complete healing (RR, 1.27; 95% CI, 0.84-1.91). Surgical debridement was associated with shorter healing time compared with conventional wound care (one RCT). Insufficient evidence was found for comparisons

between autolytic and larval debridement (one RCT), between ultrasound-guided and surgical debridement, and between hydrosurgical and surgical debridement. *CONCLUSIONS*: The available literature supports the efficacy of several debridement methods, including surgical, autolytic, and larval debridement. Comparative effectiveness evidence between these methods and supportive evidence for other methods is of low quality due to methodologic limitations and imprecision. Hence, the choice of debridement method at the present time should be based on the available expertise, patient preferences, the clinical context and cost.

Hall, M. J., Wall, R. L., and Stevens, J. R. Traumatic Myiasis: A Neglected Disease in a Changing World. Annu.Rev.Entomol. 3-11-2016; 61:159-176

ABSTRACT: Traumatic myiasis, the parasitic infestation by fly larvae in traumatic lesions of the tissues of living vertebrates, is a serious medical condition in humans and a welfare and economic issue in domestic animals. New molecular studies are providing insights into its evolution and epidemiology. Nevertheless, its incidence in humans is generally underreported, particularly in tropical and subtropical regions. Myiasis in domestic animals has been studied more extensively, but continuous management is difficult and expensive. A key concern is the inadvertent introduction and global spread of agents of myiasis into nonendemic areas, facilitated by climate change and global transport. The incursion of the New World screwworm fly (Cochliomyia hominivorax) into Libya is the most notable of many such range shifts and demonstrates the potential risks of these parasites and the costs of removing them once established in a geographic area. Nevertheless, the insect agents of myiasis can be of societal benefit to forensic science and in medicine as an aid to wound treatment (larval therapy).

Masiero, F. S. and Thyssen, P. J. Evaluation of conventional therapeutic methods versus maggot therapy in the evolution of healing of tegumental injuries in Wistar rats with and without diabetes mellitus. Parasitol.Res. 3-15-2016

ABSTRACT: Larval therapy consists on the application of sterilized carrion flies larvae, reared in laboratory, on acute, chronic, and/or infected wounds in order to promote healing. Conventional methods for treating injuries include mechanical debridement or silver-based dressings; however, they are not always effective for wound healing. Larval therapy is a feasible and safe treatment for therapeutic application and, in many cases, the only and the most recommended alternative for difficult healing injuries. Thus, this study aimed to evaluate the competence of Cochliomyia macellaria F. (Diptera: Calliphoridae) as a suitable species for therapeutic application and evaluate time and effectiveness of the types of treatments most commonly used to treat integumental injuries. C. macellaria eggs were obtained from colonies established in laboratory and sterilized prior to application. Twenty-five larvae were applied for each centimeter squared of lesion. Lesions were induced in 24 Wistar rats; type 1 diabetes mellitus was induced in 12 of them. Animals were divided in four groups with three individuals each, being denominated: larval therapy, larval therapy associated with foam dressing with silver release, mechanical debridement with foam dressing silver and control group, without treatment. All treatments were applied once and held for 24 h. Medical application of larvae was found to be safe, as only dead tissue was removed, and efficient to accelerate healing process when compared to other treatments.

Poppel, A. K., Kahl, M., Baumann, A., Wiesner, J., Gokcen, A., Beckert, A., Preissner, K. T., Vilcinskas, A., and Franta, Z. A Jonah-like chymotrypsin from the therapeutic maggot Lucilia sericata plays a role in wound debridement and coagulation. Insect Biochem.Mol.Biol. 2016; 70:138-147

ABSTRACT: Lucilia sericata larvae are used in maggot debridement therapy, a traditional wound healing approach that has recently been approved for the treatment of chronic wounds. Maggot excretion products (MEP) contain many different proteases that promote disinfection, debridement and the acceleration of wound healing, e.g. by activating the host contact phase/intrinsic pathway of coagulation. In order to characterise relevant procoagulant proteases, we analysed MEP and identified a chymotrypsin-like serine protease with similarities to Jonah proteases from Drosophila melanogaster and a chymotrypsin from Lucilia cuprina. A recombinant form of the L. sericata Jonah chymotrypsin was produced in Escherichia coli. The activated enzyme (Jonahm) had a pH optimum of 8.0 and a temperature optimum of 37 degrees C, based on the cleavage of the chromogenic peptide s-7388 and casein. Jonahm reduced the clotting time of human plasma even in the absence of the endogenous protease kallikrein, factor XI or factor XII and digested the extracellular matrix proteins fibronectin, laminin and collagen IV, suggesting a potential mechanism of wound debridement. Based on these characteristics, the novel L. sericata chymotrypsin-like serine protease appears to be an ideal candidate for the development of topical drugs for wound healing applications.

Wilson, M. R., Nigam, Y., Jung, W., Knight, J., and Pritchard, D. I. The impacts of larval density and protease inhibition on feeding in medicinal larvae of the greenbottle fly Lucilia sericata. Med.Vet.Entomol. 2016; 30(1):1-7

ABSTRACT: Larval therapy, the therapeutic use of blowfly larvae to treat chronic wounds, is primarily used in debridement. There are, however, gaps in current knowledge of the optimal clinical application of the therapy and mechanisms of action in the debridement process. Using an artificial assay, two studies were undertaken to investigate these aspects of larval debridement by Lucilia sericata Meigen (Diptera: Calliphoridae); the first studied the effects of the density of larvae on tissue digestion and larval mass, and the second considered the effects on the same parameters of incorporating protease inhibitors into the feeding substrate. The total mass of tissue digested increased with larval density until saturation was observed at 5.0-7.5 larvae/cm(2) . This range was considered optimal as lower doses resulted in the removal of less tissue and higher doses offered no additional tissue removal and appeared to exacerbate competition for feeding. In the second study, increased protease inhibitor concentration led to significant decreases in tissue digestion and larval mass, suggesting that serine proteases, particularly trypsin, may play major roles in larval digestion. Such information is important in elucidating the main constituents that make up larval digestive products and may be significant in the development of new therapies.

G. Olfactory Detection and Diagnosis

Chan, K. Q., Holland, R. W., van, Loon R., Arts, R., and van, Knippenberg A. Disgust and fear lower olfactory threshold. Emotion. 2016; 16(5):740-749

ABSTRACT: Odors provide information regarding the chemical properties of potential environment hazards. Some of this information may be disgust-related (e.g., organic decay), whereas other information may be fear-related (e.g., smoke). Many studies have focused on how disgust and fear, as prototypical avoidant emotions, facilitate the detection of possible threats, but these studies have typically confined to the visual modality. Here, we examine how disgust and fear influence olfactory detection at a particular level-the level at which a subliminal olfactory stimulus crosses into conscious perception, also known as a detection threshold. Here, using psychophysical methods that allow us to test perceptual capabilities directly, we show that one way that disgust (Experiments 1-3) and fear (Experiment 3) facilitate detection is by lowering the amount of physical input that is needed to trigger a conscious experience of that input. This effect is particularly strong among individuals with high disgust sensitivity (Experiments 2-3). Our research suggests that a fundamental way in which avoidant emotions foster threat detection is through lowering perceptual thresholds. (PsycINFO Database Record.

Sarrafchi, A. and Laska, M. Olfactory Sensitivity for the Mammalian Blood Odor Component Trans-4,5-epoxy-(E)-2-decenal in CD-1 Mice. Perception. 6-1-2016

ABSTRACT: Using a conditioning paradigm and an automated olfactometer, we investigated the olfactory sensitivity of CD-1 mice for the mammalian blood odor component trans-4,5-epoxy-(E)-2-decenal. We found that two of the animals significantly discriminated concentrations down to 3.0 ppt (parts per trillion) from the solvent, and three animals even successfully detected dilutions as low as 0.3 ppt. Intraspecific comparisons between the olfactory detection thresholds obtained here with those obtained in earlier studies with other odorants show that mice are extraordinarily sensitive to this blood odor component. Interspecific comparisons of olfactory detection thresholds show that human subjects are even more sensitive to trans-4,5-epoxy-(E)-2-decenal than the mice tested here. Both intra- and inter-specific comparisons suggest that neither neuroanatomical properties such as the size of the olfactory epithelium, the total number of olfactory receptor neurons, or the size of olfactory brain structures, nor genetic properties such as the number of functional olfactory receptor genes or the proportion of functional relative to the total number of olfactory receptor genes allow us to reliably predict a species' olfactory sensitivity. In contrast, the results support the notion that the behavioral relevance of an odorant rather than neuroanatomical or genetic properties may determine a species' olfactory sensitivity.

Sun, X., Zeng, F. F., Yan, M. J., Zhang, A., Lu, Z. X., and Wang, M. Q. Interactions of two odorant-binding proteins influence insect chemoreception. Insect Mol.Biol. 8-9-2016

ABSTRACT: It is well known that the odorant-binding proteins (OBPs) play crucial roles in insect olfactory detection. To explore if interactions of OBPs affect olfactory coding in the rice leaffolder Cnaphalocrocis medinalis ligand-binding experiments, molecular docking, RNA interference and electrophysiological recording were performed. The binding activity of two C. medinalis OBPs (CmedOBPs) to rice plant volatiles showed wide flexibility depending on the structure of ligands and interactions of CmedOBPs involved.

The binding sites of CmedOBP2 and CmedOBP3 to rice plant volatiles were well predicted by three-dimensional structure modelling and molecular docking experiments. In addition, the interactions of these two CmedOBPs in the perception of rice volatiles were demonstrated by RNA interference experiments. When a single double-stranded RNA (dsRNA)-CmedOBP2 was injected, the expression of CmedOBP2 was significantly reduced and the expression of CmedOBP3 was significantly increased, and vice versa. When both dsRNA-CmedOBP2 and 3 were injected together, greater reduction of electroantennogram responses to rice plant volatiles was induced than that seen with individual injection of either dsRNA-CmedOBP2 or dsRNA-CmedOBP3. These results clearly indicate that the interactions of CmedOBP2 and CmedOBP3 have significant effects on C. medinalis during the detection of host plant volatiles.

Wackermannova, M., Pinc, L., and Jebavy, L. Olfactory sensitivity in mammalian species. Physiol Res. 7-18-2016; 65(3):369-390

ABSTRACT: Olfaction enables most mammalian species to detect and discriminate vast numbers of chemical structures called odorants and pheromones. The perception of such chemical compounds is mediated via two major olfactory systems, the main olfactory system and the vomeronasal system, as well as minor systems, such as the septal organ and the Grueneberg ganglion. Distinct differences exist not only among species but also among individuals in terms of their olfactory sensitivity; however, little is known about the mechanisms that determine these differences. In research on the olfactory sensitivity of mammals, scientists thus depend in most cases on behavioral testing. In this article, we reviewed scientific studies performed on various mammalian species using different methodologies and target chemical substances. Human and non-human primates as well as rodents and dogs are the most frequently studied species. Olfactory threshold studies on other species do not exist with the exception of domestic pigs. Olfactory testing performed on seals, elephants, and bats focused more on discriminative abilities than on sensitivity. An overview of olfactory sensitivity studies as well as olfactory detection ability in most studied mammalian species is presented here, focusing on comparable olfactory detection thresholds. The basics of olfactory perception and olfactory sensitivity factors are also described.

Willis, C. M., Britton, L. E., Swindells, M. A., Jones, E. M., Kemp, A. E., Muirhead, N. L., Gul, A., Matin, R. N., Knutsson, L., and Ali, M. Invasive melanoma in-vivo can be distinguished from basal cell carcinoma, benign naevi and healthy skin by canine olfaction: a proof of principle study of differential volatile organic compound emission. Br.J.Dermatol. 7-25-2016

ABSTRACT: *BACKGROUND*: Volatile organic compounds (VOCs) are continuously released by the body during normal metabolic processes, but their profiles change in the presence of cancer, offering an objective, non-invasive approach to diagnosis. Robust evidence that invasive melanoma in-vivo emits a characteristic VOC signature is currently lacking. *OBJECTIVE*: To conduct a canine olfactory, proof of principle study, to investigate whether VOCs captured from the surface of invasive melanoma are distinguishable from those of basal cell carcinoma (BCC), benign naevi and healthy skin in-vivo. *METHODS*: After a 13 month training period, the dog's ability to discriminate melanoma was evaluated in a series of 20 double-blind tests, each requiring the selection of one melanoma sample from amongst nine controls (three each of BCC, naevi and healthy skin; all samples being new to the dog), assuring a power of 88% with respect to the analysis. *RESULTS*: The dog correctly selected the melanoma sample on

nine of the 20 occasions, a success rate of 45% (exact 95% CI [0.23, 0.68]), compared with the 10% expected by chance alone. A one-sided exact binomial test gave a p-value of <0.001, supporting the hypothesis that samples were not chosen at random, but that some degree of VOC signal from the melanoma samples significantly increased the probability of their detection. Use of a discrete choice model confirmed melanoma as the most influential of the recorded medical/personal covariates in determining the dog's choice of sample. Notably, accuracy rates based on familiar samples during training were not a reliable indicator of the dog's ability to distinguish melanoma, when confronted with new, unknown samples. *CONCLUSIONS*: Our study demonstrates that invasive melanoma in-vivo releases odorous VOCs which are distinct from those of BCC, benign naevi and healthy skin, adding to the body of evidence that the volatile metabolome of melanoma contains diag nostically useful biomarkers. This article is protected by copyright. All rights reserved.

Zhang, S. F., Kong, X. B., Wang, H. B., Zhou, G., Yu, J. X., Liu, F., and Zhang, Z. Sensory and immune genes identification and analysis in a widely used parasitoid wasp Trichogramma dendrolimi (Hymenoptera: Trichogrammatidae). Insect Sci. 2016; 23(3):417-429

ABSTRACT: Trichogramma dendrolimi Matsumura (Hymenoptera: Trichogrammatidae) is one of the preponderant egg parasitoids of Dendrolimus spp., which are important defoliators of coniferous forests. This parasitoid wasp has been widely released to control pine caterpillar and other lepidopteran pests, but its control efficiency needs to be improved. Sensory systems are crucial for T. dendrolimi to locate hosts, and immunity is probably involved after egg deposition in the host cavity; however, few reports have focused on the molecular mechanism of olfactory detection and survival of T. dendrolimi. It is necessary to identify these genes before further functional research is conducted. In this study, we assembled and analyzed the transcriptome of T. dendrolimi using next-generation sequencing technology. The sequencing and assembly resulted in 38 565 contigs with N50 of 3422 bp. Sequence comparison indicate that T. dendrolimi sequences are very similar to those of another parasitoid Nasonia vitripennis. Then the olfactory, vision, and immune-related gene families were identified, and phylogenetic analyses were performed with these genes from T. dendrolimi and other model insect species. Furthermore, phylogenetic tree with odorant binding proteins of T. dendrolimi and their host Dendrolimus was constructed to determine whether convergent evolution exists. These genes can be valid targets for further gene function research. The present study may help us to understand host location and survival mechanisms of T. dendrolimi and to use them more efficiently for pest control in the future.

H. Phage Therapy

AlMalki, F. A., Flemming, C. S., Zhang, J., Feng, M., Sedelnikova, S. E., Ceska, T., Rafferty, J. B., Sayers, J. R., and Artymiuk, P. J. Direct observation of DNA threading in flap endonuclease complexes. Nat.Struct.Mol.Biol. 2016; 23(7):640-646.

ABSTRACT: Maintenance of genome integrity requires that branched nucleic acid molecules be accurately processed to produce double-helical DNA. Flap endonucleases are essential enzymes that trim such branched molecules generated by Okazaki-fragment synthesis during replication. Here, we report crystal structures of bacteriophage T5 flap endonuclease in complexes with intact DNA substrates and products, at resolutions of 1.9-2.2 A. They reveal single-stranded DNA threading through a hole in the enzyme, which is enclosed by an inverted V-shaped helical arch straddling the active site. Residues lining the hole induce an unusual barb-like conformation in the DNA substrate, thereby juxtaposing the scissile phosphate and essential catalytic metal ions. A series of complexes and biochemical analyses show how the substrate's single-stranded branch approaches, threads through and finally emerges on the far side of the enzyme. Our studies suggest that substrate recognition involves an unusual 'fly-casting, thread, bend and barb' mechanism.

Amundsen, S. K., Sharp, J. W., and Smith, G. R. RecBCD Enzyme "Chi Recognition" Mutants Recognize Chi Recombination Hotpots in the Right DNA Context. Genetics. 7-8-2016

ABSTRACT: RecBCD enzyme is a complex, three-subunit protein machine essential for the major pathway of DNA double-strand break repair and homologous recombination in Escherichia coli Upon encountering a Chi recombination hotspot during DNA unwinding, RecBCD nicks DNA to produce a single-stranded DNA end onto which it loads RecA protein. Conformational changes that regulate RecBCD's helicase and nuclease activities are induced upon its interaction with Chi, defined historically as 5' GCTGGTGG 3'. Chi is thought to be recognized as single-stranded DNA passing through a tunnel in RecC. To define the Chi-recognition domain in RecC and thus the mechanism of the RecBCD-Chi interaction, we altered by random mutagenesis eight RecC amino acids lining the tunnel. We screened for loss of Chi activity with Chi at one site in bacteriophage lambda. The 25 recC mutants analyzed thoroughly had undetectable or strongly reduced Chi hotspot activity with previously reported Chi sites. Remarkably, most of these mutants had readily detectable, and some nearly wild-type, activity with Chi at newly generated Chi sites. Like wild-type RecBCD, these mutants had Chi activity that responded dramatically (up to 5-fold, equivalent to Chi's hotspot activity) to nucleotide changes flanking 5' GCTGGTGG 3'. Thus, these and previously published RecC mutants thought to be Chi-recognition mutants are actually Chi context-dependence mutants. Our results fundamentally alter the view that Chi is a simple eight base-pair sequence recognized by the RecC tunnel. We propose that Chi hotspots have dual nucleotide sequence interactions, with both the RecC tunnel and the RecB nuclease domain.

Arias-Sanchez, F. I. and Hall, A. R. Effects of antibiotic resistance alleles on bacterial evolutionary responses to viral parasites. Biol.Lett. 2016; 12(5)

ABSTRACT: Antibiotic resistance has wide-ranging effects on bacterial phenotypes and evolution. However, the influence of antibiotic resistance on bacterial responses to

parasitic viruses remains unclear, despite the ubiquity of such viruses in nature and current interest in therapeutic applications. We experimentally investigated this by exposing various Escherichia coli genotypes, including eight antibiotic-resistant genotypes and a mutator, to different viruses (lytic bacteriophages). Across 960 populations, we measured changes in population density and sensitivity to viruses, and tested whether variation among bacterial genotypes was explained by their relative growth in the absence of parasites, or mutation rate towards phage resistance measured by fluctuation tests for each phage. We found that antibiotic resistance had relatively weak effects on adaptation to phages, although some antibiotic-resistance alleles impeded the evolution of resistance to phages via growth costs. By contrast, a mutator allele, often found in antibiotic-resistant lineages in pathogenic populations, had a relatively large positive effect on phage-resistance evolution and population density under parasitism. This suggests costs of antibiotic resistance may modify the outcome of phage therapy against pathogenic populations previously exposed to antibiotics, but the effects of any co-occurring mutator alleles are likely to be stronger.

Arribas, M., Cabanillas, L., Kubota, K., and Lazaro, E. Impact of increased mutagenesis on adaptation to high temperature in bacteriophage Qbeta. Virology. 7-26-2016; 497:163-170.

ABSTRACT: RNA viruses replicate with very high error rates, which makes them more sensitive to additional increases in this parameter. This fact has inspired an antiviral strategy named lethal mutagenesis, which is based on the artificial increase of the error rate above a threshold incompatible with virus infectivity. A relevant issue concerning lethal mutagenesis is whether incomplete treatments might enhance the adaptive possibilities of viruses. We have addressed this question by subjecting an RNA virus, the bacteriophage Qbeta, to different transmission regimes in the presence or the absence of sublethal concentrations of the mutagenic nucleoside analogue 5-azacytidine (AZC). Populations obtained were subsequently exposed to a non-optimal temperature and analyzed to determine their consensus sequences. Our results show that previously mutagenized populations rapidly fixed a specific set of mutations upon propagation at the new temperature, suggesting that the expansion of the mutant spectrum caused by AZC has an influence on later evolutionary behavior.

Bai, J., Kim, Y. T., Ryu, S., and Lee, J. H. Biocontrol and Rapid Detection of Food-Borne Pathogens Using Bacteriophages and Endolysins. Front Microbiol. 2016; 7:474

ABSTRACT: Bacteriophages have been suggested as natural food preservatives as well as rapid detection materials for food-borne pathogens in various foods. Since Listeria monocytogenes-targeting phage cocktail (ListShield) was approved for applications in foods, numerous phages have been screened and experimentally characterized for phage applications in foods. A single phage and phage cocktail treatments to various foods contaminated with food-borne pathogens including E. coli O157:H7, Salmonella enterica, Campylobacter jejuni, Listeria monocytogenes, Staphylococcus aureus, Cronobacter sakazakii, and Vibrio spp. revealed that they have great potential to control various food-borne pathogens and may be alternative for conventional food preservatives. In addition, phage-derived endolysins with high host specificity and host lysis activities may be preferred to food applications rather than phages. For rapid detection of food-borne pathogens, cell-wall binding domains (CBDs) from endolysins have been suggested due to their high host-specific binding. Fluorescence-tagged CBDs have been successfully evaluated and suggested to be alternative materials of

expensive antibodies for various detection applications. Most recently, reporter phage systems have been developed and tested to confirm their usability and accuracy for specific detection. These systems revealed some advantages like rapid detection of only viable pathogenic cells without interference by food components in a very short reaction time, suggesting that these systems may be suitable for monitoring of pathogens in foods. Consequently, phage is the next-generation biocontrol agent as well as rapid detection tool to confirm and even identify the food-borne pathogens present in various foods.

Barbu, E. M., Cady, K. C., and Hubby, B. Phage Therapy in the Era of Synthetic Biology. Cold Spring Harb.Perspect.Biol. 8-1-2016

ABSTRACT: For more than a century, bacteriophage (or phage) research has enabled some of the most important discoveries in biological sciences and has equipped scientists with many of the molecular biology tools that have advanced our understanding of replication, maintenance, and expression of genetic material. Phages have also been recognized and exploited as natural antimicrobial agents and nanovectors for gene therapy, but their potential as therapeutics has not been fully exploited in Western medicine because of challenges such as narrow host range, bacterial resistance, and unique pharmacokinetics. However, increasing concern related to the emergence of bacteria resistant to multiple antibiotics has heightened interest in phage therapy and the development of strategies to overcome hurdles associated with bacteriophage therapeutics. Recent progress in sequencing technologies, DNA manipulation, and synthetic biology allowed scientists to refactor the entire bacterial genome of Mycoplasma mycoides, thereby creating the first synthetic cell. These new strategies for engineering genomes may have the potential to accelerate the construction of designer phage genomes with superior therapeutic potential. Here, we discuss the use of phage as therapeutics, as well as how synthetic biology can create bacteriophage with desirable attributes.

Bardina, C., Colom, J., Spricigo, D. A., Otero, J., Sanchez-Osuna, M., Cortes, P., and Llagostera, M. Genomics of Three New Bacteriophages Useful in the Biocontrol of Salmonella. Front Microbiol. 2016; 7:545

ABSTRACT: Non-typhoid Salmonella is the principal pathogen related to food-borne diseases throughout the world. Widespread antibiotic resistance has adversely affected human health and has encouraged the search for alternative antimicrobial agents. The advances in bacteriophage therapy highlight their use in controlling a broad spectrum of food-borne pathogens. One requirement for the use of bacteriophages as antibacterials is the characterization of their genomes. In this work, complete genome sequencing and molecular analyses were carried out for three new virulent Salmonella-specific bacteriophages (UAB_Phi20, UAB_Phi78, and UAB_Phi87) able to infect a broad range of Salmonella strains. Sequence analysis of the genomes of UAB_Phi20, UAB_Phi78, and UAB_Phi87 bacteriophages did not evidence the presence of known virulence-associated and antibiotic resistance genes, and potential immunoreactive food allergens. The UAB_Phi20 genome comprised 41,809 base pairs with 80 open reading frames (ORFs); 24 of them with assigned function. Genome sequence showed a high homology of UAB_Phi20 with Salmonella bacteriophage P22 and other P22likeviruses genus of the Podoviridae family, including ST64T and ST104. The DNA of UAB_Phi78 contained 44,110 bp including direct terminal repeats (DTR) of 179 bp and 58 putative ORFs were predicted and 20 were assigned function. This bacteriophage was assigned to the SP6likeviruses genus of the Podoviridae family based on its high similarity not only

with SP6 but also with the K1-5, K1E, and K1F bacteriophages, all of which infect Escherichia coli. The UAB_Phi87 genome sequence consisted of 87,669 bp with terminal direct repeats of 608 bp; although 148 ORFs were identified, putative functions could be assigned to only 29 of them. Sequence comparisons revealed the mosaic structure of UAB_Phi87 and its high similarity with bacteriophages Felix O1 and wV8 of E. coli with respect to genetic content and functional organization. Phylogenetic analysis of large terminase subunits confirms their packaging strategies and grouping to the different phage genus type. All these studies are necessary for the development and the use of an efficient cocktail with commercial applications in bacteriophage therapy against Salmonella.

Bardy, P., Pantucek, R., Benesik, M., and Doskar, J. Genetically modified bacteriophages in applied microbiology. J.Appl.Microbiol. 6-20-2016

ABSTRACT: Bacteriophages represent a simple viral model of basic research with many possibilities for practical application. Due to their ability to infect and kill bacteria, their potential in the treatment of bacterial infection has been examined since their discovery. With advances in molecular biology and gene engineering, the phage application spectrum has been expanded to various medical and biotechnological fields. The construction of bacteriophages with an extended host range or longer viability in the mammalian bloodstream enhances their potential as an alternative to conventional antibiotic treatment. Insertion of active depolymerase genes to their genomes can enforce the biofilm disposal. They can also be engineered to transfer various compounds to the eukaryotic organisms and the bacterial culture, applicable for the vaccine, drug or gene delivery. Phage recombinant lytic enzymes can be applied as enzybiotics in medicine as well as in biotechnology for pathogen detection or programmed cell death in bacterial expression strains. Besides, modified bacteriophages with high specificity can be applied as bioprobes in detection tools to estimate the presence of pathogens in food industry, or utilized in the control of food-borne pathogens as part of the constructed phage-based biosorbents.

Barrett, M., Fitzhenry, K., O'Flaherty, V., Dore, W., Keaveney, S., Cormican, M., Rowan, N., and Clifford, E. Detection, fate and inactivation of pathogenic norovirus employing settlement and UV treatment in wastewater treatment facilities. Sci.Total Environ. 6-24-2016

ABSTRACT: It is accepted that discharged wastewaters can be a significant source of pathogenic viruses in receiving water bodies contributing to pollution and may in turn enter the human food chain and pose a risk to human health, thus norovirus (NoV) is often a predominant cause of gastroenteritis globally. Working with NoV poses particular challenges as it cannot be readily identified and detection by molecular methods does not assess infectivity. It has been proposed that the infectivity of NoV may be modelled through the use of an alternative virus; F-specific RNA (FRNA) bacteriophages; GA genotype and other FRNA bacteriophages have been used as a surrogate in studies of NoV inactivation. This study investigated the efficiency of novel pulsed ultraviolet irradiation and low pressure ultraviolet irradiation as a potential pathogen inactivation system for NoV and FRNA bacteriophage (GA) in secondary treated wastewaters. The role of UV dose and the impact of suspended solids concentration on removal efficiency were also examined. The study also investigated the role of settlement processes in wastewater treatment plants in removing NoV. While NoV inactivation could not be determined it was found that at a maximum UV dose of 6.9J/cm2 (6900mJ/cm2) an average 2.4 log removal of FRNA bacteriophage (GA) was observed; indicating the potential need for high UV doses to remove NoV if FRNA bacteriophage prove a suitable

indicator for NoV. The study found that increasing concentrations of suspended solids impacted on PUV efficiency however, it appears the extent of the impact may be site specific. Furthermore, the study found that settlement processes can play a significant role in the removal of FRNA bacteriophage, thus potentially NoV.

Bearden, R. L. and Casanova, L. M. Survival of an Enveloped Virus on Toys. Pediatr.Infect.Dis.J. 2016; 35(8):923-924.

ABSTRACT: Children's toys may carry respiratory viruses. Inactivation of a lipid-enveloped bacteriophage, Phi6, was measured on a nonporous toy at indoor temperature and relative humidity (RH). Inactivation was approximately 2log10 after 24 hours at 60% RH and 6.8log10 at 10 hours at 40% RH. Enveloped viruses can potentially survive on toys long enough to result in exposures.

Beck, H. J., Fleming, I. M., and Janssen, G. R. 5'-Terminal AUGs in Escherichia coli mRNAs with Shine-Dalgarno Sequences: Identification and Analysis of Their Roles in Non-Canonical Translation Initiation. PLoS.One. 2016; 11(7):e0160144

ABSTRACT: Analysis of the Escherichia coli transcriptome identified a unique subset of messenger RNAs (mRNAs) that contain a conventional untranslated leader and Shine-Dalgarno (SD) sequence upstream of the gene's start codon while also containing an AUG triplet at the mRNA's 5'- terminus (5'-uAUG). Fusion of the coding sequence specified by the 5'-terminal putative AUG start codon to a lacZ reporter gene, as well as primer extension inhibition assays, reveal that the majority of the 5'-terminal upstream open reading frames (5'-uORFs) tested support some level of lacZ translation, indicating that these mRNAs can function both as leaderless and canonical SD-leadered mRNAs. Although some of the uORFs were expressed at low levels, others were expressed at levels close to that of the respective downstream genes and as high as the naturally leaderless cI mRNA of bacteriophage lambda. These 5'-terminal uORFs potentially encode peptides of varying lengths, but their functions, if any, are unknown. In an effort to determine whether expression from the 5'-terminal uORFs impact expression of the immediately downstream cistron, we examined expression from the downstream coding sequence after mutations were introduced that inhibit efficient 5'-uORF translation. These mutations were found to affect expression from the downstream cistrons to varying degrees, suggesting that some 5'-uORFs may play roles in downstream regulation. Since the 5'-uAUGs found on these conventionally leadered mRNAs can function to bind ribosomes and initiate translation, this indicates that canonical mRNAs containing 5'-uAUGs should be examined for their potential to function also as leaderless mRNAs.

Beke, G., Stano, M., and Klucar, L. Modelling the interaction between bacteriophages and their bacterial hosts. Math.Biosci. 2016; 279:27-32.

ABSTRACT: A mathematical model simulating the interaction between bacteriophages and their bacterial hosts has been developed. It is based on other known models describing this type of interaction, enhanced with an ability to model the system influenced by other environmental factor such as pH and temperature. This could be used for numerous estimations of growth rate, when the pH and/or the temperature of the environment are not constant. The change of pH or the temperature greatly affects the specific growth rate which has an effect on the final results of the simulation. Since the model aims on practical application and easy accessibility, an interactive website

has been developed where users can run simulations with their own parameters and easily calculate and visualise the result of simulation. The web simulation is accessible at the URL http://www.phisite.org/model.

Bhardwaj, N., Bhardwaj, S. K., Mehta, J., Mohanta, G. C., and Deep, A. Bacteriophage immobilized graphene electrodes for impedimetric sensing of bacteria (Staphylococcus arlettae). Anal.Biochem. 7-15-2016; 505:18-25.

ABSTRACT: Bacteriophages are a class of viruses that specifically infect and replicate within a bacterium. They possess inherent affinity and specificity to the particular bacterial cells. This property of bacteriophages makes them an attractive biorecognition element in the field of biosensor development. In this work, we report the use of an immobilized bacteriophage for the development of a highly sensitive electrochemical sensor for Staphylococcus arlettae, bacteria from the pathogenic family of coagulase-negative staphylococci (CNS). The specific bacteriophages were covalently immobilized on the screen-printed graphene electrodes. Thus, the fabricated bacteriophage biosensor displayed quantitative response for the target bacteria (S. arlettae) for a broad detection range (2.0-2.0 x 10(6) cfu). A fast response time (2 min), low limit of detection (2 cfu), specificity, and stability over a prolonged period (3 months) are some of the important highlights of the proposed sensor. The practical utility of the developed sensor has been demonstrated by the analysis of S. arlettae in spiked water and apple juice samples.

Bohne, A. V., Teubner, M., Liere, K., Weihe, A., and Borner, T. In vitro promoter recognition by the catalytic subunit of plant phage-type RNA polymerases. Plant Mol.Biol. 8-6-2016;

ABSTRACT: KEY MESSAGE: We identified sequence motifs, which enhance or reduce the ability of the Arabidopsis phage-type RNA polymerases RPOTm (mitochondrial RNAP), RPOTp (plastidial RNAP), and RPOTmp (active in both organelles) to recognize their promoters in vitro with help of a 'specificity loop'. The importance of this data for the evolution and function of the organellar RNA polymerases is discussed. The single-subunit RNA polymerase (RNAP) of bacteriophage T7 is able to perform all steps of transcription without additional transcription factors. Dicotyledonous plants possess three phage-type RNAPs, RPOTm-the mitochondrial RNAP, RPOTp-the plastidial RNAP, and RPOTmp-an RNAP active in both organelles. RPOTm and RPOTp, like the T7 polymerase, are able to recognize promoters, while RPOTmp displays no significant promoter specificity in vitro. To find out which promoter motifs are crucial for recognition by the polymerases we performed in vitro transcription assays with recombinant Arabidopsis RPOTm and RPOTp enzymes. By comparing different truncated and mutagenized promoter constructs, we observed the same minimal promoter sequence supposed to be needed in vivo for transcription initiation. Moreover, we identified elements of core and flanking sequences, which are of critical importance for promoter recognition and activity in vitro. We further intended to reveal why RPOTmp does not efficiently recognize promoters in vitro and if promoter recognition is based on a structurally defined specificity loop of the plant enzymes as described for the yeast and T7 RNAPs. Interestingly, the exchange of only three amino acids within the putative specificity loop of RPOTmp enabled the enzyme for specific promoter transcription in vitro. Thus, also in plant phage-type RNAPs the specificity loop is engaged in promoter recognition. The results are discussed with respect to their relevance for transcription in organello and to the evolution of RPOT enzymes including the divergence of their functions.

Bollivar, D. W., Bernardoni, B., Bockman, M. R., Miller, B. M., Russell, D. A., Delesalle, V. A., Krukonis, G. P., Hatfull, G. F., Cross, M. R., Szewczyk, M. M., and Eppurath, A. Complete

Genome Sequences of Five Bacteriophages That Infect Rhodobacter capsulatus. Genome Announc. 2016; 4(3)

ABSTRACT: Five bacteriophages that infect the Rhodobacter capsulatus strain YW1 were isolated from stream water near Bloomington, Illinois, USA. Two distinct genome types are represented in the newly isolated bacteriophages. These genomes are different from other bacteriophage genomes previously described.

Braff, D., Shis, D., and Collins, J. J. Synthetic biology platform technologies for antimicrobial applications. Adv.Drug Deliv.Rev. 4-18-2016;

ABSTRACT: The growing prevalence of antibiotic resistance calls for new approaches in the development of antimicrobial therapeutics. Likewise, improved diagnostic measures are essential in guiding the application of targeted therapies and preventing the evolution of therapeutic resistance. Discovery platforms are also needed to form new treatment strategies and identify novel antimicrobial agents. By applying engineering principles to molecular biology, synthetic biologists have developed platforms that improve upon, supplement, and will perhaps supplant traditional broad-spectrum antibiotics. Efforts in engineering bacteriophages and synthetic probiotics demonstrate targeted antimicrobial approaches that can be fine-tuned using synthetic biology-derived principles. Further, the development of paper-based, cell-free expression systems holds promise in promoting the clinical translation of molecular biology tools for diagnostic purposes. In this review, we highlight emerging synthetic biology platform technologies that are geared toward the generation of new antimicrobial therapies, diagnostics, and discovery channels.

Brie, A., Bertrand, I., Meo, M., Boudaud, N., and Gantzer, C. The Effect of Heat on the Physicochemical Properties of Bacteriophage MS2. Food Environ.Virol. 6-14-2016;

ABSTRACT: The differences in physicochemical characteristics between infectious and non-infectious viral particles are poorly known. Even for heat, which is known as one of the most efficient treatments to inactivate enteric viruses, the global inactivation mechanisms have not been described yet. Such knowledge would help distinguish between both types of particles and therefore clarify the interpretation of the presence of viral genomes in food after heat treatment. In this study, we examined in particular the differences in electrostatic charge and hydrophobicity between the two particle types. MS2 phage, a common surrogate for enteric viruses, was used as a model virus. The heat-induced inactivation process of the infectious phages caused hydrophobic domains to be transiently exposed and their charge to become less negative. The particles also became progressively permeable to small molecules such as SYPRO Orange dye. The presence of non-infectious phage particles in which the genome was not accessible to RNases has been clearly demonstrated. These observations were done for MS2 phages exposed to a temperature of 60 degrees C. When exposed to a temperature higher than their critical temperature (72 degrees C), the particles were disrupted and the genome became available for RNases. At lower temperatures, 60 degrees C in this study, the transient expression of hydrophobic domains of remaining infectious phages appeared as an interesting parameter for improving their specific detection.

Brussow, H. Targeting the gut to protect the bladder: Oral Phage therapy approaches against urinary Escherichia coli infections? Environ.Microbiol. 2016; 18(7):2084-2088.

No abstract currently available.

Brzozowska, E., Koba, M., Smietana, M., Gorska, S., Janik, M., Gamian, A., and Bock, W. J. Label-free Gram-negative bacteria detection using bacteriophage-adhesin-coated long-period gratings. Biomed.Opt.Express. 3-1-2016; 7(3):829-840.

ABSTRACT: This paper presents a novel application of a highly sensitive sensor based on long-period gratings (LPGs) coated with T4 bacteriophage adhesin for Gram-negative bacteria detection. We show here, that the sensor evidently recognizes Escherichia coli K-12 (PCM2560), whereas in the reference tests - ELISA and BIAcore - the results are questionable. For LPGs sensor the resonant wavelength shift observed for E. coli K-12 was approximately half of that measured for E.coli B (positive control). The BIAcore readings (RU) for E. coli K-12 were at 10% level of the signal obtained for E .coli B. These results confirm the improved sensitivity of the LPGs sensor. Moreover, we also show that application of adhesin may allow for efficient detection of E. coli O111 (PCM418), Klebsiella pneumoniae O1 (PCM1) and Yersinia enterocolitica O1 (PCM1879). The specificity of binding bacteria by the adhesin is discussed and it is determined by a distinct region of lipopolysaccharide receptors and/or by the presence of outer-membrane protein C in an outer membrane of Gram-negative bacteria.

Cao, B., Yang, M., and Mao, C. Phage as a Genetically Modifiable Supramacromolecule in Chemistry, Materials and Medicine. Acc.Chem.Res. 6-21-2016; 49(6):1111-1120.

ABSTRACT: Filamentous bacteriophage (phage) is a genetically modifiable supramacromolecule. It can be pictured as a semiflexible nanofiber (approximately 900 nm long and approximately 8 nm wide) made of a DNA core and a protein shell with the former genetically encoding the latter. Although phage bioengineering and phage display techniques were developed before the 1990s, these techniques have not been widely used for chemistry, materials, and biomedical research from the perspective of supramolecular chemistry until recently. Powered by our expertise in displaying a foreign peptide on its surface through engineering phage DNA, we have employed phage to identify target-specific peptides, construct novel organic-inorganic nanohybrids, develop biomaterials for disease treatment, and generate bioanalytical methods for disease diagnosis. Compared with conventional biomimetic chemistry, phage-based supramolecular chemistry represents a new frontier in chemistry, materials science, and medicine. In this Account, we introduce our recent successful efforts in phage-based supramolecular chemistry, by integrating the unique nanofiber-like phage structure and powerful peptide display techniques into the fields of chemistry, materials science, and medicine: (1) successfully synthesized and assembled silica, hydroxyapatite, and gold nanoparticles using phage templates to form novel functional materials; (2) chemically introduced azo units onto the phage to form photoresponsive functional azo-phage nanofibers via a diazotization reaction between aromatic amino groups and the tyrosine residues genetically displayed on phage surfaces; (3) assembled phage into 2D films for studying the effects of both biochemical (the peptide sequences displayed on the phages) and biophysical (the topographies of the phage films) cues on the proliferation and differentiation of mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) and identified peptides and topographies that can induce their osteogenic differentiation; (4) discovered that phage could induce angiogenesis and osteogenesis

for MSC-based vascularized bone regeneration; (5) identified novel breast cancer cell-targeting and MSC-targeting peptides and used them to significantly improve the efficiency of targeted cancer therapy and MSC-based gene delivery, respectively; (6) employed engineered phage as a probe to achieve ultrasensitive detection of biomarkers from serum of human patients for disease diagnosis; and (7) constructed centimeter-scale 3D multilayered phage assemblies with the potential application as scaffolds for bone regeneration and functional device fabrication. Our findings demonstrated that phage is indeed a very powerful supramacromolecule suitable for not only developing novel nanostructures and biomaterials but also advancing important fields in biomedicine, including molecular targeting, cancer diagnosis and treatment, drug and gene delivery, stem cell fate direction, and tissue regeneration. Our successes in exploiting phage in chemistry, materials, and medicine suggest that phage itself is nontoxic at the cell level and can be safely used for detecting biomarkers in vitro. Moreover, although we have demonstrated successful in vivo tissue regeneration induced by phage, we believe future studies are needed to evaluate the in vivo biodistribution and potential risks of the phage-based biomaterials.

Carlson-Jones, J. A., Paterson, J. S., Newton, K., Smith, R. J., Dann, L. M., Speck, P., Mitchell, J. G., and Wormald, P. J. Enumerating Virus-Like Particles and Bacterial Populations in the Sinuses of Chronic Rhinosinusitis Patients Using Flow Cytometry. PLoS.One. 2016; 11(5):e0155003

ABSTRACT: There is increasing evidence to suggest that the sinus microbiome plays a role in the pathogenesis of chronic rhinosinusitis (CRS). However, the concentration of these microorganisms within the sinuses is still unknown. We show that flow cytometry can be used to enumerate bacteria and virus-like particles (VLPs) in sinus flush samples of CRS patients. This was achieved through trialling 5 sample preparation techniques for flow cytometry. We found high concentrations of bacteria and VLPs in these samples. Untreated samples produced the highest average bacterial and VLP counts with 3.3 +/- 0.74 x 107 bacteria ml-1 and 2.4 +/- 1.23 x 109 VLP ml-1 of sinus flush (n = 9). These counts were significantly higher than most of the treated samples ($p < 0.05$). Results showed 103 and 104 times inter-patient variation for bacteria and VLP concentrations. This wide variation suggests that diagnosis and treatment need to be personalised and that utilising flow cytometry is useful and efficient for this. This study is the first to enumerate bacterial and VLP populations in the maxillary sinus of CRS patients. The relevance of enumeration is that with increasing antimicrobial resistance, antibiotics are becoming less effective at treating bacterial infections of the sinuses, so alternative therapies are needed. Phage therapy has been proposed as one such alternative, but for dosing, the abundance of bacteria is required. Knowledge of whether phages are normally present in the sinuses will assist in gauging the safety of applying phage therapy to sinuses. Our finding, that large numbers of VLP are frequently present in sinuses, indicates that phage therapy may represent a minimally disruptive intervention towards the nasal microbiome. We propose that flow cytometry can be used as a tool to assess microbial biomass dynamics in sinuses and other anatomical locations where infection can cause disease.

Carow, B., Gao, Y., Coquet, J., Reilly, M., and Rottenberg, M. E. Ick-Driven Cre Expression Alters T Cell Development in the Thymus and the Frequencies and Functions of Peripheral T Cell Subsets. J.Immunol. 8-8-2016;

ABSTRACT: Conditional gene targeting using the bacteriophage-derived Cre recombinase is widely applied for functional gene studies in mice. Mice transgenic for Cre under the control of the lck gene promoter are used to study the role of loxP-targeted genes in T cell development and function. In this article, we show a striking 65% reduction in cellularity, preferential development of gammadelta versus alphabeta T cells, and increased expression of IL-7R in the thymus of mice expressing Cre under the proximal lck promoter (lck-cre+ mice). The transition from CD4/CD8 double-negative to double-positive cells was blocked, and lck-cre+ double-positive cells were more prone to apoptosis and showed higher levels of Cre expression. Importantly, numbers of naive T cells were reduced in spleens and lymph nodes of lck-cre+ mice. In contrast, frequencies of gammadelta T cells, CD44+C.

Carter, C. C., Fierer, J., Chiu, W. W., Looney, D. J., Strain, M., and Mehta, S. R. A Novel Shiga Toxin 1a-Converting Bacteriophage of Shigella sonnei With Close Relationship to Shiga Toxin 2-Converting Pages of Escherichia coli. Open.Forum Infect.Dis. 2016; 3(2):ofw079

ABSTRACT: In recent studies, strains of non-dysenteriae 1 Shigella (NDS) expressing Shiga toxin have been reported. In this study, we report a novel stx1a-converting bacteriophage of Shigella sonnei associated with travel to Mexico. Phylogenetic comparison between this and other stx-converting phages suggests that toxigenic NDS strains have arisen through separate horizontal transfer events from toxigenic Escherichia coli.

Casjens, S. R. and Grose, J. H. Contributions of P2- and P22-like prophages to understanding the enormous diversity and abundance of tailed bacteriophages. Virology. 2016; 496:255-276.

ABSTRACT: We identified 9371 tailed phage prophages of 20 known types in reported complete genome sequences of 3298 bacteria in the Salmonella genus. These include 4758 P2 type and 744 P22 type prophages. The latter prophage types were found in the genome sequences of 127 and 24 bacterial host genera, increasing the known host ranges of phages in these groups by 114 and 20 genera, respectively. These prophage nucleotide sequences displayed much more diversity than was previously known from the 48 P2 and 24 P22 type authentic phages whose genomes have been sequenced. More detailed analysis of these prophage sequences indicated that major capsid protein (MCP) gene exchange between tailed phage clusters or types is extremely rare and that P22 prophage-encoded tailspikes correspond perfectly with their hosts' surface polysaccharide structure; thus, MCP and tailspike sequences accurately predict tailed phage type (and thus lifestyle) and host cell surface polysaccharide structure, respectively.

Castillo, D., Christiansen, R. H., Dalsgaard, I., Madsen, L., Espejo, R., and Middelboe, M. Comparative Genome Analysis Provides Insights into the Pathogenicity of Flavobacterium psychrophilum. PLoS.One. 2016; 11(4):e0152515

ABSTRACT: Flavobacterium psychrophilum is a fish pathogen in salmonid aquaculture worldwide that causes cold water disease (CWD) and rainbow trout fry syndrome (RTFS). Comparative genome analyses of 11 F. psychrophilum isolates representing temporally and geographically distant populations were used to describe the F. psychrophilum pan-

genome and to examine virulence factors, prophages, CRISPR arrays, and genomic islands present in the genomes. Analysis of the genomic DNA sequences were complemented with selected phenotypic characteristics of the strains. The pan genome analysis showed that F. psychrophilum could hold at least 3373 genes, while the core genome contained 1743 genes. On average, 67 new genes were detected for every new genome added to the analysis, indicating that F. psychrophilum possesses an open pan genome. The putative virulence factors were equally distributed among isolates, independent of geographic location, year of isolation and source of isolates. Only one prophage-related sequence was found which corresponded to the previously described prophage 6H, and appeared in 5 out of 11 isolates. CRISPR array analysis revealed two different loci with dissimilar spacer content, which only matched one sequence in the database, the temperate bacteriophage 6H. Genomic Islands (GIs) were identified in F. psychrophilum isolates 950106-1/1 and CSF 259-93, associated with toxins and antibiotic resistance. Finally, phenotypic characterization revealed a high degree of similarity among the strains with respect to biofilm formation and secretion of extracellular enzymes. Global scale dispersion of virulence factors in the genomes and the abilities for biofilm formation, hemolytic activity and secretion of extracellular enzymes among the strains suggested that F. psychrophilum isolates have a similar mode of action on adhesion, colonization and destruction of fish tissues across large spatial and temporal scales of occurrence. Overall, the genomic characterization and phenotypic properties may provide new insights to the mechanisms of pathogenicity in F. psychrophilum.

Chadha, P., Katare, O. P., and Chhibber, S. In vivo efficacy of single phage versus phage cocktail in resolving burn wound infection in BALB/c mice. Microb.Pathog. 8-4-2016;

ABSTRACT: Klebsiella pneumoniae is one of the most predominant pathogens associated with burn wound infections, causing considerable morbidity and mortality. The indiscriminate usage of antibiotics has led to the development of resistant strains, which have contributed towards the inefficacy of antibiotics. Phage therapy is a promising alternative to hinder the progression of pathogenic bacteria. However, phage bacterial resistance is already well known but the use of phage cocktails can overcome this drawback. The aim of the study was to evaluate the therapeutic efficacy of monophage (Kpn1, Kpn2, Kpn3, Kpn4 and Kpn5) in comparison to phage cocktail in resolving the course of burn wound infection in mice. Although, animals receiving monophage therapy exhibited efficacy in resolving the course of infection but phage cocktail was highly effective in arresting the entire infection process (bacterial load, wound contraction, skin myeloperoxidase activity, collagen formation and histopathological analysis). In comparison to untreated control mice, a significant reduction in bacterial load to 4.32, 4.64, 4.42, 4.11 and 4.27 log CFU/ml in Kpn1, Kpn2, Kpn3 Kpn4 and Kpn5 treated animals was obtained respectively was on peak day (3rd day). However, the group receiving phage cocktail (group 7) showed maximum reduction in bacterial load in the skin tissue. The bacterial load was significantly reduced to 3.01 log CFU/ml on peak day. This accounts for a significant reduction of 6 log cycles ($p < 0.01$) as compared to that of untreated control animals where a peak of 8.81 log CFU/ml was seen followed by steady decrease thereafter. Thus, phage cocktail gave maximum protection against burn wound infection by K. pneumoniae B5055. Compared to any single phage, phage cocktail significantly checked the emergence of resistant mutants. Hence this approach can serve as an effective strategy in treating Klebsiella mediated burn wound infections in individuals who do not respond to conventional antibiotic therapy.

Chan, B. K., Sistrom, M., Wertz, J. E., Kortright, K. E., Narayan, D., and Turner, P. E. Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. Sci.Rep. 2016; 6:26717

ABSTRACT: Increasing prevalence and severity of multi-drug-resistant (MDR) bacterial infections has necessitated novel antibacterial strategies. Ideally, new approaches would target bacterial pathogens while exerting selection for reduced pathogenesis when these bacteria inevitably evolve resistance to therapeutic intervention. As an example of such a management strategy, we isolated a lytic bacteriophage, OMKO1, (family Myoviridae) of Pseudomonas aeruginosa that utilizes the outer membrane porin M (OprM) of the multidrug efflux systems MexAB and MexXY as a receptor-binding site. Results show that phage selection produces an evolutionary trade-off in MDR P. aeruginosa, whereby the evolution of bacterial resistance to phage attack changes the efflux pump mechanism, causing increased sensitivity to drugs from several antibiotic classes. Although modern phage therapy is still in its infancy, we conclude that phages, such as OMKO1, represent a new approach to phage therapy where bacteriophages exert selection for MDR bacteria to become increasingly sensitive to traditional antibiotics. This approach, using phages as targeted antibacterials, could extend the lifetime of our current antibiotics and potentially reduce the incidence of antibiotic resistant infections.

Chanishvili, N. Bacteriophages as Therapeutic and Prophylactic Means: Summary of the Soviet and Post Soviet Experiences. Curr.Drug Deliv. 2016; 13(3):309-323.

ABSTRACT: Bacteriophage (from 'bacteria' and Greek phialphagammaepsilonnu phagein "to devour" or bacterial eaters) are bacterial viruses that infect and kill bacteria. Bacteriophages (shortly "phages") are among the most common and diverse entities in the biosphere. The estimated number of phages on earth is about 1032. Bacteriophages are often isolated from environmental sources, such as water samples, etc. Felix d'Herelle, one of the discoverers of bacteriophages, was the one who suggested them for therapy of human and animal bacterial infections. This idea was very popular in the world until the advent of antibiotics commercial after which production of therapeutic phages ceased in most of the Western countries, but not in the former Soviet Union. The application of antibiotics in the clinical practice, besides the well-known side effects, entails, in addition, the appearance of the forms of bacteria, resistant to newly synthesized preparations. It was concluded that a European and global strategy to address this gap is urgently needed. Now, faced with the alarming growth of a variety of antibiotic resistant bacterial infections, Western researchers and governments are giving phages a serious look. The phages nowadays are seen as a possible therapy against multi-drug-resistant strains of many bacteria. The therapeutic action of bacteriophages significantly differs from antibiotics, which makes them still active against multi-drug-resistant bacteria. Bacteriophages have a number of other advantages in comparison with antibiotics. First of all, they are efficient against multi-drug-resistant bacteria. The aim of this review was to provide an overview of the past and current experiences in the field of phage therapy in the countries where it has been traditionally applied in the clinical practice. Although the style and quality of old Soviet scientific publications dedicated to phage therapy are not challenging the international standards, there is still valuable information which may not be neglected by modern researchers. This information is especially important as it remained unavailable for the Western scientists before because of the language barriers until now. The goal of this article is to encourage further research on this topic, and facilitate rapid decisions on the development of appropriate

regulations, which would ultimately permit the use of phages as therapeutic or preventative medicines in daily clinical practice in the Western countries where multiplying drug-resistant bacteria gradually becomes the greatest life threatening problem.

Chen, X., Xi, Y., Zhang, H., Wang, Z., Fan, M., Liu, Y., and Wu, W. Characterization and adsorption of Lactobacillus virulent phage P1. J.Dairy Sci. 6-29-2016;

ABSTRACT: Bacteriophage infection of lactic acid bacteria is considered an important problem worldwide in the food fermentation industry, as it may produce low quality or unsafe foods, cause fermentation failure, and result in economic losses. To increase current knowledge on the properties of Lactobacillus virulent phages, we evaluated the effect of divalent cations, temperature, pH, and chloramphenicol on the adsorption ability of Lactobacillus virulent phage P1. Phage P1 was isolated from the abnormal fermentation liquid of Lactobacillus plantarum IMAU10120. The results showed that this phage belonged to the Siphoviridae family. The latent period of this phage was 45 min, and the burst time was 90 min. Burst size was 132.88 +/- 2.37 phage counts expressed per milliliter per infective center. This phage showed good tolerance at different temperatures, but incubation at 50 degrees C only affected its adsorption. Adsorption rate reached a maximum value between 30 and 42 degrees C. A high adsorption value of phage infectivity was obtained from pH 6 to 8. Moreover, calcium ions promoted and increased the adsorption capacity of phage P1, but magnesium ions had negative effects. Chloramphenicol had no effect on phage adsorption. This study increased current knowledge on the characterization and biological aspects of Lactobacillus virulent phages, and may provide some basic information that can be used to design successful antiphage strategies in the food industry.

Chen, Z., Li, N., Chen, L., Lee, J., and Gassensmith, J. J. Dual Functionalized Bacteriophage Qbeta as a Photocaged Drug Carrier. Small. 6-28-2016;

ABSTRACT: Proteinatious nanoparticles are emerging as promising materials in biomedical research owing to their many unique properties and our interest focuses on integrating environmental responsivity into these systems. In this work, the use of a virus-like particle (VLP) derived from bacteriophage Qbeta as a photocaged drug delivery system is investigated. Ideally, a photocaged nanoparticle platform should be harmless and inert without activation by light yet, upon photoirradiation, should cause cell death. Approximately 530 photocleavable doxorubicin complexes are installed initially onto the surface of Qbeta by CuAAC reaction for photocaging therapy; however, aggregation and precipitation are found to cause cell death at higher concentrations. In order to improve solution stability, thiol-dibromomaleimide chemistry has been developed to orthogonally modify the VLP. This chemistry provides a robust method of incorporating additional functionality at the disulfides on Qbeta, which was used to increase the stability and solubility of the drug-loaded VLPs. As a result, the dual functionalied VLPs with polyethylene glycol and photocaged doxorubicin show not only negligible cytotoxicity before photoactivation but also highly controllable photorelease and cell killing power.

Chevallereau, A., Blasdel, B. G., De, Smet J., Monot, M., Zimmermann, M., Kogadeeva, M., Sauer, U., Jorth, P., Whiteley, M., Debarbieux, L., and Lavigne, R. Next-Generation "-omics"

Approaches Reveal a Massive Alteration of Host RNA Metabolism during Bacteriophage Infection of Pseudomonas aeruginosa. PLoS.Genet. 2016; 12(7):e1006134

ABSTRACT: As interest in the therapeutic and biotechnological potentials of bacteriophages has grown, so has value in understanding their basic biology. However, detailed knowledge of infection cycles has been limited to a small number of model bacteriophages, mostly infecting Escherichia coli. We present here the first analysis coupling data obtained from global next-generation approaches, RNA-Sequencing and metabolomics, to characterize interactions between the virulent bacteriophage PAK_P3 and its host Pseudomonas aeruginosa. We detected a dramatic global depletion of bacterial transcripts coupled with their replacement by viral RNAs over the course of infection, eventually leading to drastic changes in pyrimidine metabolism. This process relies on host machinery hijacking as suggested by the strong up-regulation of one bacterial operon involved in RNA processing. Moreover, we found that RNA-based regulation plays a central role in PAK_P3 lifecycle as antisense transcripts are produced mainly during the early stage of infection and viral small non coding RNAs are massively expressed at the end of infection. This work highlights the prominent role of RNA metabolism in the infection strategy of a bacteriophage belonging to a new characterized sub-family of viruses with promising therapeutic potential.

Christie, G. E. and Calendar, R. Bacteriophage P2. Bacteriophage. 2016; 6(1):e1145782ABSTRACT: P2 is the original member of a highly successful family of temperate phages that are frequently found in the genomes of gram-negative bacteria. This article focuses on the organization of the P2 genome and reviews current knowledge about the function of each open reading frame.

No abstract currently available.

Cianfanelli, F. R., Alcoforado, Diniz J., Guo, M., De, Cesare, V, Trost, M., and Coulthurst, S. J. VgrG and PAAR Proteins Define Distinct Versions of a Functional Type VI Secretion System. PLoS.Pathog. 2016; 12(6):e1005735

ABSTRACT: The Type VI secretion system (T6SS) is widespread among bacterial pathogens and acts as an effective weapon against competitor bacteria and eukaryotic hosts by delivering toxic effector proteins directly into target cells. The T6SS utilises a bacteriophage-like contractile machinery to expel a puncturing device based on a tube of Hcp topped with a VgrG spike, which can be extended by a final tip from a PAAR domain-containing protein. Effector proteins are believed to be delivered by specifically associating with particular Hcp, VgrG or PAAR proteins, either covalently ('specialised') or non-covalently ('cargo' effectors). Here we used the T6SS of the opportunistic pathogen Serratia marcescens, together with integratecd genetic, proteomic and biochemical approaches, to elucidate the role of specific VgrG and PAAR homologues in T6SS function and effector specificity, revealing new aspects and unexpected subtleties in effector delivery by the T6SS. We identified effectors, both cargo and specialised, absolutely dependent on a particular VgrG for delivery to target cells, and discovered that other cargo effectors can show a preference for a particular VgrG. The presence of at least one PAAR protein was found to be essential for T6SS function, consistent with designation as a 'core' T6SS component. We showed that specific VgrG-PAAR combinations are required to assemble a functional T6SS and that the three distinct VgrG-PAAR assemblies in S. marcescens exhibit distinct effector specificity and

efficiency. Unexpectedly, we discovered that two different PAAR-containing Rhs proteins can functionally pair with the same VgrG protein. Showing that accessory EagR proteins are involved in these interactions, native VgrG-Rhs-EagR complexes were isolated and specific interactions between EagR and cognate Rhs proteins identified. This study defines an essential yet flexible role for PAAR proteins in the T6SS and highlights the existence of distinct versions of the machinery with differential effector specificity and efficiency of target cell delivery.

Cooper, I. R. A review of current methods using bacteriophages in live animals, food and animal products intended for human consumption. J.Microbiol.Methods. 7-30-2016;

ABSTRACT: Bacteriophages are utilised in the food industry as biocontrol agents to reduce the load of bacteria, and thus reduce potential for human infection. This review focuses on current methods using bacteriophages within the food chain. Limitations of research will be discussed, and the potential for future food-based bacteriophage research.

Cornelissen, A., Sadovskaya, I., Vinogradov, E., Blangy, S., Spinelli, S., Casey, E., Mahony, J., Noben, J. P., Dal, Bello F., Cambillau, C., and van, Sinderen D. The Baseplate of Lactobacillus delbrueckii Bacteriophage Ld17 Harbors a Glycerophosphodiesterase. J.Biol.Chem. 8-5-2016; 291(32):16816-16827.

ABSTRACT: Glycerophosphodiester phosphodiesterases (GDPDs; EC 3.1.4.46) typically hydrolyze glycerophosphodiesters to sn-glycerol 3-phosphate (Gro3P) and their corresponding alcohol during patho/physiological processes in bacteria and eukaryotes. GDPD(-like) domains were identified in the structural particle of bacterial viruses (bacteriophages) specifically infecting Gram-positive bacteria. The GDPD of phage 17 (Ld17; GDPDLd17), representative of the group b Lactobacillus delbrueckii subsp. bulgaricus (Ldb)-infecting bacteriophages, was shown to hydrolyze, besides the simple glycerophosphodiester, two complex surface-associated carbohydrates of the Ldb17 cell envelope: the Gro3P decoration of the major surface polysaccharide d-galactan and the oligo(glycerol phosphate) backbone of the partially glycosylated cell wall teichoic acid, a minor Ldb17 cell envelope component. Degradation of cell wall teichoic acid occurs according to an exolytic mechanism, and Gro3P substitution is presumed to be inhibitory for GDPDLd17 activity. The presence of the GDPDLd17 homotrimer in the viral baseplate structure involved in phage-host interaction together with the dependence of native GDPD activity, adsorption, and efficiency of plating of Ca(2+) ions supports a role for GDPDLd17 activity during phage adsorption and/or phage genome injection. In contrast to GDPDLd17, we could not identify any enzymatic activity for the GDPD-like domain in the neck passage structure of phage 340, a 936-type Lactococcus lactis subsp. lactis bacteriophage.

Dalmasso, M., Strain, R., Neve, H., Franz, C. M., Cousin, F. J., Ross, R. P., and Hill, C. Three New Escherichia coli Phages from the Human Gut Show Promising Potential for Phage Therapy. PLoS.One. 2016; 11(6):e0156773

ABSTRACT: With the emergence of multi-drug resistant bacteria the use of bacteriophages (phages) is gaining renewed interest as promising anti-microbial agents. The aim of this study was to isolate and characterize phages from human fecal samples.

Three new coliphages, APCEc01, APCEc02 and APCEc03, were isolated. Their phenotypic and genomic characteristics, and lytic activity against biofilm, and in combination with ciprofloxacin, were investigated. All three phages reduced the growth of E. coli strain DPC6051 at multiplicity of infection (MOI) between 10-3 and 105. A cocktail of all three phages completely inhibited the growth of E. coli. The phage cocktail also reduced biofilm formation and prevented the emergence of phage-resistant mutants which occurred with single phage. When combined with ciprofloxacin, phage alone or in cocktail inhibited the growth of E. coli and prevented the emergence of resistant mutants. These three new phages are promising biocontrol agents for E. coli infections.

Davies, E. V., James, C. E., Williams, D., O'Brien, S., Fothergill, J. L., Haldenby, S., Paterson, S., Winstanley, C., and Brockhurst, M. A. Temperate phages both mediate and drive adaptive evolution in pathogen biofilms. Proc.Natl.Acad.Sci.U.S.A. 7-19-2016; 113(29):8266-8271.

ABSTRACT: Temperate phages drive genomic diversification in bacterial pathogens. Phage-derived sequences are more common in pathogenic than nonpathogenic taxa and are associated with changes in pathogen virulence. High abundance and mobilization of temperate phages within hosts suggests that temperate phages could promote within-host evolution of bacterial pathogens. However, their role in pathogen evolution has not been experimentally tested. We experimentally evolved replicate populations of Pseudomonas aeruginosa with or without a community of three temperate phages active in cystic fibrosis (CF) lung infections, including the transposable phage, 4, which is closely related to phage D3112. Populations grew as free-floating biofilms in artificial sputum medium, mimicking sputum of CF lungs where P. aeruginosa is an important pathogen and undergoes evolutionary adaptation and diversification during chronic infection. Although bacterial populations adapted to the biofilm environment in both treatments, population genomic analysis revealed that phages altered both the trajectory and mode of evolution. Populations evolving with phages exhibited a greater degree of parallel evolution and faster selective sweeps than populations without phages. Phage 4 integrated randomly into the bacterial chromosome, but integrations into motility-associated genes and regulators of quorum sensing systems essential for virulence were selected in parallel, strongly suggesting that these insertional inactivation mutations were adaptive. Temperate phages, and in particular transposable phages, are therefore likely to facilitate adaptive evolution of bacterial pathogens within hosts.

Danis-Wlodarczyk, K., Vandenheuvel, D., Jang, H. B., Briers, Y., Olszak, T., Arabski, M., Wasik, S., Drabik, M., Higgins, G., Tyrrell, J., Harvey, B. J., Noben, J. P., Lavigne, R., and Drulis-Kawa, Z. A proposed integrated approach for the preclinical evaluation of phage therapy in Pseudomonas infections. Sci.Rep. 2016; 6:28115

ABSTRACT: Bacteriophage therapy is currently resurging as a potential complement/alternative to antibiotic treatment. However, preclinical evaluation lacks streamlined approaches. We here focus on preclinical approaches which have been implemented to assess bacteriophage efficacy against Pseudomonas biofilms and infections. Laser interferometry and profilometry were applied to measure biofilm matrix permeability and surface geometry changes, respectively. These biophysical approaches were combined with an advanced Airway Surface Liquid infection model,

which mimics in vitro the normal and CF lung environments, and an in vivo Galleria larvae model. These assays have been implemented to analyze KTN4 (279,593 bp dsDNA genome), a type-IV pili dependent, giant phage resembling phiKZ. Upon contact, KTN4 immediately disrupts the P. aeruginosa PAO1 biofilm and reduces pyocyanin and siderophore production. The gentamicin exclusion assay on NuLi-1 and CuFi-1 cell lines revealed the decrease of extracellular bacterial load between 4 and 7 logs and successfully prevents wild-type Pseudomonas internalization into CF epithelial cells. These properties and the significant rescue of Galleria larvae indicate that giant KTN4 phage is a suitable candidate for in vivo phage therapy evaluation for lung infection applications.

delToro, D., Ortiz, D., Ordyan, M., Sippy, J., Oh, C. S., Keller, N., Feiss, M., Catalano, C. E., and Smith, D. E. Walker-A Motif Acts to Coordinate ATP Hydrolysis with Motor Output in Viral DNA Packaging. J.Mol.Biol. 7-3-2016; 428(13):2709-2729.

ABSTRACT: During the assembly of many viruses, a powerful ATP-driven motor translocates DNA into a preformed procapsid. A Walker-A "P-loop" motif is proposed to coordinate ATP binding and hydrolysis with DNA translocation. We use genetic, biochemical, and biophysical techniques to survey the roles of P-loop residues in bacteriophage lambda motor function. We identify 55 point mutations that reduce virus yield to below detectable levels in a highly sensitive genetic complementation assay and 33 that cause varying reductions in yield. Most changes in the predicted conserved residues K76, R79, G81, and S83 produce no detectable yield. Biochemical analyses show that R79A and S83A mutant proteins fold, assemble, and display genome maturation activity similar to wild-type (WT) but exhibit little ATPase or DNA packaging activity. Kinetic DNA cleavage and ATPase measurements implicate R79 in motor ring assembly on DNA, supporting recent structural models that locate the P-loop at the interface between motor subunits. Single-molecule measurements detect no translocation for K76A and K76R, while G81A and S83A exhibit strong impairments, consistent with their predicted roles in ATP binding. We identify eight residue changes spanning A78-K84 that yield impaired translocation phenotypes and show that Walker-A residues play important roles in determining motor velocity, pausing, and processivity. The efficiency of initiation of packaging correlates strongly with motor velocity. Frequent pausing and slipping caused by changes A78V and R79K suggest that these residues are important for ATP alignment and coupling of ATP binding to DNA gripping. Our findings support recent structural models implicating the P-loop arginine in ATP hydrolysis and mechanochemical coupling.

Deng, L., Linero, F., and Saelens, X. Production and Purification of Recombinant Filamentous Bacteriophages Displaying Immunogenic Heterologous Epitopes. Methods Mol.Biol. 2016; 1404:483-495.

ABSTRACT: Viruslike particles often combine high physical stability with robust immunogenicity. Furthermore, when such particles are based on bacteriophages, they can be produced in high amounts at minimal cost and typically will require only standard biologically contained facilities. We provide protocols for the characterization and purification of recombinant viruslike particles derived from filamentous bacteriophages. As an example, we focus on filamentous Escherichia coli fd phage displaying a conserved influenza A virus epitope that is fused genetically to the N-terminus of the major coat protein of this phage. A step-by-step procedure to obtain a high-titer, pure recombinant phage preparation is provided. We also describe a quality

control experiment based on a biological readout of the purified fd phage preparation. These protocols together with the highlighted critical steps may facilitate generic implementation of the provided procedures for the display of other epitopes by recombinant fd phages.

Dieterle, M. E., Fina, Martin J., Duran, R., Nemirovsky, S. I., Sanchez, Rivas C., Bowman, C., Russell, D., Hatfull, G. F., Cambillau, C., and Piuri, M. Characterization of prophages containing "evolved" Dit/Tal modules in the genome of Lactobacillus casei BL23. Appl.Microbiol.Biotechnol. 7-23-2016;

ABSTRACT: Lactic acid bacteria (LAB) have many applications in food and industrial fermentations. Prophage induction and generation of new virulent phages is a risk for the dairy industry. We identified three complete prophages (PLE1, PLE2, and PLE3) in the genome of the well-studied probiotic strain Lactobacillus casei BL23. All of them have mosaic architectures with homologous sequences to Streptococcus, Lactococcus, Lactobacillus, and Listeria phages or strains. Using a combination of quantitative real-time PCR, genomics, and proteomics, we showed that PLE2 and PLE3 can be induced-but with different kinetics-in the presence of mitomycin C, although PLE1 remains as a prophage. A structural analysis of the distal tail (Dit) and tail associated lysin (Tal) baseplate proteins of these prophages and other L. casei/paracasei phages and prophages provides evidence that carbohydrate-binding modules (CBM) located within these "evolved" proteins may replace receptor binding proteins (RBPs) present in other well-studied LAB phages. The detailed study of prophage induction in this prototype strain in combination with characterization of the proteins involved in host recognition will facilitate the design of new strategies for avoiding phage propagation in the dairy industry.

Ding, H., Yang, W., Tang, H., Feng, P. M., Huang, J., Chen, W., and Lin, H. PHYPred: a tool for identifying bacteriophage enzymes and hydrolases. Virol.Sin. 5-4-2016.

No abstract currently available.

Domotor, D., Frank, T., Rakhely, G., Doffkay, Z., Schneider, G., and Kovacs, T. Comparative analysis of two bacteriophages of Xanthomonas arboricola pv. juglandis. Infect.Genet.Evol. 2016; 43:371-377.

ABSTRACT: Walnut blight caused by Xanthomonas arboricola pv. juglandis (Xaj) is one of the most frequent infective diseases of walnut, resulting in serious economic losses. One potential solution to control this disease could be the application of bacteriophages. In this study, 24 phages were isolated from soil and walnut aerial tissues infected with Xaj. Two polyvalent bacteriophages, Xaj2 and Xaj24 were chosen for further characterization including their morphological, physiological and genomic analyses. Xaj2 was classified as Siphoviridae whereas Xaj24 belonged to the Podoviridae family. Both phages demonstrated lytic effect on Xaj in laboratory trials. Complete genomes of Xaj2 and Xaj24 were determined. Genomes of Xaj2 and Xaj24 consisted of 49.241 and 44.861 nucleotides encoding 80 and 53 genes, respectively. Comparative genome analyses have revealed that Xaj2 had a unique genome sequence, while Xaj24 was a phiKMV-like phage and it was most similar to the Prado phage which is virulent for Xylella fastidiosa

and Xanthomonas spp. In this study, we present the first two complete Xaj phage sequences enabling an insight into the genomics of Xaj phages.

Dover, J. A., Burmeister, A. R., Molineux, I. J., and Parent, K. N. Evolved populations of Shigella flexneri phage Sf6 acquire large deletions, altered genomic architecture, and faster life cycles. Genome Biol.Evol. 8-6-2016;

ABSTRACT: Genomic architecture is the framework within which genes and regulatory elements evolve and where specific constructs may constrain or potentiate particular adaptations. One such construct is evident in phages that use a headful packaging strategy that results in progeny phage heads packaged with DNA until full rather than encapsidating a simple unit-length genome. Here, we investigate the evolution of the headful packaging phage Sf6 in response to barriers that impede efficient phage adsorption to the host cell. Ten replicate populations evolved faster Sf6 life cycles by parallel mutations found in a phage lysis gene and/or by a large, 1.2 - 4.0 kbp deletions that remove a mobile genetic IS911 element present in the ancestral phage genome. The fastest life cycles were found in phages that acquired both mutations. No mutations were found in genes encoding phage structural proteins, which were a priori expected from the experimental design that imposed a challenge for phage adsorption by using a Shigella flexneri host lacking receptors preferred by Sf6. We used DNA sequencing, molecular approaches, and physiological experiments on 82 clonal isolates taken from all 10 populations to reveal the genetic basis of the faster Sf6 life cycle. The majority of our evolved isolates acquired deletions in the phage genome. Our results suggest that deletions are adaptive and can influence the duration of the phage life cycle while acting in conjunction with other lysis time-determining point mutations.

Dufour, N., Clermont, O., La, Combe B., Messika, J., Dion, S., Khanna, V., Denamur, E., Ricard, J. D., and Debarbieux, L. Bacteriophage LM33_P1, a fast-acting weapon against the pandemic ST131-O25b:H4 Escherichia coli clonal complex. J.Antimicrob.Chemother. 7-7-2016;

ABSTRACT: OBJECTIVES: Amongst the highly diverse Escherichia coli population, the ST131-O25b:H4 clonal complex is particularly worrisome as it is associated with a high level of antibiotic resistance. The lack of new antibiotics, the worldwide continuous increase of infections caused by MDR bacteria and the need for narrow-spectrum antimicrobial agents have revived interest in phage therapy. In this article, we describe a virulent bacteriophage, LM33_P1, which specifically infects O25b strains, and provide data related to its therapeutic potential. METHODS: A large panel of E. coli strains (n = 283) was used to assess both the specificity and the activity of bacteriophage LM33_P1. Immunology, biochemistry and genetics-based methods confirmed this specificity. Virology methods and sequencing were used to characterize this bacteriophage in vitro, while three relevant mouse models were employed to show its in vivo efficacy. RESULTS: Bacteriophage LM33_P1 exclusively infects O25b E. coli strains with a 70% coverage on sequence types associated with high antibiotic resistance (ST131 and ST69). This specificity is due to an interaction with the LPS mediated by an original tail fibre. LM33_P1 also has exceptional intrinsic properties with a high adsorption constant and produces over 300 virions per cell in <10 min. Using animal pneumonia, septicaemia and urinary tract infection models, we showed the in vivo efficacy of LM33_P1 to reduce the bacterial load in several organs. CONCLUSIONS: Bacteriophage LM33_P1 represents the first weapon that specifically and quickly kills O25b E. coli strains. Therapeutic

approaches derived from this bacteriophage could be developed to stop or slow down the spread of the ST131-O25b:H4 drug-resistant clonal complex in humans.

Dufour, N., Henry, M., Ricard, J. D., and Debarbieux, L. Commentary: Morphologically Distinct Escherichia coli Bacteriophages Differ in Their Efficacy and Ability to Stimulate Cytokine Release In Vitro. Front Microbiol. 2016; 7:1029.

No abstract currently available.

Easwaran, M., Dananjaya, S. H., Park, S. C., Lee, J., Shin, H. J., and De, Zoysa M. Characterization of bacteriophage pAh-1 and its protective effects on experimental infection of Aeromonas hydrophila in Zebrafish (Danio rerio). J.Fish.Dis. 7-25-2016.

No abstract currently available.

Echeverria-Vega, A., Morales-Vicencio, P., Saez-Saavedra, C., Ceh, J., and Araya, R. The complete genome sequence and analysis of vB_VorS-PVo5, a Vibrio phage infectious to the pathogenic bacterium Vibrio ordalii ATCC-33509. Stand.Genomic.Sci. 2016; 11:45

ABSTRACT: The bacterium Vibrio ordalii is best known as the causative agent of vibriosis outbreaks in fish and thus recognized for generating serious production losses in aquaculture systems. Here we report for the first time on the isolation and the genome sequencing of phage vB_VorS-PVo5, infectious to Vibrio ordalii ATCC 33509. The features as well as the complete genome sequence and annotation of the Vibrio phage are described; vB_VorS-PVo5 consists of a lineal double stranded DNA totaling ~ 80.6 Kb in length. Considering its ability to lyse Vibrio ordalii ATCC 33509, the phage is likely to gain importance in future aquaculture applications by controlling the pathogen and as such replacing antibiotics as the treatment of choice.

Elias, A., Spector, I., Sogolovsky-Bard, I., Gritsenko, N., Rask, L., Mainbakh, Y., Zilberstein, Y., Yagil, E., and Kolot, M. Cancer-specific binary expression system activated in mice by bacteriophage HK022 Integrase. Sci.Rep. 2016; 6:24971

ABSTRACT: Binary systems based on site-specific recombination have been used for tumor specific transcription targeting of suicide genes in animal models. In these binary systems a site specific recombinase or integrase that is expressed from a tumor specific promoter drives tumor specific expression of a cytotoxic gene. In the present study we developed a new cancer specific binary expression system activated by the Integrase (Int) of the lambdoid phage HK022. We demonstrate the validity of this system by the specific expression of a luciferase (luc) reporter in human embryonic kidney 293T (HEK293T) cells and in a lung cancer mouse model. Due to the absence viral vectors and of cytotoxicity the Int based binary system offers advantages over previously described counterparts and may therefore be developed into a safer cancer cell killing system.

Fan, J., Zeng, Z., Mai, K., Yang, Y., Feng, J., Bai, Y., Sun, B., Xie, Q., Tong, Y., and Ma, J. Preliminary treatment of bovine mastitis caused by Staphylococcus aureus, with trx-SA1,

recombinant endolysin of S. aureus bacteriophage IME-SA1. Vet.Microbiol. 8-15-2016; 191:65-71.

ABSTRACT: Methicillin-resistant Staphylococcus aureus (MRSA) has become a great threat to human and animal health and there is an urgent need to develop novel antibacterial agents to control this pathogen. The objective of this study was to obtain an active recombinant endolysin from the novel bacteriophage (IME-SA1), and conduct an efficacy trial of its effectiveness against bovine mastitis. We isolated a phage that was virulent and specific for S. aureus with an optimal multiplicity of infection of 0.01. Electron microscopy revealed that IME-SA1 was a member of the family Myoviridae, with an isometric head (98nm) and a long contractile tail (200nm). Experimental lysis experiments indicated the phage had an incubation period of 20min with a burst size of 80. When host bacteria were in early exponential growth stages, a multiplicity of infection of 0.01 resulted in a complete bacterial lysis after 9h. The endolysin gene (804bp) was cloned into the pET-32a bacterial expression vector and recombinant endolysin Trx-SA1 was successfully obtained with molecular size of about 47kDa. Preliminary results of therapeutic trials in cow udders showed that Trx-SA1 could effectively control mild clinical mastitis caused by S. aureus. The endolysin Trx-SA1 might be an alternative treatment strategy for infections caused by S. aureus, including MRSA.

Farley, M. M., Tu, J., Kearns, D. B., Molineux, I. J., and Liu, J. Ultrastructural analysis of bacteriophage Phi29 during infection of Bacillus subtilis. J.Struct.Biol. 7-29-2016;

ABSTRACT: Recent advances in cryo-electron tomography (cryo-ET) have allowed direct visualization of the initial interactions between bacteriophages and their hosts. Previous studies focused on phage infection in Gram-negative bacteria but it is of particular interest how phages penetrate the thick, highly cross-linked Gram-positive cell wall. Here we detail structural intermediates of phage Phi29 during infection of Bacillus subtilis. Use of a minicell-producing strain facilitated in situ tomographic reconstructions of infecting phage particles. Phi29 initially contacts the cell wall at an angle through a subset of the twelve appendages, which are attached to the collar at the head proximal portion of the tail knob. The appendages are flexible and switch between extended and downward conformations during this stage of reversible adsorption; appendages enzymatically hydrolyze wall teichoic acids to bring the phage closer to the cell. A cell wall-degrading enzyme at the distal tip of the tail knob locally digests peptidoglycan, facilitating penetration of the tail further into the cell wall, and the phage particle reorients so that the tail becomes perpendicular to the cell surface. All twelve appendages attain the same "down" conformation during this stage of adsorption. Once the tail has become totally embedded in the cell wall, the tip can fuse with the cytoplasmic membrane. The membrane bulges out, presumably to facilitate genome ejection into the cytoplasm, and the deformation remains after complete ejection. This study provides the first visualization of the structural changes occurring in a phage particle during adsorption and genome transfer into a Gram-positive bacterium.

Fernandes, S., Labarde, A., Baptista, C., Jakutyte, L., Tavares, P., and Sao-Jose, C. A non-invasive method for studying viral DNA delivery to bacteria reveals key requirements for phage SPP1 DNA entry in Bacillus subtilis cells. Virology. 2016; 495:79-91.

ABSTRACT: Bacteriophages use most frequently a tail apparatus to create a channel across the entire bacterial cell envelope to transfer the viral genome to the host cell

cytoplasm, initiating infection. Characterization of this critical step remains a major challenge due to the difficulty to monitor DNA entry in the bacterium and its requirements. In this work we developed a new method to study phage DNA entry that has the potential to be extended to many tailed phages. Its application to study genome delivery of bacteriophage SPP1 into Bacillus subtilis disclosed a key role of the host cell membrane potential in the DNA entry process. An energized B. subtilis membrane and a millimolar concentration of calcium ions are shown to be major requirements for SPP1 DNA entry following the irreversible binding of phage particles to the receptor YueB.

Fish, R., Kutter, E., Wheat, G., Blasdel, B., Kutateladze, M., and Kuhl, S. Bacteriophage treatment of intransigent diabetic toe ulcers: a case series. J.Wound.Care. 2016; 25 Suppl 7:S27-S33.

ABSTRACT: OBJECTIVE: Diabetic foot ulcer (DFU) infections are a growing public health problem, with increasing prevalence, poor response to antibiotics and bacterial resistance to traditional antimicrobials leading to increased morbidity and mortality. Bacteriophages (phages), the viruses that target specific bacteria, are one option for addressing bacterial infections, especially where antibiotics fail. Of particular value is a class of virulent staphylococcal phages that hit almost all Staphylococcus aureus, including most methicillin-resistant Staphylococcus aureus (MRSA) strains. Here we report a continuous case series assessing the effectiveness of treating infected and poorly vascularised toe ulcers with exposed bone, after failure of recommended antibiotic therapy, using topically applied Staphylococcus aureus-specific phage. METHOD: This was a compassionate-use case series of nine patients with diabetes and poorly perfused toe ulcers containing culture-proven Staphylococcus aureus infected bone and soft tissue, who had responded poorly to recommended antibiotic therapy. Six representative cases are presented here. The only generally accepted other option in each case was toe amputation. Exposed portions of the infected phalanges were removed in three cases and left in place in two cases. One case presented as a micro-clot induced gangrene following vascular stenting. In this case, phage were used to prevent infection. The phage used was a commercially available fully sequenced preparation of staphylococcal phage Sb-1. Phage solution was applied topically to the ulcerations once weekly, following standard good wound care. The amount of phage solution applied varied from 0.1 to 0.5 cc depending on volume and area of the ulceration. RESULTS: All infections responded to the phage applications and the ulcers healed in an average of seven weeks with infected bone debridement. One ulcer, where vascularity was extremely poor and bone was not removed to preserve hallux function, required 18 weeks of treatment. In the case of the toe with the micro-clot gangrene, the toe was salvaged and healed in seven weeks without complications. CONCLUSION: Topical application of a staph mono-phage preparation can be used successfully to treat infected toe ulcerations with bone involvement, despite very poor vascularity and failure of antibiotic treatment. The success within this small series provides the groundwork for controlled clinical trials of staph phage for diabetic foot infections.

Fratamico, P. M., DebRoy, C., Liu, Y., Needleman, D. S., Baranzoni, G. M., and Feng, P. Advances in Molecular Serotyping and Subtyping of Escherichia coli. Front Microbiol. 2016; 7:644

ABSTRACT: Escherichia coli plays an important role as a member of the gut microbiota; however, pathogenic strains also exist, including various diarrheagenic E. coli pathotypes and extraintestinal pathogenic E. coli that cause illness outside of the GI-tract. E. coli

have traditionally been serotyped using antisera against the ca. 186 O-antigens and 53 H-flagellar antigens. Phenotypic methods, including bacteriophage typing and O- and H- serotyping for differentiating and characterizing E. coli have been used for many years; however, these methods are generally time consuming and not always accurate. Advances in next generation sequencing technologies have made it possible to develop genetic-based subtyping and molecular serotyping methods for E. coli, which are more discriminatory compared to phenotypic typing methods. Furthermore, whole genome sequencing (WGS) of E. coli is replacing established subtyping methods such as pulsed-field gel electrophoresis, providing a major advancement in the ability to investigate food-borne disease outbreaks and for trace-back to sources. A variety of sequence analysis tools and bioinformatic pipelines are being developed to analyze the vast amount of data generated by WGS and to obtain specific information such as O- and H-group determination and the presence of virulence genes and other genetic markers.

Frutos, Md, Leforestier, A., Degrouard, J., Zambrano, N., Wien, F., Boulanger, P., Brasiles, S., Renouard, M., Durand, D., and Livolant, F. Can Changes in Temperature or Ionic Conditions Modify the DNA Organization in the Full Bacteriophage Capsid? J.Phys.Chem.B. 7-7-2016; 120(26):5975-5986.

ABSTRACT: We compared four bacteriophage species, T5, lambda, T7, and Phi29, to explore the possibilities of DNA reorganization in the capsid where the chain is highly concentrated and confined. First, we did not detect any change in DNA organization as a function of temperature between 20 to 40 degrees C. Second, the presence of spermine (4+) induces a significant enlargement of the typical size of the hexagonal domains in all phages. We interpret these changes as a reorganization of DNA by slight movements of defects in the structure, triggered by a partial screening of repulsive interactions. We did not detect any signal characteristic of a long-range chiral organization of the encapsidated DNA in the presence and in the absence of spermine.

Frykholm, K., Berntsson, R. P., Claesson, M., de, Battice L., Odegrip, R., Stenmark, P., and Westerlund, F. DNA compaction by the bacteriophage protein Cox studied on the single DNA molecule level using nanofluidic channels. Nucleic Acids Res. 4-29-2016;

ABSTRACT: The Cox protein from bacteriophage P2 forms oligomeric filaments and it has been proposed that DNA can be wound up around these filaments, similar to how histones condense DNA. We here use fluorescence microscopy to study single DNA-Cox complexes in nanofluidic channels and compare how the Cox homologs from phages P2 and WPhi affect DNA. By measuring the extension of nanoconfined DNA in absence and presence of Cox we show that the protein compacts DNA and that the binding is highly cooperative, in agreement with the model of a Cox filament around which DNA is wrapped. Furthermore, comparing microscopy images for the wild-type P2 Cox protein and two mutants allows us to discriminate between compaction due to filament formation and compaction by monomeric Cox. P2 and WPhi Cox have similar effects on the physical properties of DNA and the subtle, but significant, differences in DNA binding are due to differences in binding affinity rather than binding mode. The presented work highlights the use of single DNA molecule studies to confirm structural predictions from X-ray crystallography. It also shows how a small protein by oligomerization can have great impact on the organization of DNA and thereby fulfill multiple regulatory functions.

Fujino, Y., Tanoue, R., Yokoyama, T., and Doi, K. A tightly regulated expression system for E. coli using supersaturated silicic acid. Biotechnol.Lett. 2016; 38(8):1381-1387.

ABSTRACT: OBJECTIVE: To develop a new expression system regulated by a ferric uptake regulator in which silicic acid is used as an inducer. RESULTS: Fur box (binding site for Fur) was substituted for the lac operator to regulate the expression of GFP with the lac promoter. Since the addition of supersaturated silicic acid invokes iron deficiency, supersaturated silicic acids were used as an inducer. GFP expression was dependent on silica concentration, and the expression level without silica was negligible. Basal expression level of this lac-Fur system was extremely low and, hence, lytic enzyme gene E from bacteriophage varphiX174 could be retained in this system. Furthermore, the expression of genes of interest was spontaneously initiated as the cell density increased and the costs of the inducer are considerably less than IPTG. CONCLUSION: The combination of lac promoter and Ferric uptake repressor allowed the protein expression by supersaturated silicic acid as an inducer in an easy and cost-effective way.

Furusawa, T., Iwano, H., Higuchi, H., Usui, M., Maruyama, F., Nakagawa, I., Yokota, H., and Tamura, Y. Complete Genome Sequences of Broad-Host-Range Pseudomonas aeruginosa Bacteriophages PhiR18 and PhiS12-1. Genome Announc. 2016; 4(3)

ABSTRACT: Pseudomonas aeruginosa is an important cause of racehorse keratitis. Bacteriophage therapy has the potential to aid in the prevention and treatment of diseases caused by P. aeruginosa We present here the complete genome sequences of two phages, PhiR18 and PhiS12-1, which exhibit infectivity for a broad range of P. aeruginosa isolates.

Furusawa, T., Iwano, H., Hiyashimizu, Y., Matsubara, K., Higuchi, H., Nagahata, H., Niwa, H., Katayama, Y., Kinoshita, Y., Hagiwara, K., Iwasaki, T., Tanji, Y., Yokota, H., and Tamura, Y. Phage therapy is effective in a mouse model of bacterial equine keratitis. Appl.Environ.Microbiol. 6-24-2016;

ABSTRACT: Bacterial keratitis of the horse is mainly caused by staphylococci, streptococci, and pseudomonas. Of these bacteria, Pseudomonas aeruginosa sometimes causes rapid corneal corruption and, in some cases, blindness. Antimicrobial resistance can make treatment very difficult. Therefore, new strategies to control bacterial infection are required. A bacteriophage (phage) is a virus that specifically infects and kills bacteria. Since phage often can lyse antibiotic-resistant bacteria because the killing mechanism is different, we examined the use of phage to treat horse bacterial keratitis. We isolated Myoviridae or Podoviridae phages, which together have a broad host range. They adsorb efficiently to host bacteria; over 80% of PhiR18 phage were adsorbed to host cells after 30 seconds. In our keratitis mouse model, administration of phage within 3 hours also could kill bacteria and suppress keratitis. A phage MOI of 100 times the host bacteria number could kill host bacteria effectively. A cocktail of two phages suppressed bacteria in the keratitis model mouse. These data demonstrated that phages in this study could completely prevent the keratitis caused by P. aeruginosa in a keratitis mouse model. Furthermore, these results suggest phage may be more effective prophylaxis for horse keratitis than is the current preventive use of antibiotics. Such treatment may reduce use of antibiotics and, therefore, antibiotic resistance. Further studies are required to assess phage therapy as a candidate for treatment of horse keratitis. IMPORTANCE: Now, antibiotic-resistant bacteria is emerging all over the world.

Bacteriophages have great potential for resolution of this problem. Bacteriophage, or phage, is a virus that infects bacteria specifically. As one of the novel therapeutic strategy against race horse keratitis caused by Pseudomonas aeruginosa, we will propose application of phages for treatment. Phages isolated in this work had in vitro effectiveness for broad P. aeruginosa strains. Indeed, great reduction of bacterial proliferation was shown in phage therapy for mouse models of the P. aeruginosa keratitis. Therefore, to reduce antibiotic usage, phage therapy should be investigated and developed further.

Gaca, A. O. and Gilmore, M. S. A lysin to kill. Elife. 2016; 5ABSTRACT: An enzyme produced by a bacteriophage can enter human cells and kill intracellular Streptococcus pyogenes.

No abstract currently available.

Gagic, D., Ciric, M., Wen, W. X., Ng, F., and Rakonjac, J. Corrigendum: Exploring the Secretomes of Microbes and Microbial Communities Using Filamentous Phage Display. Front Microbiol. 2016; 7:927ABSTRACT: [This corrects the article on p. 429 in vol. 7, PMID: 27092113.].

No abstract currently available.

Gagic, D., Ciric, M., Wen, W. X., Ng, F., and Rakonjac, J. Exploring the Secretomes of Microbes and Microbial Communities Using Filamentous Phage Display. Front Microbiol. 2016; 7:429

ABSTRACT: Microbial surface and secreted proteins (the secretome) contain a large number of proteins that interact with other microbes, host and/or environment. These proteins are exported by the coordinated activities of the protein secretion machinery present in the cell. A group of bacteriophage, called filamentous phage, have the ability to hijack bacterial protein secretion machinery in order to amplify and assemble via a secretion-like process. This ability has been harnessed in the use of filamentous phage of Escherichia coli in biotechnology applications, including screening large libraries of variants for binding to "bait" of interest, from tissues in vivo to pure proteins or even inorganic substrates. In this review we discuss the roles of secretome proteins in pathogenic and non-pathogenic bacteria and corresponding secretion pathways. We describe the basics of phage display technology and its variants applied to discovery of bacterial proteins that are implicated in colonization of host tissues and pathogenesis, as well as vaccine candidates through filamentous phage display library screening. Secretome selection aided by next-generation sequence analysis was successfully applied for selective display of the secretome at a microbial community scale, the latter revealing the richness of secretome functions of interest and surprising versatility in filamentous phage display of secretome proteins from large number of Gram-negative as well as Gram-positive bacteria and archaea.

Garcia-Pino, A., De, Gieter S., Talavera, A., De, Greve H., Efremov, R. G., and Loris, R. An intrinsically disordered entropic switch determines allostery in Phd-Doc regulation. Nat.Chem.Biol. 2016; 12(7):490-496.

ABSTRACT: Conditional cooperativity is a common mechanism involved in transcriptional regulation of prokaryotic type II toxin-antitoxin operons and is intricately related to bacterial persistence. It allows the toxin component of a toxin-antitoxin module to act as a co-repressor at low doses of toxin as compared to antitoxin. When toxin level exceeds a certain threshold, however, the toxin becomes a de-repressor. Most antitoxins contain an intrinsically disordered region (IDR) that typically is involved in toxin neutralization and repressor complex formation. To address how the antitoxin IDR is involved in transcription regulation, we studied the phd-doc operon from bacteriophage P1. We provide evidence that the IDR of Phd provides an entropic barrier precluding full operon repression in the absence of Doc. Binding of Doc results in a cooperativity switch and consequent strong operon repression, enabling context-specific modulation of the regulatory process. Variations of this theme are likely to be a common mechanism in the autoregulation of bacterial operons that involve intrinsically disordered regions.

Glasser, C. A., Vila, M. M., Pereira, J. C., Chaud, M. V., Oliveira Junior, J. M., Tubino, M., and Balcao, V. M. Development of a water-in-oil-in-water multiple emulsion system integrating biomimetic aqueous-core lipid nanodroplets for protein entity stabilization. Part II: process and product characterization. Drug Dev.Ind.Pharm. 5-25-2016; 1-11.

ABSTRACT: The aqueous-core enclosed in lipid nanoballoons integrating multiple emulsions of the type water-in-oil-in-water mimic, at least in theory, the environment within viable cells, thus being suitable for housing hydrophilic protein entities such as bioactive proteins, peptides and bacteriophage particles. This study reports a complete physicochemical characterization of optimized biomimetic aqueous-core lipid nanoballoons housing hydrophilic (BSA) protein entities, evolved from a statistical 23x31 factorial design study (three variables at two levels and one variable at three levels) that was the subject of the first paper of a series of three, aiming at complete stabilization of the three-dimensional structure of protein entities attempted via housing the said molecular entities within biomimetic aqueous-core lipid nanoballoons integrating a multiple (W/O/W) emulsion. The statistical factorial design followed led to the production of an optimum W/O/W multiple emulsion possessing quite homogeneous particles with an average hydrodynamic size of (186.2 +/- 2.6) nm and average Zeta potential of (-36.5 +/- 0.9) mV, and exhibiting a polydispersity index of 0.206 +/- 0.014. Additionally, the results obtained for the diffusion coefficient of the lipid nanoballoons integrating the optimized W/O/W multiple emulsion were comparable and of the same order of magnitude (10-12 m2 s-1) as those published by other authors since, typically, diffusion coefficients for molecules range from 10-10 to 10-7 m2 s-1, but diffusion coefficients for nanoparticles are typically of the order of magnitude of 10-12 m2 s-1.

Gleditzsch, D., Muller-Esparza, H., Pausch, P., Sharma, K., Dwarakanath, S., Urlaub, H., Bange, G., and Randau, L. Modulating the Cascade architecture of a minimal Type I-F CRISPR-Cas system. Nucleic Acids Res. 7-8-2016; 44(12):5872-5882.

ABSTRACT: Shewanella putrefaciens CN-32 contains a single Type I-Fv CRISPR-Cas system which confers adaptive immunity against bacteriophage infection. Three Cas proteins (Cas6f, Cas7fv, Cas5fv) and mature CRISPR RNAs were shown to be required for the assembly of an interference complex termed Cascade. The Cas protein-CRISPR RNA interaction sites within this complex were identified via mass spectrometry. Additional Cas proteins, commonly described as large and small subunits, that are present in all other investigated Cascade structures, were not detected. We introduced this minimal

Type I system in Escherichia coli and show that it provides heterologous protection against lambda phage. The absence of a large subunit suggests that the length of the crRNA might not be fixed and recombinant Cascade complexes with drastically shortened and elongated crRNAs were engineered. Size-exclusion chromatography and small-angle X-ray scattering analyses revealed that the number of Cas7fv backbone subunits is adjusted in these shortened and extended Cascade variants. Larger Cascade complexes can still confer immunity against lambda phage infection in E. coli Minimized Type I CRISPR-Cas systems expand our understanding of the evolution of Cascade assembly and diversity. Their adjustable crRNA length opens the possibility for customizing target DNA specificity.

Golding, I. Single-Cell Studies of Phage lambda: Hidden Treasures Under Occam's Rug. Annu.Rev.Virol. 7-22-2016;

ABSTRACT: Studies over more than half a century have resulted in what some consider a complete narrative for the life cycle of bacteriophage lambda. However, this narrative is only complete within the limited resolution offered by the traditional genetic and biochemical approaches that were used to create it. A recent series of studies performed at the single-cell and single-phage levels has revealed a wealth of previously unknown features. By pointing to many open questions, these new studies highlight the limitations of our current understanding of lambda, but they also initiate the process of forming a more detailed and quantitative narrative for the system. Expected final online publication date for the Annual Review of Virology Volume 3 is September 29, 2016. Please see http://www.annualreviews.org/catalog/pubdates.aspx for revised estimates.

Gone, S., fonso-Prieto, M., Paudyal, S., and Nicholson, A. W. Mechanism of Ribonuclease III Catalytic Regulation by Serine Phosphorylation. Sci.Rep. 2016; 6:25448

ABSTRACT: Ribonuclease III (RNase III) is a conserved, gene-regulatory bacterial endonuclease that cleaves double-helical structures in diverse coding and noncoding RNAs. RNase III is subject to multiple levels of control, reflective of its global regulatory functions. Escherichia coli (Ec) RNase III catalytic activity is known to increase during bacteriophage T7 infection, reflecting the expression of the phage-encoded protein kinase, T7PK. However, the mechanism of catalytic enhancement is unknown. This study shows that Ec-RNase III is phosphorylated on serine in vitro by purified T7PK, and identifies the targets as Ser33 and Ser34 in the N-terminal catalytic domain. Kinetic experiments reveal a 5-fold increase in kcat and a 1.4-fold decrease in Km following phosphorylation, providing a 7.4-fold increase in catalytic efficiency. Phosphorylation does not change the rate of substrate cleavage under single-turnover conditions, indicating that phosphorylation enhances product release, which also is the rate-limiting step in the steady-state. Molecular dynamics simulations provide a mechanism for facilitated product release, in which the Ser33 phosphomonoester forms a salt bridge with the Arg95 guanidinium group, thereby weakening RNase III engagement of product. The simulations also show why glutamic acid substitution at either serine does not confer enhancement, thus underscoring the specific requirement for a phosphomonoester.

Gruber, C. J., Lang, S., Rajendra, V. K., Nuk, M., Raffl, S., Schildbach, J. F., and Zechner, E. L. Conjugative DNA Transfer Is Enhanced by Plasmid R1 Partitioning Proteins. Front Mol.Biosci. 2016; 3:32

ABSTRACT: Bacterial conjugation is a form of type IV secretion used to transport protein and DNA directly to recipient bacteria. The process is cell contact-dependent, yet the mechanisms enabling extracellular events to trigger plasmid transfer to begin inside the cell remain obscure. In this study of plasmid R1 we investigated the role of plasmid proteins in the initiation of gene transfer. We find that TraI, the central regulator of conjugative DNA processing, interacts physically, and functionally with the plasmid partitioning proteins ParM and ParR. These interactions stimulate TraI catalyzed relaxation of plasmid DNA in vivo and in vitro and increase ParM ATPase activity. ParM also binds the coupling protein TraD and VirB4-like channel ATPase TraC. Together, these protein-protein interactions probably act to co-localize the transfer components intracellularly and promote assembly of the conjugation machinery. Importantly these data also indicate that the continued association of ParM and ParR at the conjugative pore is necessary for plasmid transfer to start efficiently. Moreover, the conjugative pilus and underlying secretion machinery assembled in the absence of Par proteins mediate poor biofilm formation and are completely dysfunctional for pilus specific R17 bacteriophage uptake. Thus, functional integration of Par components at the interface of relaxosome, coupling protein, and channel ATPases appears important for an optimal conformation and effective activation of the transfer machinery. We conclude that low copy plasmid R1 has evolved an active segregation system that optimizes both its vertical and lateral modes of dissemination.

Gu, J., Li, X., Yang, M., Du, C., Cui, Z., Gong, P., Xia, F., Song, J., Zhang, L., Li, J., Yu, C., Sun, C., Feng, X., Lei, L., and Han, W. Therapeutic effect of Pseudomonas aeruginosa phage YH30 on mink hemorrhagic pneumonia. Vet.Microbiol. 7-15-2016; 190:5-11.

ABSTRACT: Hemorrhagic pneumonia caused by Pseudomonas aeruginosa remains one of the most costly infectious diseases among farmed mink and commonly leads to large economic losses during mink production. The objective of this study was to investigate the potential of using phages as a therapy against hemorrhagic pneumonia in mink. A broad-host-range phage from the Podoviridae family, YH30, was isolated using the mink-originating P. aeruginosa (serotype G) D7 strain as a host. The genome of YH30 was 72,192bp (54.92% G+C), contained 86 open reading frames and lacked regions encoding known virulence factors, integration-related proteins or antibiotic resistance determinants. These characteristics make YH30 eligible for use in phage therapy. The results of a curative treatment experiment demonstrated that a single intranasal administration of YH30 was sufficient to cure hemorrhagic pneumonia in mink. The mean colony count of P. aeruginosa in the blood and lung of YH30-protected mink was less than 10(3) CFU/mL (g) within 24h of bacterial challenge and ultimately became undetectable, whereas that in unprotected mink reached more than 10(8) CFU/mL (g). Additionally, YH30 dramatically improved the pathological manifestations of lung injury in mink with hemorrhagic pneumonia. Our work demonstrates the potential of phages to treat P. aeruginosa-caused hemorrhagic pneumonia in mink.

Guang-Han, O., Leang-Chung, C., Vellasamy, K. M., Mariappan, V., Li-Yen, C., and Vadivelu, J. Experimental Phage Therapy for Burkholderia pseudomallei Infection. PLoS.One. 2016; 11(7):e0158213

ABSTRACT: Burkholderia pseudomallei is an intracellular Gram-negative bacterial pathogen intrinsically resistant to a variety of antibiotics. Phages have been developed

for use as an alternative treatment therapy, particularly for bacterial infections that do not respond to conventional antibiotics. In this study, we investigated the use of phages to treat cells infected with B. pseudomallei. Phage C34 isolated from seawater was purified and characterised on the basis of its host range and morphology using transmission electron microscopy (TEM). Phage C34 was able to lyse 39.5% of B. pseudomallei clinical strains. Due to the presence of contractile tail, phage C34 is classified as a member of the family Myoviridae, a tailed double-stranded DNA virus. When 2 x 105 A549 cells were exposed to 2 x 107 PFU of phage C34, 24 hours prior to infection with 2 x 106 CFU of B. pseudomallei, it was found that the survivability of the cells increased to 41.6 +/- 6.8% as compared to 22.8 +/- 6.0% in untreated control. Additionally, application of phage successfully rescued 33.3% of mice infected with B. pseudomallei and significantly reduced the bacterial load in the spleen of the phage-treated mice. These findings indicate that phage can be a potential antimicrobial agent for B. pseudomallei infections.

Guest, R. L. and Raivio, T. L. Role of the Gram-Negative Envelope Stress Response in the Presence of Antimicrobial Agents. Trends Microbiol. 2016; 24(5):377-390.

ABSTRACT: Bacterial survival necessitates endurance of many types of antimicrobial compound. Many Gram-negative envelope stress responses, which must contend with an outer membrane and a dense periplasm containing the cell wall, have been associated with the status of protein folding, membrane homeostasis, and physiological functions such as efflux and the proton motive force (PMF). In this review, we discuss evidence that indicates an emerging role for Gram-negative envelope stress responses in enduring exposure to diverse antimicrobial substances, focusing on recent studies of the gamma-proteobacterial Cpx envelope stress response.

Guliy, O. I., Karavaeva, O. A., Velikov, V. A., Sokolov, O. I., Pavily, S. A., Larionova, O. S., Burov, A. M., and Ignatov, O. V. [A STUDY OF THE ISOLATED BACTERIOPHAGE PhiAB-SP7 ADSORPTION ON THE CELL SURFACE OF THE AZOSPIRILLUM BRASILENSE SP7]. Vopr.Virusol. 2016; 61(1):45-48.

ABSTRACT: The bacteriophage PhiAb-Sp7 was isolated from the cells of the Azospirillum brasilense Sp7. The morphology, size of the gram-negative colonies, and range of lytic activity against other strains and species of the genus Azospirillum was tested. The isolated phage DNA was examined using electrophoretic and restriction analysis, and the size of the genome were established. The electron microscopy. results show that the phage (capsid) has a strand-like form. The electron microscopy study of the bacteriophage PhiAb-Sp7 adsorption on the A. brasilense Sp7 bacterial surface was performed.

Gundogdu, A., Kilic, H., Ulu, Kilic A., and Kutateladze, M. [Susceptibilities of multidrug-resistant pathogens responsible for complicated skin and soft tissue infections to standard bacteriophage cocktails]. Mikrobiyol.Bul. 2016; 50(2):215-223.

ABSTRACT: Skin and soft tissue infections (SSTIs) may represent a wide clinical spectrum from cellulitis to high-mortality associated necrotizing fasciitis. Limitations in therapy due to the multiple drug resistance, leads to increase in the morbidity and mortality rates, especially in complicated SSTIs such as diabetic foot, decubitus, and surgical wound

infections. Therefore, alternative treatment strategies other than antibiotics are needed in appropriate clinical conditions. "Bacteriophage therapy", which is an old method and has been used as part of standard treatment in some countries such as Georgia and Russia, has again become popular worldwide. The aim of this study was to investigate the in vitro susceptibilities of multidrug-resistant (MDR) pathogens isolated from patients with complicated SSTIs, against standard bacteriophage (phage) cocktails. Six different ready-made phage preparations [Pyophage, Intestiphage, ENKO, SES, Fersisi and Staphylococcal Bacteriophage (Sb)] used in this study have been provided by G. Eliava Institute, Georgia. Because of the absence of ready-made phage preparations for Acinetobacter baumannii and Klebsiella pneumoniae, Phi1-Phi7 and PhiKL1- PhiKL3 phages were used provided from the same institute's phage library, respectively. Isolation and identification of the pathogens from abscess and wound samples of patients with SSTIs were performed by conventional methods and automatized VITEK((R))-2 (bioMerieux, ABD) system. Antimicrobial susceptibility testing was conducted complying CLSI standards' and the bacteria that were resistant to at least two different antibiotic groups were considered as MDR. Accordingly, a total of 33 isolates, nine of them were E.coli (8 ESBL and 1 ESBL + carbapenemase positive); nine were MDR P.aeruginosa; nine were MDR A.baumannii; three were methicillin-resistant Staphylococcus aureus (MRSA) and three were K.pneumoniae (1 ESBL, 1 carbapenemase and 1 ESBL + carbapenemase positive) were included in the study. The phage susceptibilities of the pathogens were performed by using spot test. In the study, 29 (87.9%) out of 33 MDR pathogens were found to be susceptible to at least one of the tested phage/phage preparations. All MRSA (3/3) strains were susceptible to ENKO, SES, Fersisi and Sb phage cocktails, while all A.baumannii isolates (9/9) were susceptible to Phi5 and Phi7 phages. However, two E.coli, one K. pneumoniae and one P.aeruginosa strains were resistant to the all phage preparations tested. Although the clinical use of phages has not been approved yet, except a few Eastern European countries, this study exhibits the potential use of the topical bacteriophage therapy in the treatment of complicated SSTIs caused by MDR pathogens with limited treatment options, such as diabetic foot, decubitus, and surgical wound infections.

Gutierrez, D., Rodriguez-Rubio, L., Garcia, P., Billington, C., Premarante, A., Rodriguez, A., and Martinez, B. Phage sensitivity and prophage carriage in Staphylococcus aureus isolated from foods in Spain and New Zealand. Int.J.Food Microbiol. 8-2-2016; 230:16-20.

ABSTRACT: Bacteriophages (phages) are a promising tool for the biocontrol of pathogenic bacteria, including those contaminating food products and causing infectious diseases. However, the success of phage preparations is limited by the host ranges of their constituent phages. The phage resistance/sensitivity profile of eighty seven Staphylococcus aureus strains isolated in Spain and New Zealand from dairy, meat and seafood sources was determined for six phages (Phi11, K, PhiH5, PhiA72, CAPSa1 and CAPSa3). Most of the S. aureus strains were sensitive to phage K (Myoviridae) and CAPSa1 (Siphoviridae) regardless of their origin. There was a higher sensitivity of New Zealand S. aureus strains to phages isolated from both Spain (PhiH5 and PhiA72) and New Zealand (CAPSa1 and CAPSa3). Spanish phages had a higher infectivity on S. aureus strains of Spanish dairy origin, while Spanish strains isolated from other environments were more sensitive to New Zealand phages. Lysogeny was more prevalent in Spanish S. aureus compared to New Zealand strains. A multiplex PCR reaction, which detected PhiH5 and PhiA72 sequences, indicated a high prevalence of these prophages in Spanish S. aureus strains, but were infrequently detected in New

Zealand strains. Overall, the correlation between phage resistance and lysogeny in S. aureus strains was found to be weak.

Gutierrez, D., Rodriguez-Rubio, L., Martinez, B., Rodriguez, A., and Garcia, P. Bacteriophages as Weapons Against Bacterial Biofilms in the Food Industry. Front Microbiol. 2016; 7:825

ABSTRACT: Microbiological contamination in the food industry is often attributed to the presence of biofilms in processing plants. Bacterial biofilms are complex communities of bacteria attached to a surface and surrounded by an extracellular polymeric material. Their extreme resistance to cleaning and disinfecting processes is related to a unique organization, which implies a differential bacterial growth and gene expression inside the biofilm. The impact of biofilms on health, and the economic consequences, has promoted the development of different approaches to control or remove biofilm formation. Recently, successful results in phage therapy have boosted new research in bacteriophages and phage lytic proteins for biofilm eradication. In this regard, this review examines the environmental factors that determine biofilm development in food-processing equipment. In addition, future perspectives for the use of bacteriophage-derived tools as disinfectants are discussed.

Guzina, J. and Djordjevic, M. Promoter Recognition by Extracytoplasmic Function sigma Factors: Analyzing DNA and Protein Interaction Motifs. J.Bacteriol. 7-15-2016; 198(14):1927-1938.

ABSTRACT: Extracytoplasmic function (ECF) sigma factors are the largest and the most diverse group of alternative sigma factors, but their mechanisms of transcription are poorly studied. This subfamily is considered to exhibit a rigid promoter structure and an absence of mixing and matching; both -35 and -10 elements are considered necessary for initiating transcription. This paradigm, however, is based on very limited data, which bias the analysis of diverse ECF sigma subgroups. Here we investigate DNA and protein recognition motifs involved in ECF sigma factor transcription by a computational analysis of canonical ECF subfamily members, much less studied ECF sigma subgroups, and the group outliers, obtained from recently sequenced bacteriophages. The analysis identifies an extended -10 element in promoters for phage ECF sigma factors; a comparison with bacterial sigma factors points to a putative 6-amino-acid motif just C-terminal of domain sigma2, which is responsible for the interaction with the identified extension of the -10 element. Interestingly, a similar protein motif is found C-terminal of domain sigma2 in canonical ECF sigma factors, at a position where it is expected to interact with a conserved motif further upstream of the -10 element. Moreover, the phiEco32 ECF sigma factor lacks a recognizable -35 element and sigma4 domain, which we identify in a homologous phage, 7-11, indicating that the extended -10 element can compensate for the lack of -35 element interactions. Overall, the results reveal greater flexibility in promoter recognition by ECF sigma factors than previously recognized and raise the possibility that mixing and matching also apply to this group, a notion that remains to be biochemically tested. IMPORTANCE: ECF sigma factors are the most numerous group of alternative sigma factors but have been little studied. Their promoter recognition mechanisms are obscured by the large diversity within the ECF sigma factor group and the limited similarity with the well-studied housekeeping sigma factors. Here we extensively compare bacterial and bacteriophage ECF sigma factors and their promoters in order to infer DNA and protein recognition motifs involved in transcription initiation. We predict a more flexible promoter structure than is recognized by the current paradigm, which assumes rigidness, and propose that ECF sigma promoter elements

may complement (mix and match with) each other's strengths. These results warrant the refocusing of research efforts from the well-studied housekeeping sigma factors toward the physiologically highly important, but insufficiently understood, alternative sigma factors.

Hao, N., Palmer, A. C., hlgren-Berg, A., Shearwin, K. E., and Dodd, I. B. The role of repressor kinetics in relief of transcriptional interference between convergent promoters. Nucleic Acids Res. 7-4-2016;

ABSTRACT: Transcriptional interference (TI), where transcription from a promoter is inhibited by the activity of other promoters in its vicinity on the same DNA, enables transcription factors to regulate a target promoter indirectly, inducing or relieving TI by controlling the interfering promoter. For convergent promoters, stochastic simulations indicate that relief of TI can be inhibited if the repressor at the interfering promoter has slow binding kinetics, making it either sensitive to frequent dislodgement by elongating RNA polymerases (RNAPs) from the target promoter, or able to be a strong roadblock to these RNAPs. In vivo measurements of relief of TI by CI or Cro repressors in the bacteriophage lambda PR-PRE system show strong relief of TI and a lack of dislodgement and roadblocking effects, indicative of rapid CI and Cro binding kinetics. However, repression of the same lambda promoter by a catalytically dead CRISPR Cas9 protein gave either compromised or no relief of TI depending on the orientation at which it binds DNA, consistent with dCas9 being a slow kinetics repressor. This analysis shows how the intrinsic properties of a repressor can be evolutionarily tuned to set the magnitude of relief of TI.

Hao, Y. and Kieft, J. S. Three-way junction conformation dictates self-association of phage packaging RNAs. RNA.Biol. 7-2-2016; 13(7):635-645.

ABSTRACT: The packaging RNA (pRNA) found in the phi29 family of bacteriophage is an essential component of a powerful molecular motor used to package the phage's DNA genome into the capsid. The pRNA forms homomultimers mediated by intermolecular "kissing-loop" interactions, thus it is an example of the unusual phenomenon of a self-associating RNA that can form symmetric higher-order multimers. Previous research showed the pRNAs from phi29 family phages have diverse self-association properties and the kissing-loop interaction is not the sole structural element dictating multimerization. We found that a 3-way junction (3wj) within each pRNA, despite not making direct intermolecular contacts, plays important roles in stabilizing the intermolecular interactions and dictating the size of the multimer formed (dimer, trimer, etc.). Specifically, the 3wj in the pRNA from phage M2 appears to favor a different conformation compared to the 3wj in the phi29 pRNA, and the M2 junction facilitates formation of a higher-order multimer that is more thermostable. This behavior provides insights into the fundamental principles of RNA self-association, and additionally may be useful to engineer fine-tuned properties into pRNAs for nanotechnology.

Hata, E. Bovine mastitis outbreak in Japan caused by methicillin-resistant Staphylococcus aureus New York/Japan clone. J.Vet.Diagn.Invest. 2016; 28(3):291-298.

ABSTRACT: Many methicillin-resistant Staphylococcus aureus (MRSA) strains are multidrug-resistant; consequently, infectious diseases involving MRSA are recognized as

troublesome diseases not only in human health care but also in animal health care. A bovine mastitis case caused by MRSA isolates of the New York/Japan clone (NJC), which occurred in Japan in 2005, was monitored in the current study. Isolates of the NJC are typical of hospital-acquired MRSA in Japan. The genetic backgrounds of these strains differ from those of bovine-associated S. aureus, which are typically of clonal complex (CC)97, CC705, and CC133. Moreover, the NJC isolates in this bovine outbreak possessed a beta-hemolysin-converting bacteriophage and an immune evasion cluster, as found in the NJC isolates from humans, so it is possible that this clone was introduced into the dairy herd by a human carrier. Most bovine intramammary infections (IMIs) caused by the NJC isolates in our study were asymptomatic, and obvious clinical signs were recognized in only the first 3 infected cows. Of a total of 78 cows, 31 cows were MRSA carriers, and these carrier cows were detected by testing the milk of all lactating cows at 1-month intervals. These S. aureus carrier cows were culled or the infected quarter was dried off and no longer milked. Both IMI and mastitis caused by MRSA were completely eradicated after 5 months. Genotyping data suggested that exchanging of the staphylococcal cassette chromosome mec (the determining factor in methicillin resistance) occurred easily between MRSA and methicillin-sensitive S. aureus in the udders of carrier cows. This case study demonstrates an effective procedure against the spread of MRSA in a dairy herd, and highlights the risk of emergence of new MRSA strains in a dairy herd.

Hauser, A. R., Mecsas, J., and Moir, D. T. Beyond Antibiotics: New Therapeutic Approaches for Bacterial Infections. Clin.Infect.Dis. 7-1-2016; 63(1):89-95.

ABSTRACT: The utility of conventional antibiotics for the treatment of bacterial infections has become increasingly strained due to increased rates of resistance coupled with reduced rates of development of new agents. As a result, multidrug-resistant, extensively drug-resistant, and pandrug-resistant bacterial strains are now frequently encountered. This has led to fears of a "postantibiotic era" in which many bacterial infections will be untreatable. Alternative nonantibiotic treatment strategies need to be explored to ensure that a robust pipeline of effective therapies is available to clinicians. In this review, we highlight some of the recent developments in this area, such as the targeting of bacterial virulence factors, utilization of bacteriophages to kill bacteria, and manipulation of the microbiome to combat infections.

Hayes, S., Wang, W., Rajamanickam, K., Chu, A., Banerjee, A., and Hayes, C. Lambda gpP-DnaB Helicase Sequestration and gpP-RpoB Associated Effects: On Screens for Auxotrophs, Selection for Rif(R), Toxicity, Mutagenicity, Plasmid Curing. Viruses. 2016; 8(6)

ABSTRACT: The bacteriophage lambda replication initiation protein P exhibits a toxic effect on its Escherichia coli (E. coli) host, likely due to the formation of a dead-end P-DnaB complex, sequestering the replicative DnaB helicase from further activity. Intracellular expression of P triggers SOS-independent cellular filamentation and rapidly cures resident ColE1 plasmids. The toxicity of P is suppressed by alleles of P or dnaB. We asked whether P buildup within a cell can influence E. coli replication fidelity. The influence of P expression from a defective prophage, or when cloned and expressed from a plasmid was examined by screening for auxotrophic mutants, or by selection for rifampicin resistant (Rif(R)) cells acquiring mutations within the rpoB gene encoding the beta-subunit of RNA polymerase (RNAP), nine of which proved unique. Using fluctuation assays, we show that the intracellular expression of P evokes a mutator effect. Most of

the Rif(R) mutants remained P(S) and localized to the Rif binding pocket in RNAP, but a subset acquired a P(R) phenotype, lost sensitivity to ColE1 plasmid curing, and localized outside of the pocket. One P(R) mutation was identical to rpo*Q148P, which alleviates the UV-sensitivity of ruv strains defective in the migration and resolution of Holliday junctions and destabilizes stalled RNAP elongation complexes. The results suggest that P-DnaB sequestration is mutagenic and supports an earlier observation that P can interact with RNAP.

Hernandez, A. J., Lee, S. J., and Richardson, C. C. Primer release is the rate-limiting event in lagging-strand synthesis mediated by the T7 replisome. Proc.Natl.Acad.Sci.U.S.A. 5-24-2016; 113(21):5916-5921.

ABSTRACT: DNA replication occurs semidiscontinuously due to the antiparallel DNA strands and polarity of enzymatic DNA synthesis. Although the leading strand is synthesized continuously, the lagging strand is synthesized in small segments designated Okazaki fragments. Lagging-strand synthesis is a complex event requiring repeated cycles of RNA primer synthesis, transfer to the lagging-strand polymerase, and extension effected by cooperation between DNA primase and the lagging-strand polymerase. We examined events controlling Okazaki fragment initiation using the bacteriophage T7 replication system. Primer utilization by T7 DNA polymerase is slower than primer formation. Slow primer release from DNA primase allows the polymerase to engage the complex and is followed by a slow primer handoff step. The T7 single-stranded DNA binding protein increases primer formation and extension efficiency but promotes limited rounds of primer extension. We present a model describing Okazaki fragment initiation, the regulation of fragment length, and their implications for coordinated leading- and lagging-strand DNA synthesis.

Hirata, H., Kashihara, M., Horiike, T., Suzuki, T., Dohra, H., Netsu, O., and Tsuyumu, S. Genome Sequence of Pectobacterium carotovorum Phage PPWS1, Isolated from Japanese Horseradish [Eutrema japonicum (Miq.) Koidz] Showing Soft-Rot Symptoms. Genome Announc. 2016; 4(2)

ABSTRACT: *Pectobacterium carotovorumsubsp*. carotovorumand its lytic bacteriophage PPWS1 were isolated from a Japanese horseradish rhizome with soft rot. Sequencing of the phage genomic DNA suggested that PPWS1 is a new species of the family ITALIC! Podoviridaeand has high similarity to the bacteriophage Peat1 infectious to *P. atrosepticum*.

Ho, J., Seidel, M., Niessner, R., Eggers, J., and Tiehm, A. Long amplicon (LA)-qPCR for the discrimination of infectious and noninfectious phix174 bacteriophages after UV inactivation. Water Res. 7-15-2016; 103:141-148.

ABSTRACT: Waterborne viruses are increasingly being considered in risk assessment schemes. In general, virus detection by culture methods is time consuming. In contrast, detection by quantitative polymerase chain reaction (qPCR) is more rapid and therefore, more suitable for monitoring. At present, qPCR lacks the essential ability for discriminating between infectious and non-infectious viruses, thus limiting its applicability for monitoring disinfection processes. In this study, a method was developed to quantify UV inactivation by long amplicon (LA)-qPCR. Bacteriophage phiX174 was used as a

surrogate for human pathogenic viruses. A qPCR protocol was developed with new sets of primers, resulting in amplicon lengths of 108, 250, 456, 568, 955, 1063, 1544, and 1764 nucleotides. The log reduction of gene copies increased with increasing amplicon length. Additional treatment with the intercalating dye, PMA, had no effect, indicating that the bacteriophage capsids were not damaged by low pressure UV irradiation. A qPCR of nearly the complete genome (approx. 5000 nucleotides) showed similar results to the plaque assay. The log reduction in qPCR correlates with [specific amplicon length x UV dose]. The normalized DNA effect constant can be applied to calculate phiX174 inactivation based on qPCR detection.

Hoai, T. D., Nishiki, I., and Yoshida, T. Properties and genomic analysis of Lactococcus garvieae lysogenic bacteriophage PLgT-1, a new member of Siphoviridae, with homology to Lactococcus lactis phages. Virus Res. 8-15-2016; 222:13-23.

ABSTRACT: The lysogenic phage PLgT-1 is highly prevalent in Lactococcus garvieae, which is a serious bacterial pathogen in marine fish. Therefore, information regarding this phage is one of the key factors to predict the evolution of this bacterium. However, many properties of this phage, its complete genome sequence, and its relationship with other viral communities has not been investigated to date. Here, we demonstrated that the phage PLgT-1 was not only induced by an induction agent (Mitomycin C), but could be released frequently during cell division in a nutrient-rich environment or in natural seawater. Integration of PLgT-1 into non-lysogenic bacteria via transduction changed the genotype, resulting in the diversification of L. garvieae. The complete DNA sequence of PLgT-1 was also determined. This phage has a dsDNA genome of 40,273bp with 66 open reading frames (ORFs). Of these, the biological functions of 24 ORFs could be predicted but those of 42 ORFs are unknown. Thus, PLgT-1 is a novel phage with several novel proteins encoded in its genome. The strict MegaBLAST search program for the PLgT-1 genome revealed that this phage had no similarities with other previously investigated phages specific to L. garvieae (WP-2 and GE1). Notably, PLgT-1 was relatively homologous with several phages of Lactococcus lactis and 17 of the 24 predicted proteins encoded in PLgT-1 were homologous with the deduced proteins of various phages from these dairy bacteria. Comparative genome analysis revealed that the L. garvieae phage PLgT-1 was most closely related to the L. lactis phage TP712. However, they differed from each other in genome size and gene arrangement. The results obtained in this study suggest that the lysogenic phage PLgT-1 is a new member of the family Siphoviridae and has been involved in horizontal gene exchange with microbial communities, especially with L. lactis and its phages.

Hoai, T. D. and Yoshida, T. Induction and characterization of a lysogenic bacteriophage of Lactococcus garvieae isolated from marine fish species. J.Fish.Dis. 2016; 39(7):799-808.

ABSTRACT: This study investigated the presence of prophages in Lactococcus garvieae isolated from several marine fish species in Japan. Representative strains of 16 bacterial genotypes (S1-S16) selected from more than 400 L. garvieae isolates were used to induce lysogenic bacteriophages. These strains were treated with 500 ng mL(-1) freshly prepared mitomycin C. A cross-spotting assay was performed to validate the lysogenic and indicator strains. The lysogenic strains were selected for isolation and concentration of the phages. Phage DNA was digested with EcoRI for biased sinusoidal field gel electrophoresis analysis. Polymerase chain reaction (PCR) was used to detect integrated prophage DNA. Of the 16 representative bacterial genotypes, 12 strains integrated

prophages as indicated by the PCR assay, and 10 phages were detected and isolated using two indicator bacterial strains. Analysis of genomic DNA showed that these phages were homologous and named as PLgT-1. Transmission electron microscopy revealed that the morphology of PLgT-1 was consistent with the virus family Siphoviridae. PCR analysis of the prophage DNA revealed that all of the S1 genotype strains were lysogenic (30/30), but none of the S16 genotype strains were lysogenic (0/30). This is the first study to investigate lysogenic bacteriophages from L. garvieae.

Hock, L., Gillis, A., and Mahillon, J. Complete Genome Sequence of Bacteriophage Deep-Blue Infecting Emetic Bacillus cereus. Genome Announc. 2016; 4(3)

ABSTRACT: The Bacillus cereus emetic pathotype is responsible for important food-borne intoxications. Here, we describe the complete genome sequence of bacteriophage Deep-Blue, which is able to infect emetic strains of B. cereus Deep-Blue is a 159-kb myophage of the Bastille-like group within the Spounavirinae.

Hong, X., Wen, J., Xiong, X., and Hu, Y. Silver nanowire-carbon fiber cloth nanocomposites synthesized by UV curing adhesive for electrochemical point-of-use water disinfection. Chemosphere. 2016; 154:537-545.

ABSTRACT: Novel silver nanowire (AgNW) - carbon fiber cloth (CC) nanocomposites were synthesized by a rapid and facile method. Acting as filter in an electrical gravity filtration device, the AgNW-CC nanocomposites were applied to electrochemical point-of-use water disinfection. AgNW-CC nanocomposites were characterized by FESEM, XRD, and FTIR. Their disinfection performance toward Escherichia coli and bacteriophage MS2 was evaluated by inhibition zone tests, optical density growth curve tests, and flow tests. The results showed that complex 3D AgNW networks with controllable silver release (<100 ppb) were fabricated on CC by using UV curing adhesive. AgNW-CC nanocomposites exhibited excellent intrinsic antibacterial activities against E. coli. The concentration of AgNWs and UV adhesive controlled the released silver and hence led to the change in antibacterial activity. The external electric field significantly enhanced the disinfection efficiency of AgNW-CC nanocomposites. Over 99.999% removal of E. coli and MS2 could be achieved. More complex AgNW networks contributed to higher disinfection efficiency under 10 V and 10(6) CFU (PFU) mL(-1) of microorganism. UV adhesive could keep the disinfection performance from being affected by flow rate. The convenient synthesis and outstanding disinfection performance offer AgNW-CC nanocomposites opportunities in the application of electrochemical point-of-use drinking water disinfection.

Hood, I. V. and Berger, J. M. Viral hijacking of a replicative helicase loader and its implications for helicase loading control and phage replication. Elife. 2016; 5

ABSTRACT: Replisome assembly requires the loading of replicative hexameric helicases onto origins by AAA+ ATPases. How loader activity is appropriately controlled remains unclear. Here, we use structural and biochemical analyses to establish how an antimicrobial phage protein interferes with the function of the Staphylococcus aureus replicative helicase loader, DnaI. The viral protein binds to the loader's AAA+ ATPase domain, allowing binding of the host replicative helicase but impeding loader self-assembly and ATPase activity. Close inspection of the complex highlights an unexpected locus for the binding of an interdomain linker element in DnaI/DnaC-family proteins. We

find that the inhibitor protein is genetically coupled to a phage-encoded homolog of the bacterial helicase loader, which we show binds to the host helicase but not to the inhibitor itself. These findings establish a new approach by which viruses can hijack host replication processes and explain how loader activity is internally regulated to prevent aberrant auto-association.

Hooton, S. P., Brathwaite, K. J., and Connerton, I. F. The Bacteriophage Carrier State of Campylobacter jejuni Features Changes in Host Non-coding RNAs and the Acquisition of New Host-derived CRISPR Spacer Sequences. Front Microbiol. 2016; 7:355

ABSTRACT: Incorporation of self-derived CRISPR DNA protospacers in Campylobacter jejuni PT14 occurs in the presence of bacteriophages encoding a CRISPR-like Cas4 protein. This phenomenon was evident in carrier state infections where both bacteriophages and host are maintained for seemingly indefinite periods as stable populations following serial passage. Carrier state cultures of C. jejuni PT14 have greater aerotolerance in nutrient limited conditions, and may have arisen as an evolutionary response to selective pressures imposed during periods in the extra-intestinal environment. A consequence of this is that bacteriophage and host remain associated and able to survive transition periods where the chances of replicative success are greatly diminished. The majority of the bacteriophage population do not commit to lytic infection, and conversely the bacterial population tolerates low-level bacteriophage replication. We recently examined the effects of Campylobacter bacteriophage/C. jejuni PT14 CRISPR spacer acquisition using deep sequencing strategies of DNA and RNA-Seq to analyze carrier state cultures. This approach identified de novo spacer acquisition in C. jejuni PT14 associated with Class III Campylobacter phages CP8/CP30A but spacer acquisition was oriented toward the capture of host DNA. In the absence of bacteriophage predation the CRISPR spacers in uninfected C. jejuni PT14 cultures remain unchanged. A distinct preference was observed for incorporation of self-derived protospacers into the third spacer position of the C. jejuni PT14 CRISPR array, with the first and second spacers remaining fixed. RNA-Seq also revealed the variation in the synthesis of non-coding RNAs with the potential to bind bacteriophage genes and/or transcript sequences.

Hsiao, V., Hori, Y., Rothemund, P. W., and Murray, R. M. A population-based temporal logic gate for timing and recording chemical events. Mol.Syst.Biol. 2016; 12(5):869

ABSTRACT: Engineered bacterial sensors have potential applications in human health monitoring, environmental chemical detection, and materials biosynthesis. While such bacterial devices have long been engineered to differentiate between combinations of inputs, their potential to process signal timing and duration has been overlooked. In this work, we present a two-input temporal logic gate that can sense and record the order of the inputs, the timing between inputs, and the duration of input pulses. Our temporal logic gate design relies on unidirectional DNA recombination mediated by bacteriophage integrases to detect and encode sequences of input events. For an E. coli strain engineered to contain our temporal logic gate, we compare predictions of Markov model simulations with laboratory measurements of final population distributions for both step and pulse inputs. Although single cells were engineered to have digital outputs, stochastic noise created heterogeneous single-cell responses that translated into analog population responses. Furthermore, when single-cell genetic states were aggregated into population-level distributions, these distributions contained unique

information not encoded in individual cells. Thus, final differentiated sub-populations could be used to deduce order, timing, and duration of transient chemical events.

Hu, Y., Yang, H., Wang, J., Zhang, Y., Yu, J., and Wei, H. Comparison between a chimeric lysin ClyH and other enzymes for extracting DNA to detect methicillin resistant Staphylococcus aureus by quantitative PCR. World J.Microbiol.Biotechnol. 2016; 32(1):1

ABSTRACT: Extracting DNA from Staphylococcus aureus cells is important for detecting MRSA by PCR. However, S. aureus cells are known to be difficult to disrupt due to their compact cell walls. Here, we systematically studied the efficiency of a highly active lysin ClyH for extracting DNA of S. aureus in comparison with commonly used enzymes, such as lysostaphin and achromopeptidase (ACP), and its compatibility in quantitative PCR (qPCR) detection of MRSA. qPCR analysis of S. aureus specific gene femB showed that ClyH was much faster than lysostaphin, ACP and lysozyme for releasing DNA. Five minutes disruption with ClyH at room temperature was enough to release all the DNA from S. aureus. Analysis of the spiked nasal swabs by a dual qPCR assay of the beta-lactam resistance mecA gene and the staphylococcal cassette chromosome (SCCmec)-open reading frame X (orfX) junction (SCCmec-orfX) after ClyH lysis showed 100% sensitivity and specificity to the commercial BD GeneOhm MRSA test with ACP lysis, but the lysis time was reduced from 20 min by ACP to 5 min by ClyH. Our research shows that ClyH could be a better option than the currently used enzymes for DNA extraction from S. aureus, which can provide simpler and faster PCR detection of MRSA.

Hung, M. E. and Leonard, J. N. A platform for actively loading cargo RNA to elucidate limiting steps in EV-mediated delivery. J.Extracell.Vesicles. 2016; 5:31027

ABSTRACT: Extracellular vesicles (EVs) mediate intercellular communication through transfer of RNA and protein between cells. Thus, understanding how cargo molecules are loaded and delivered by EVs is of central importance for elucidating the biological roles of EVs and developing EV-based therapeutics. While some motifs modulating the loading of biomolecular cargo into EVs have been elucidated, the general rules governing cargo loading and delivery remain poorly understood. To investigate how general biophysical properties impact loading and delivery of RNA by EVs, we developed a platform for actively loading engineered cargo RNAs into EVs. In our system, the MS2 bacteriophage coat protein was fused to EV-associated proteins, and the cognate MS2 stem loop was engineered into cargo RNAs. Using this Targeted and Modular EV Loading (TAMEL) approach, we identified a configuration that substantially enhanced cargo RNA loading (up to 6-fold) into EVs. When applied to vesicles expressing the vesicular stomatitis virus glycoprotein (VSVG) - gesicles - we observed a 40-fold enrichment in cargo RNA loading. While active loading of mRNA-length (>1.5 kb) cargo molecules was possible, active loading was much more efficient for smaller (~0.5 kb) RNA molecules. We next leveraged the TAMEL platform to elucidate the limiting steps in EV-mediated delivery of mRNA and protein to prostate cancer cells, as a model system. Overall, most cargo was rapidly degraded in recipient cells, despite high EV-loading efficiencies and substantial EV uptake by recipient cells. While gesicles were efficiently internalized via a VSVG-mediated mechanism, most cargo molecules were rapidly degraded. Thus, in this model system, inefficient endosomal fusion or escape likely represents a limiting barrier to EV-mediated transfer. Altogether, the TAMEL platform enabled a comparative analysis elucidating a key opportunity for enhancing EV-mediated delivery to prostate cancer cells, and this technology should be of general utility for investigations and applications of EV-mediated transfer in other systems.

Hynes, A. P., Labrie, S. J., and Moineau, S. Programming Native CRISPR Arrays for the Generation of Targeted Immunity. MBio. 2016; 7(3)

ABSTRACT: The adaptive immune system of prokaryotes, called CRISPR-Cas (clustered regularly interspaced short palindromic repeats and CRISPR-associated genes), results in specific cleavage of invading nucleic acid sequences recognized by the cell's "memory" of past encounters. Here, we exploited the properties of native CRISPR-Cas systems to program the natural "memorization" process, efficiently generating immunity not only to a bacteriophage or plasmid but to any specifically chosen DNA sequence. IMPORTANCE: CRISPR-Cas systems have entered the public consciousness as genome editing tools due to their readily programmable nature. In industrial settings, natural CRISPR-Cas immunity is already exploited to generate strains resistant to potentially disruptive viruses. However, the natural process by which bacteria acquire new target specificities (adaptation) is difficult to study and manipulate. The target against which immunity is conferred is selected stochastically. By biasing the immunization process, we offer a means to generate customized immunity, as well as provide a new tool to study adaptation.

Ikonomova, S. P., He, Z., and Karlsson, A. J. A simple and robust approach to immobilization of antibody fragments. J.Immunol.Methods. 2016; 435:7-16.

ABSTRACT: Antibody fragments, such as the single-chain variable fragment (scFv), have much potential in research and diagnostics because of their antigen-binding ability similar to a full-sized antibody and their ease of production in microorganisms. Some applications of antibody fragments require immobilization on a surface, and we have established a simple immobilization method that is based on the biotin-streptavidin interaction and does not require a separate purification step. We genetically fused two biotinylation tags-the biotin carboxyl carrier protein (BCCP) or the AviTag minimal sequence-to six different scFvs (scFv13R4, scFvD10, scFv26-10, scFv3, scFv5, and scFv12) for site-specific biotinylation in vivo by endogenous biotin ligases produced by Escherichia coli. The biotinylated scFvs were immobilized onto streptavidin-coated plates directly from cell lysates, and immobilization was detected through enzyme-linked immunosorbent assays. All scFvs fusions were successfully immobilized, and scFvs biotinylated via the BCCP tag tended to immobilize better than those biotinylated via the AviTag, even when biotinylation efficiency was improved with the biotin ligase BirA. The ability of immobilized scFvs to bind antigens was confirmed using scFv13R4 and scFvD10 with their respective targets beta-galactosidase and bacteriophage lambda head protein D (gpD). The immobilized scFv13R4 bound to beta-galactosidase at the same level for both biotinylation tags when the surface was saturated with the scFv, and immobilized scFvs retained their functionality for at least 100days after immobilization. The simplicity and robustness of our method make it a promising approach for future applications that require antibody fragment immobilization.

Ioffe, I. V. and Lesnoy, V. V. CORRECTION OF ENTERAL INSUFFICIENCY SYNDROME IN PATIENTS, SUFFERING DIFFUSE PERITONITIS. Klin.Khir. 2016; (2):15-17.

ABSTRACT: The results of treatment of 65 patients, suffering diffuse peritonitis, were analyzed. For the abdominal cavity sanation and intestinal decontamination the adopted selective bacteriophages (polyvalent pyobacteriophage, intesti-bacteriophage, and the coliproteus one) were applied. The abdominal cavity state was estimated while doing a programmed relaparotomy. Bacteriologic investigation of

exudate, excreted along nasointestinal probe, and of peritoneal exudate was conducted. The intestinal motor-evacuation function restoration was estimated in accordance to data of ultrasonographic investigation. Application of the procedure proposed have promoted earlier restoration of intestinal motor and the barrier functions, and elimination of enteral insufficiency syndrome.

Jackson, A. A., Hinkley, T. C., Talbert, J. N., Nugen, S. R., and Sela, D. A. Genetic optimization of a bacteriophage-delivered alkaline phosphatase reporter to detect Escherichia coli. Analyst. 7-14-2016;

ABSTRACT: A large fraction of foodborne illnesses are linked to (approximately 46%) leafy green vegetables contaminated by pathogens harbored in agricultural water. To prevent this, accurate point-of-production detection tools are required to identify and quantify bacterial contaminants in produce before consumers are impacted. In this study, a proof-of-concept model was engineered for a phage-based Escherichia coli detection system. We engineered the coliphage T7 to express alkaline phosphatase (ALP) to serve as the signal for E. coli detection. Wild type phoA (T7ALP) and a dominant-active allele, phoA D153G D330N (T7ALP*) was inserted into the T7 genome, with engineered constructs selected by CRISPR-mediated cleavage of unaltered chromosomes and confirmed by PCR. Engineered phages and E. coli target cells were co-incubated for 16 hours to produce lysates with liberated ALP correlated with input cell concentrations. A colorimetric assay used p-nitrophenyl phosphate (pNPP) to demonstrate significant ALP production by T7ALP and T7ALP* compared to the vector control (T7EV) (p </= 0.05). Furthermore, T7ALP* produced 2.5-fold more signal than T7ALP (p </= 0.05) at pH 10. Due to the increase in signal for the modified ALP* allele, we assessed T7ALP* sensitivity in a dose-responsive manner. We observed 3-fold higher signal for target cell populations as low as approximately 2 x 105 CFU mL-1 (p </= 0.05 vs. no-phage control).

Jakutyte-Giraitiene, L. and Gasiunas, G. Design of a CRISPR-Cas system to increase resistance of Bacillus subtilis to bacteriophage SPP1. J.Ind.Microbiol.Biotechnol. 2016; 43(8):1183-1188.

ABSTRACT: Clustered regularly interspaced short palindromic repeats (CRISPR) together with CRISPR-associated (cas) genes form an adaptive prokaryotic immune system which provides acquired resistance against viruses and plasmids. Bacillus subtilis presently is the best-characterized laboratory model for Gram-positive bacteria and also widely used for industrial production of enzymes, vitamins and antibiotics. In this study, we show that type II-A CRISPR-Cas system from Streptococcus thermophilus can be transferred into B. subtilis and provides heterologous protection against phage infection. We engineered a heterologous host by cloning S. thermophilus Cas9 and a spacer targeting bacteriophage SPP1 into the chromosome of B. subtilis, which does not harbor its own CRISPR-Cas systems. We found that the heterologous CRISPR-Cas system is functionally active in B. subtilis and provides resistance against bacteriophage SPP1 infection. The high efficiency of the acquired immunity against phage could be useful in generation of biotechnologically important B. subtilis strains with engineered chromosomes.

James, T. D., Cardozo, T., Abell, L. E., Hsieh, M. L., Jenkins, L. M., Jha, S. S., and Hinton, D. M. Visualizing the phage T4 activated transcription complex of DNA and E. coli RNA polymerase. Nucleic Acids Res. 7-25-2016;

ABSTRACT: The ability of RNA polymerase (RNAP) to select the right promoter sequence at the right time is fundamental to the control of gene expression in all organisms. However, there is only one crystallized structure of a complete activator/RNAP/DNA complex. In a process called sigma appropriation, bacteriophage T4 activates a class of phage promoters using an activator (MotA) and a co-activator (AsiA), which function through interactions with the sigma70 subunit of RNAP. We have developed a holistic, structure-based model for sigma appropriation using multiple experimentally determined 3D structures (Escherichia coli RNAP, the Thermus aquaticus RNAP/DNA complex, AsiA /sigma70 Region 4, the N-terminal domain of MotA [MotANTD], and the C-terminal domain of MotA [MotACTD]), molecular modeling, and extensive biochemical observations indicating the position of the proteins relative to each other and to the DNA. Our results visualize how AsiA/MotA redirects sigma, and therefore RNAP activity, to T4 promoter DNA, and demonstrate at a molecular level how the tactful interaction of transcriptional factors with even small segments of RNAP can alter promoter specificity. Furthermore, our model provides a rational basis for understanding how a mutation within the beta subunit of RNAP (G1249D), which is far removed from AsiA or MotA, impairs sigma appropriation.

Janner, A. Symmetry-adapted digital modeling III. Coarse-grained icosahedral viruses. Acta Crystallogr.A Found.Adv. 5-1-2016; 72(Pt 3):324-337.

ABSTRACT: Considered is the coarse-grained modeling of icosahedral viruses in terms of a three-dimensional lattice (the digital modeling lattice) selected among the projected points in space of a six-dimensional icosahedral lattice. Backbone atomic positions (Calpha's for the residues of the capsid and phosphorus atoms P for the genome nucleotides) are then indexed by their nearest lattice point. This leads to a fine-grained lattice point characterization of the full viral chains in the backbone approximation (denoted as digital modeling). Coarse-grained models then follow by a proper selection of the indexed backbone positions, where for each chain one can choose the desired coarseness. This approach is applied to three viruses, the Satellite tobacco mosaic virus, the bacteriophage MS2 and the Pariacoto virus, on the basis of structural data from the Brookhaven Protein Data Bank. In each case the various stages of the procedure are illustrated for a given coarse-grained model and the corresponding indexed positions are listed. Alternative coarse-grained models have been derived and compared. Comments on related results and approaches, found among the very large set of publications in this field, conclude this article.

Jeon, J., Ryu, C. M., Lee, J. Y., Park, J. H., Yong, D., and Lee, K. In Vivo Application of Bacteriophage as a Potential Therapeutic Agent To Control OXA-66-Like Carbapenemase-Producing Acinetobacter baumannii Strains Belonging to Sequence Type 357. Appl.Environ.Microbiol. 7-15-2016; 82(14):4200-4208.

ABSTRACT: The increasing prevalence of carbapenem-resistant Acinetobacter baumannii (CRAB) strains in intensive care units has caused major problems in public health worldwide. Our aim was to determine whether this phage could be used as an alternative therapeutic agent against multidrug-resistant bacterial strains, specifically CRAB clinical isolates, using a mouse model. Ten bacteriophages that caused lysis in CRAB strains, including blaOXA-66-like genes, were isolated. YMC13/01/C62 ABA BP (phage Bvarphi-C62), which showed the strongest lysis activity, was chosen for further

study by transmission electron microscopy (TEM), host range test, one-step growth and phage adsorption rate, thermal and pH stability, bacteriolytic activity test, genome sequencing and bioinformatics analysis, and therapeutic effect of phage using a mouse intranasal infection model. The phage Bvarphi-C62 displayed high stability at various temperatures and pH values and strong cell lysis activity in vitro The phage Bvarphi-C62 genome has a double-stranded linear DNA with a length of 44,844 bp, and known virulence genes were not identified in silico. In vivo study showed that all mice treated with phage Bvarphi-C62 survived after intranasal bacterial challenge. Bacterial clearance in the lung was observed within 3 days after bacterial challenge, and histologic damage also improved significantly; moreover, no side effects were observed. IMPORTANCE: In our study, the novel A. baumannii phage Bvarphi-C62 was characterized and evaluated in vitro, in silico, and in vivo These results, including strong lytic activities and the improvement of survival rates, showed the therapeutic potential of the phage Bvarphi-C62 as an antimicrobial agent. This study reports the potential of a novel phage as a therapeutic candidate or nontoxic disinfectant against CRAB clinical isolates in vitro and in vivo.

Ji, Z., Wang, S., Zhao, Z., Zhou, Z., Haque, F., and Guo, P. Fingerprinting of Peptides with a Large Channel of Bacteriophage Phi29 DNA Packaging Motor. Small. 7-20-2016;

ABSTRACT: Nanopore technology has become a highly sensitive and powerful tool for single molecule sensing of chemicals and biopolymers. Protein pores have the advantages of size amenability, channel homogeneity, and fabrication reproducibility. But most well-studied protein pores for sensing are too small for passage of peptide analytes that are typically a few nanometers in dimension. The funnel-shaped channel of bacteriophage phi29 DNA packaging motor has previously been inserted into a lipid membrane to serve as a larger pore with a narrowest N-terminal constriction of 3.6 nm and a wider C-terminal end of 6 nm. Here, the utility of phi29 motor channel for fingerprinting of various peptides using single molecule electrophysiological assays is reported. The translocation of peptides is proved unequivocally by single molecule fluorescence imaging. Current blockage percentage and distinctive current signatures are used to distinguish peptides with high confidence. Each peptide generated one or two distinct current blockage peaks, serving as typical fingerprint for each peptide. The oligomeric states of peptides can also be studied in real time at single molecule level. The results demonstrate the potential for further development of phi29 motor channel for detection of disease-associated peptide biomarkers.

Jiang, X., Pan, M., Hering, S. V., Lednicky, J., Wu, C. Y., and Fan, Z. H. Use of RNA Amplification and Electrophoresis for Studying Virus Aerosol Collection Efficiency and Their Comparison with Plaque Assays. Electrophoresis. 5-16-2016;

ABSTRACT: The spread of virus-induced infectious diseases through airborne routes of transmission is a global concern for economic and medical reasons. To study virus transmission, it is essential to have an effective aerosol collector such as the growth tube collector (GTC) system that utilizes water-based condensation for collecting virus-containing aerosols. In this work we characterized the GTC system using bacteriophage MS2 as a surrogate for a small RNA virus. We investigated using RNA extraction and reverse-transcriptase polymerase chain reaction (RT-PCR) to study the total virus collection efficiency of the GTC system. We also used a plaque assay (culturing collected virus samples) to characterize the GTC system and compared GTC with a

commercially available apparatus SKC(R) Biosampler. The plaque assay reports only viable viruses collected whereas RT-PCR analyzes total viruses, including those viruses inactivated during collection. The effects of relative humidity (RH) and other conditions on collection efficiency were also investigated. Our results suggest that GTC has collection efficiency of viable viruses between 0.24 - 1.8% and total collection efficiency between 18.3 - 79.0%, which is 1 - 2 orders of magnitude higher than SKC(R) Biosampler. Moreover, higher RH significantly increases both of the viable and total collection efficiency of GTC while its effect on the collection efficiency of SKC(R) Biosampler is not significant. This article is protected by copyright. All rights reserved.

Jing, P., Burris, B., and Zhang, R. Forces from the Portal Govern the Late-Stage DNA Transport in a Viral DNA Packaging Nanomotor. Biophys.J. 7-12-2016; 111(1):162-177.

ABSTRACT: In the Phi29 bacteriophage, the DNA packaging nanomotor packs its double-stranded DNA genome into the virus capsid. At the late stage of DNA packaging, the negatively charged genome is increasingly compacted at a higher density in the capsid with a higher internal pressure. During the process, two Donnan effects, osmotic pressure and Donnan equilibrium potentials, are significantly amplified, which, in turn, affect the channel activity of the portal protein, GP10, embedded in the semipermeable capsid shell. In the research, planar lipid bilayer experiments were used to study the channel activities of the viral protein. The Donnan effect on the conformational changes of the viral protein was discovered, indicating GP10 may not be a static channel at the late stage of DNA packaging. Due to the conformational changes, GP10 may generate electrostatic forces that govern the DNA transport. For the section of the genome DNA that remains outside of the connector channel, a strong repulsive force from the viral protein would be generated against the DNA entry; however, for the section of the genome DNA within the channel, the portal protein would become a Brownian motor, which adopts the flash Brownian ratchet mechanism to pump the DNA against the increasingly built-up internal pressure (up to 20 atm) in the capsid. Therefore, the DNA transport in the nanoscale viral channel at the late stage of DNA packaging could be a consequence of Brownian movement of the genomic DNA, which would be rectified and harnessed by the forces from the interior wall of the viral channel under the influence of the Donnan effect.

Julliand, V. and Grimm, P. HORSE SPECIES SYMPOSIUM: The microbiome of the horse hindgut: History and current knowledge. J.Anim Sci. 2016; 94(6):2262-2274.

ABSTRACT: In the early 1990s, the equine hindgut microbial ecosystem looked like a "black box." Its vital role in hydrolyzing and fermenting fiber, thus providing energy to the host, was recognized. Although there was a critical lack of information on the hindgut microbes, their role in preventing intestinal diseases was suggested. Traditionally, the microbes of the horse hindgut were studied using culture-dependent techniques. More recently, culture-independent methods have been used and provided further insight. This review presents the history and updated knowledge regarding the microbes that live inside the different intestinal ecosystems and which collective genomes compose the hindgut microbiome. In the first section, the quantification and diversity are described for each microbial community as well as the implication of plant fiber degradation and their crucial role for an herbivore host. The microbial communities are presented in chronological order of discovery: due to their large size, protozoa were brought to light as early as 1843 in the horse cecum; in 1897, bacteria were described in the horse

intestine; as early as 1910, monoflagellated eukaryotic organisms resembling protozoa were observed in the horse cecum; since then, they have been identified to be zoospores of anaerobic fungi; in 1970, bacteriophage-like particles were recognized in the cecum and colon of pony and horse; and finally, in 1996, archaea were identified in the horse cecum. The second section discusses the variations that can occur between digestive segments or between individuals. The representativeness of the fecal microbiota to the hindgut one is debated, especially as the majority of recent studies conducted on the horse hindgut are in fact focused on the feces, rather than the cecum or colon. Also, the representation of microbiota between individuals is questioned. It has long been suggested in the literature that some ponies or horses that were more susceptible to intestinal diseases may harbor a specific intestinal microbiota. Alternatively, some new studies aim at identifying a core microbiome between all individual equine. A deeper knowledge of the microbiome and its core may allow improvement of nutrition and health, understanding of the onset of digestive diseases, and the development tools for health monitoring and disease prevention.

Kang, I., Kang, D., and Cho, J. C. Complete genome sequence of bacteriophage P2559Y, a marine phage that infects Croceibacter atlanticus HTCC2559. Mar.Genomics. 7-7-2016;

ABSTRACT: The genus Croceibacter of the family Flavobacteriaceae represents a ubiquitous component of marine bacterioplankton, and is known to be involved in the interaction with phytoplankton. Here, we report the isolation and genome sequencing of a lytic siphovirus P2559Y that infects Croceibacter atlanticus HTCC2559, the type strain of the genus Croceibacter. The complete genome of P2559Y was 43,153bp in length, with a GC content of 38.9%. Functional annotation of 51 genes predicted in the genome showed that the P2559Y genome had a modular architecture. Comparison to the genome of P2559S, another phage that infects the same host strain, revealed an interesting feature in the genetic diversity of phages infecting the genus Croceibacter. The two phage genomes had a synteny in the structure module and shared many structural genes, while little similarity was found in the DNA replication/metabolism module.

Kanwar, N., Roberts, G. A., Cooper, L. P., Stephanou, A. S., and Dryden, D. T. The evolutionary pathway from a biologically inactive polypeptide sequence to a folded, active structural mimic of DNA. Nucleic Acids Res. 5-19-2016; 44(9):4289-4303.

ABSTRACT: The protein Ocr (overcome classical restriction) from bacteriophage T7 acts as a mimic of DNA and inhibits all Type I restriction/modification (RM) enzymes. Ocr is a homodimer of 116 amino acids and adopts an elongated structure that resembles the shape of a bent 24 bp DNA molecule. Each monomer includes 34 acidic residues and only six basic residues. We have delineated the mimicry of Ocr by focusing on the electrostatic contribution of its negatively charged amino acids using directed evolution of a synthetic form of Ocr, termed pocr, in which all of the 34 acidic residues were substituted for a neutral amino acid. In vivo analyses confirmed that pocr did not display any antirestriction activity. Here, we have subjected the gene encoding pocr to several rounds of directed evolution in which codons for the corresponding acidic residues found in Ocr were specifically re-introduced. An in vivo selection assay was used to detect antirestriction activity after each round of mutation. Our results demonstrate the variation in importance of the acidic residues in regions of Ocr corresponding to different

parts of the DNA target which it is mimicking and for the avoidance of deleterious effects on the growth of the host.

Keifer, D. Z., Motwani, T., Teschke, C. M., and Jarrold, M. F. Measurement of the accurate mass of a 50 MDa infectious virus. Rapid Commun.Mass Spectrom. 9-15-2016; 30(17):1957-1962.

ABSTRACT: RATIONALE: Bacteriophage P22 is believed to contain a total of 521 copies of 9 different proteins and a 41,724 base pair genome. Despite its enormous size and complexity, phage P22 can be electrosprayed, and it remains intact in ultra-high vacuum where its molar mass distribution has been measured. METHODS: Phage P22 virions were generated by complementation in Salmonella enterica and purified. They were transferred into 100 mM ammonium acetate and then electrosprayed. The masses of individual virions were determined using charge detection mass spectrometry. RESULTS: The stoichiometry of the protein components of phage P22 is sufficiently well known that the theoretical molar mass can be determined to within a narrow range. The measured average molar mass of phage P22, 52,180 +/- 59 kDa, is consistent with the theoretical molar mass and supports the proposed stoichiometry of the components. The intrinsic width of the phage P22 mass distribution can be accounted for by the distribution of DNA packaged by the headful mechanism. CONCLUSIONS: At over 50 MDa, phage P22 is the largest object with a well-defined molar mass to be analyzed by mass spectrometry. The narrow measured mass distribution indicates that the virions survive the transition into the gas phase intact. Copyright (c) 2016 John Wiley & Sons, Ltd.

Khan, Mirzaei M., Haileselassie, Y., Navis, M., Cooper, C., Sverremark-Ekstrom, E., and Nilsson, A. S. Morphologically Distinct Escherichia coli Bacteriophages Differ in Their Efficacy and Ability to Stimulate Cytokine Release In Vitro. Front Microbiol. 2016; 7:437

ABSTRACT: Due to a global increase in the range and number of infections caused by multi-resistant bacteria, phage therapy is currently experiencing a resurgence of interest. However, there are a number of well-known concerns over the use of phages to treat bacterial infections. In order to address concerns over safety and the poorly understood pharmacokinetics of phages and their associated cocktails, immunological characterization is required. In the current investigation, the immunogenicity of four distinct phages (taken from the main families that comprise the Caudovirales order) and their interaction with donor derived peripheral blood mononuclear cells and immortalized cell lines (HT-29 and Caco-2 intestinal epithelial cells) were investigated using standard immunological techniques. When exposed to high phage concentrations (10(9) PFU/well), cytokine driven inflammatory responses were induced from all cell types. Although phages appeared to inhibit the growth of intestinal epithelial cell lines, they also appear to be non-cytotoxic. Despite co-incubation with different cell types, phages maintained a high killing efficiency, reducing extended-spectrum beta-lactamase-producing Escherichia coli numbers by 1-4 log10 compared to untreated controls. When provided with a suitable bacterial host, phages were also able to actively reproduce in the presence of human cells resulting in an approximately 2 log10 increase in phage titer compared to the initial inoculum. Through an increased understanding of the complex pharmacokinetics of phages, it may be possible to address some of the safety concerns surrounding phage preparations prior to creating new therapeutic strategies.

Khawaja, K. A., Rauf, M., Abbas, Z., and Rehman, S. U. A virulent phage JHP against Pseudomonas aeruginosa showed infectivity against multiple genera. J.Basic Microbiol. 4-23-2016;

ABSTRACT: The resistance to antibiotics in clinically important bacteria is one of the major global health concerns. Phage therapy could be one reliable alternative therapeutic strategy to combat these superbugs. In this study, we assessed host range of a novel bacteriophage, JHP, and characterized for its potential use in phage therapy. The bacteriophage demonstrated infectivity over a broad range of genera including multidrug resistant clinical isolates of Pseudomonas aeruginosa, members of family Enterobacteracae, and other important human pathogens. The antibacterial activity was highest at pH 7, and at temperature of 37 degrees C. The phage lytic activity gradually decreased till 60 degrees C and showed no activity when temperature was further raised. The bacteriophage could safely be stored at 4 degrees C or -20 degrees C. The latent period of the bacteriophage was 25 min and showed a burst size of 433 virions per cell. The size of JHP genome was approximately 30 kb. Family, Siphoviridae was assigned to JHP based on its icosahedral head with non-contractile tail. The diameter of JHP head and tail length was found 115 and 152 nm, respectively. To sum up, the broad spectrum Siphoviridae phage JHP is an ingenious candidate for phage therapy.

Kim, J. S., Hosseindoust, A., Lee, S. H., Choi, Y. H., Kim, M. J., Lee, J. H., Kwon, I. K., and Chae, B. J. Bacteriophage cocktail and multi-strain probiotics in the feed for weanling pigs: effects on intestine morphology and targeted intestinal coliforms and Clostridium. Animal. 6-29-2016; 1-9.

ABSTRACT: Two experiments were conducted to investigate the effects of dietary supplementation of bacteriophage cocktail, probiotics and a combination of these two supplements on performance and gut health of weanling pigs. In Experiment 1, 150 weaned piglets were randomly allotted to three treatments on the basis of BW. The dietary treatments included a basal diet supplemented with 0 (control), 1.0 and 1.5 g/kg bacteriophage cocktail. Pigs fed 1.0 and 1.5 g/kg bacteriophage product had greater ($P<0.05$) average daily gain (ADG), apparent total tract digestibility of dry matter from day 22 to 35, ileal Lactobacillus spp., villus height (duodenum and jejunum), and fewer coliforms (ileum) and Clostridium spp. (ileum). In Experiment 2, 200 weaned piglets were randomly allotted to four treatments. Dietary treatments included basal diet, basal diet supplemented with 3.0 g/kg fermented probiotic product (P), 1.0 g/kg bacteriophage cocktail (B) and combination of 1.0 g/kg bacteriophage cocktail and 3.0 g/kg fermented probiotic product. Pigs fed bacteriophage cocktail diets had greater ($P<0.05$) overall ADG, gain to feed ratio (G : F), fecal score from day 8 to day 21, and pigs fed bacteriophage cocktail diets had fewer coliforms (ileum) Clostridium spp. (ileum and cecum). Probiotics significantly increased G : F, colonization of Lactobacillus spp. in ileum. At day 35, bacteriophage treatment group showed greater ($P<0.05$) villus height of the duodenum, but a deeper crypt in duodenum. The present results indicate that the bacteriophage cocktail had a potential to enhance the performance and gut health of weanling pigs, however their combination with probiotics did not show an interaction.

Kim, M., Kim, H. J., Son, S. H., Yoon, H. J., Lim, Y., Lee, J. W., Seok, Y. J., Jin, K. S., Yu, Y. G., Kim, S. K., Ryu, S., and Lee, H. H. Noncanonical DNA-binding mode of repressor and its disassembly by antirepressor. Proc.Natl.Acad.Sci.U.S.A. 5-3-2016; 113(18):E2480-E2488.

ABSTRACT: DNA-binding repressors are involved in transcriptional repression in many organisms. Disabling a repressor is a crucial step in activating expression of desired genes. Thus, several mechanisms have been identified for the removal of a stably bound repressor (Rep) from the operator. Here, we describe an uncharacterized mechanism of noncanonical DNA binding and induction by a Rep from the temperate Salmonella phage SPC32H; this mechanism was revealed using the crystal structures of homotetrameric Rep (92-198) and a hetero-octameric complex between the Rep and its antirepressor (Ant). The canonical method of inactivating a repressor is through the competitive binding of the antirepressor to the operator-binding site of the repressor; however, these studies revealed several noncanonical features. First, Ant does not compete for the DNA-binding region of Rep. Instead, the tetrameric Ant binds to the C-terminal domains of two asymmetric Rep dimers. Simultaneously, Ant facilitates the binding of the Rep N-terminal domains to Ant, resulting in the release of two Rep dimers from the bound DNA. Second, the dimer pairs of the N-terminal DNA-binding domains originate from different dimers of a Rep tetramer (trans model). This situation is different from that of other canonical Reps, in which two N-terminal DNA-binding domains from the same dimeric unit form a dimer upon DNA binding (cis model). On the basis of these observations, we propose a noncanonical model for the reversible inactivation of a Rep by an Ant.

Kim, W. G., Song, H., Kim, C., Moon, J. S., Kim, K., Lee, S. W., and Oh, J. W. Biomimetic self-templating optical structures fabricated by genetically engineered M13 bacteriophage. Biosens.Bioelectron. 6-2-2016; 85:853-859.

ABSTRACT: Here, we describe a highly sensitive and selective surface plasmon resonance sensor system by utilizing self-assembly of genetically engineered M13 bacteriophage. About 2700 copies of genetically expressed peptide copies give superior selectivity and sensitivity to M13 phage-based SPR sensor. Furthermore, the sensitivity of the M13 phage-based SPR sensor was enhanced due to the aligning of receptor matrix in specific direction. Incorporation of specific binding peptide (His Pro Gln: HPQ) gives M13 bacteriophage high selectivity for the streptavidin. Our M13 phage-based SPR sensor takes advantage of simplicity of self-assembly compared with relatively complex photolithography techniques or chemical conjugations. Additionally, designed structure which is composed of functionalized M13 bacteriophage can simultaneously improve the sensitivity and selectivity of SPR sensor evidently. By taking advantages of the genetic engineering and self-assembly, we propose the simple method for fabricating novel M13 phage-based SPR sensor system which has a high sensitivity and high selectivity.

Konevtsova, O. V., Lorman, V. L., and Rochal, S. B. Theory of morphological transformation of viral capsid shell during the maturation process in the HK97 bacteriophage and similar viruses. Phys.Rev.E. 2016; 93(5-1):052412

ABSTRACT: We consider the symmetry and physical origin of collective displacement modes playing a crucial role in the morphological transformation during the maturation of the HK97 bacteriophage and similar viruses. It is shown that the experimentally observed hexamer deformation and pentamer twist in the HK97 procapsid correspond to the simplest irreducible shear strain mode of a spherical shell. We also show that the icosahedral faceting of the bacteriophage capsid shell is driven by the simplest irreducible radial displacement field. The shear field has the rotational icosahedral

symmetry group I while the radial field has the full icosahedral symmetry I_{h}. This difference makes their actions independent. The radial field sign discriminates between the icosahedral and the dodecahedral shapes of the faceted capsid shell, thus making the approach relevant not only for the HK97-like viruses but also for the parvovirus family. In the frame of the Landau-Ginzburg formalism we propose a simple phenomenological model valid for the first reversible step of the HK97 maturation process. The calculated phase diagram illustrates the discontinuous character of the virus shape transformation. The characteristics of the virus shell faceting and expansion obtained in the in vitro and in vivo experiments are related to the decrease in the capsid shell thickness and to the increase of the internal capsid pressure.

Kot, W., Kilstrup, M., Vogensen, F. K., and Hammer, K. Clear Plaque Mutants of Lactococcal Phage TP901-1. PLoS.One. 2016; 11(6):e0155233

ABSTRACT: We report a method for obtaining turbid plaques of the lactococcal bacteriophage TP901-1 and its derivative TP901-BC1034. We have further used the method to isolate clear plaque mutants of this phage. Analysis of 8 such mutants that were unable to lysogenize the host included whole genome resequencing. Four of the mutants had different mutations in structural genes with no relation to the genetic switch. However all 8 mutants had a mutation in the cI repressor gene region. Three of these were located in the promoter and Shine-Dalgarno sequences and five in the N-terminal part of the encoded CI protein involved in the DNA binding. The conclusion is that cI is the only gene involved in clear plaque formation i.e. the CI protein is the determining factor for the lysogenic pathway and its maintenance in the lactococcal phage TP901-1.

Kulczyk, A. W. and Richardson, C. C. The Replication System of Bacteriophage T7. Enzymes. 2016; 39:89-136.

ABSTRACT: The replication system of bacteriophage T7 is remarkable in that the 40,000 nucleotide genome is replicated over 100-fold in a matter of minutes. In order to accomplish this feat T7 has evolved an efficient and economical process for the replication of its DNA. The T7 replisome provides a model system to study DNA replication. Four proteins are sufficient for reconstitution of the functional replication complex, yet the assembled replisome recapitulates all the key features of more complex prokaryotic and eukaryotic systems. In this review, we describe chemical mechanisms employed by individual proteins at the replication fork. Integration of structural, biochemical, and single-molecule data reveals a compelling view on how a nearly 1-MDa molecular machine acts as a unit to synthetize the two antiparallel DNA strands in a coordinated fashion.

Kurtboke, D. I., Palk, A., Marker, A., Neuman, C., Moss, L., Streeter, K., and Katouli, M. Isolation and characterization of Enterobacteriaceae species infesting post-harvest strawberries and their biological control using bacteriophages. Appl.Microbiol.Biotechnol. 6-29-2016;

ABSTRACT: Strawberry is a significantly consumed fruit worldwide, mostly without being subjected to disinfection processes. During the harvest and transfer from farm to consumers as well as where organic farming practises have been employed, the surface of the fruit may become contaminated by pathogenic bacteria. Post-harvest strawberry fruits in punnets available for public consumption were thus screened for the presence of

enteric bacteria in the Sunshine Coast region of Queensland, Australia. Some of the tested samples (13 %) were found to carry such bacteria and even in greater numbers if organic amendments were used (69 %). The bacteria were found to belong in the genera of Escherichia, Enterobacter, Raoultella, Klebsiella, Pantoea, Shigella, Citrobacter and Cronobacter within the family Enterobacteriaceae. Some of the isolates were found to adhere to Caco-2 cells representing human gut epithelium as well as carrying virulence and toxin genes. Resistance mostly against sulphafurazole, cefoxitin, ampicillin and nitrofurantoin was found among 14 different antimicrobial agents tested including 100 % resistance to cefoxitin and ampicillin in the genus Pantoea. In the second phase of the study, bacteriophages were isolated against the isolates and were subsequently applied to post-harvest fruits. A significant (P </= 0.001) reduction in the number of enteric bacteria was observed when a high-titre polyvalent bacteriophage suspension (x1012 PFU/mL) was applied to the fruit surface. Bacteriophages also decreased the adhesion of the Escherichia coli isolates to Caco-2 cells. Findings might indicate that biological control using bacteriophages might be of significant value for the industry targeting to reduce pathogenic loads of bacteria on the fruit.

Kutyshenko, V. P., Mikoulinskaia, G. V., Molochkov, N. V., Prokhorov, D. A., Taran, S. A., and Uversky, V. N. Structure and dynamics of the retro-form of the bacteriophage T5 endolysin. Biochim.Biophys.Acta. 7-1-2016; 1864(10):1281-1291.

ABSTRACT: Using high-resolution NMR spectroscopy we conducted a comparative analysis of the structural and dynamic properties of the bacteriophage T5 endolysin (EndoT5) and its retro-form; i.e., a protein with the reversed direction of the polypeptide chain (R-EndoT5). We show that structurally, retro-form can be described as the molten globule-like polypeptide that is easily able to form large oligomers and aggregates. To avoid complications associated with this high aggregation propensity of the retro protein, we compared EndoT5 and R-EndoT5 in the presence of strong denaturants. This analysis revealed that these two proteins possess different internal dynamics in solutions containing 8M urea, with the retro-form being characterized by larger dimensions and slower internal dynamics. We also show that in the absence of denaturant, both forms of the bacteriophage T5 endolysin are able to interact with micelles formed by the zwitterionic detergent dodecylphosphocholine (DPC), and that the formation of the protein-micelle complexes leads to the significant structural rearrangement of polypeptide chain and to the formation of stable hydrophobic core in the R-Endo T5.

Kutyshenko, V. P., Prokhorov, D. A., Mikoulinskaia, G. V., Molochkov, N. V., Paskevich, S. I., and Uversky, V. N. Evidence for the residual tertiary structure in the urea-unfolded form of bacteriophage T5 endolysin. J.Biomol.Struct.Dyn. 5-20-2016; 1-8.

ABSTRACT: Using high-resolution NMR spectroscopy, we studied peculiarities of the unfolding process of the bacteriophage T5 endolysin (EndoT5) by strong denaturants. It was shown that in the absence of zinc ions this protein is mostly unfolded in the solution of 8 M urea or 6 M guanidine hydrochloride. However, in the presence of zinc ions EndoT5 unfolding can be achieved only in acidic solutions (at pH < 4.0), whereas at pH > 4.0 NMR spectra of the metal-bound protein (Zn2+-Ca2+-EndoT5 or Zn2+-EndoT5 complexes) exhibit a few chemical shifts characteristic of the native or native-like proteins. Our data, including the pH-titration curve with the pK of ~5, suggested involvement of the zinc-binding histidines in the stabilization of this protein. Up-field signals that appear in the NMR spectra of apo-EndoT5 in the presence of high concentrations of strong

denaturants are probably derived from the amino acid residues included in the formation of structured hydrophobic cluster, which likely corresponds to the 81-93 region of EndoT5 and contains some residual tertiary structure. It is possible also that this hydrophobic fragment serves as a foundation for the formation of structured cluster in the unfolded state.

Kyrillos, A., Arora, G., Murray, B., and Rosenwald, A. G. The Presence of Phage Orthologous Genes in Helicobacter pylori Correlates with the Presence of the Virulence Factors CagA and VacA. Helicobacter. 2016; 21(3):226-233.

ABSTRACT: BACKGROUND: The bacterium Helicobacter pylori is associated with ulcers and the development of gastric cancer. Several genes, including cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), are associated with increased gastric cancer risk. Some strains of H. pylori also contain sequences related to bacteriophage phiHP33; however, the significance of these phage-related sequences remains unknown. MATERIALS AND METHODS: We assessed the extent to which phiHP33-related sequences are present in 335 H. pylori strains using homology searches then mapped shared genes between phiHP33 and H. pylori strains onto an existing phylogeny. RESULTS: One hundred and twenty-one H. pylori strains contain phage orthologous sequences, and the presence of the phage-related sequences correlates with the presence of CagA and VacA. Mapping of the phage orthologs onto a phylogeny of H. pylori is consistent with the hypothesis that these genes were acquired by horizontal gene transfer. CONCLUSIONS: phiHP33 phage orthologous sequences might be of significance in understanding virulence of different H. pylori strains.

LaCasse, D., Lute, S., Fiadeiro, M., Basha, J., Stork, M., Brorson, K., Godavarti, R., and Gallo, C. Mechanistic Failure Mode Investigation and Resolution of Parvovirus Retentive Filters. Biotechnol.Prog. 5-10-2016;

ABSTRACT: Virus retentive filters are a key product safety measure for biopharmaceuticals. A simplistic perception is that they function solely based on a size-based particle removal mechanism of mechanical sieving and retention of particles based on their hydrodynamic size. Recent observations have revealed a more nuanced picture, indicating that changes in viral particle retention can result from process pressure and/or flow interruptions. In this study, a mechanistic investigation was performed to help identify a potential mechanism leading to the reported reduced particle retention in small virus filters. Permeate flow rate or permeate driving force were varied and analyzed for their impact on particle retention in three commercially available small virus retentive filters. This article is protected by copyright. All rights reserved.

Ladero, V., Gomez-Sordo, C., Sanchez-Llana, E., Del, Rio B., Redruello, B., Fernandez, M., Martin, M. C., and Alvarez, M. A. Q69 (an E. faecalis-Infecting Bacteriophage) As a Biocontrol Agent for Reducing Tyramine in Dairy Products. Front Microbiol. 2016; 7:445

ABSTRACT: Biogenic amines (BAs) are low molecular weight nitrogenous compounds with biological activity, formed from amino acids by decarboxylation. BAs are naturally present in all living organisms playing essential roles. However, their accumulation in food through the metabolic activity of certain microorganisms constitutes a toxicological

hazard. Among foods, cheeses accumulate some of the highest concentrations of BAs since they provide an ideal environment for their accumulation. Most of the methods proposed for reducing BAs in cheese, such as milk pasteurization, have not only failed to completely solve the problem, they also affect non-BA producing lactic acid bacteria, i.e., the bacteria that participate in the development of the organoleptic characteristics of cheese. Novel technologies specifically targeted against BA producers are therefore needed to control BA accumulation. Bacteriophages have been proposed as agents for specifically controlling the presence of foodborne pathogens in food. Due to its specificity, they could be used as a biotechnological tool targeted to reduce the population of BA-producing bacteria. The present work reports the isolation, from cheese, and the characterization of bacteriophage Q69, which infects specifically Enterococcus faecalis, the species mainly responsible of the accumulation of the BA tyramine in foods. Furthermore, its capacity to reduce the accumulation of tyramine in different conditions -including a model cheese- was proven. The obtained results open up the possibility of use bacteriophages to prevent BA accumulation in fermented foods.

L**amine, J. G., DeJong, R. J., and Nelesen, S. M. PhamDB: a web-based application for building Phamerator databases. Bioinformatics. 7-1-2016; 32(13):2026-2028.**

ABSTRACT: PhamDB is a web application which creates databases of bacteriophage genes, grouped by gene similarity. It is backwards compatible with the existing Phamerator desktop software while providing an improved database creation workflow. Key features include a graphical user interface, validation of uploaded GenBank files, and abilities to import phages from existing databases, modify existing databases and queue multiple jobs. AVAILABILITY AND IMPLEMENTATION: Source code and installation instructions for Linux, Windows and Mac OSX are freely available at https://github.com/jglamine/phage PhamDB is also distributed as a docker image which can be managed via Kitematic. This docker image contains the application and all third party software dependencies as a pre-configured system, and is freely available via the installation instructions provided. CONTACT: snelesen@calvin.edu.

Latz, S., Wahida, A., Arif, A., Hafner, H., Hoss, M., Ritter, K., and Horz, H. P. Preliminary survey of local bacteriophages with lytic activity against multi-drug resistant bacteria. J.Basic Microbiol. 5-19-2016;

ABSTRACT: Bacteriophages (phages) represent a potential alternative for combating multi-drug resistant bacteria. Because of their narrow host range and the ever emergence of novel pathogen variants the continued search for phages is a prerequisite for optimal treatment of bacterial infections. Here we performed an ad hoc survey in the surroundings of a University hospital for the presence of phages with therapeutic potential. To this end, 16 aquatic samples of different origins and locations were tested simultaneously for the presence of phages with lytic activity against five current, but distinct strains each from the ESKAPE-group (i.e., Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter cloacae). Phages could be isolated for 70% of strains, covering all bacterial species except S. aureus. Apart from samples from two lakes, freshwater samples were largely devoid of phages. By contrast, one liter of hospital effluent collected at a single time point already contained phages active against two-thirds of tested strains. In conclusion, phages with lytic activity against nosocomial pathogens are

unevenly distributed across environments with the prime source being the immediate hospital vicinity.

Lavrenova, G. V., Nesterova, K. I., Yaremenko, K. V., and Nesterova, A. A. [The rationale for the conservative treatment of chronic tonsillitis in the patients of the older age groups by the <<soft>> therapy methods]. Vestn.Otorinolaringol. 2016; 81(4):22-26.

ABSTRACT: The objective of the present study was to develop an efficient system for the treatment of chronic tonsillitis in the patients of advanced and middle age based on the application of polyvalent bacteriophages in the combination with the physical factors and herbal medicines. The study involved 65 patients (39 women and 276 men) at the age from 65 to 73 years presenting with chronic tonsillitis. The treatment included washing the tonsillar lacunae with herbal infusion consisting of a tetterwort (Choledoniummajus) extract. This procedure was followed by phonophoresiswith the use of the combined polyvalent bacteriophage preparation in the non-liquid formulation during 7-10 days. The effectiveness of such treatment was evaluated based on the results of clinical examination and the analysis of the subjective feelings reported by the patients. In addition, the rosette-forming function of lymphocytes was estimated and palatine tonsil microbiotas in different patients were compared. The effectiveness of therapy was estimated at 89.2%. The positive outcome of the proposed treatment was documented in 78.6% of the cases within 6 months after the onset of therapy. It is concluded that the treatment of chronic tonsillitis with bacteriophagal preparations and herbal infusions in combination with thetraditionallow-frequency ultrasound treatment is highly efficacious (favourable outcome in 78.6% of the patients of middle and advanced age) without the use of antibiotic medications.

Lavysh, D., Sokolova, M., Minakhin, L., Yakunina, M., Artamonova, T., Kozyavkin, S., Makarova, K. S., Koonin, E. V., and Severinov, K. The genome of AR9, a giant transducing Bacillus phage encoding two multisubunit RNA polymerases. Virology. 2016; 495:185-196.

ABSTRACT: Bacteriophage AR9 and its close relative PBS1 have been extensively used to construct early Bacillus subtilis genetic maps. Here, we present the 251,042bp AR9 genome, a linear, terminally redundant double-stranded DNA containing deoxyuridine instead of thymine. Multiple AR9 genes are interrupted by non-coding sequences or sequences encoding putative endonucleases. We show that these sequences are group I and group II self-splicing introns. Eight AR9 proteins are homologous to fragments of bacterial RNA polymerase (RNAP) subunits beta/beta'. These proteins comprise two sets of paralogs of RNAP largest subunits, with each paralog encoded by two disjoint phage genes. Thus, AR9 is a phiKZ-related giant phage that relies on two multisubunit viral RNAPs to transcribe its genome independently of host transcription apparatus. Purification of one of PBS1/AR9 RNAPs has been reported previously, which makes AR9 a promising object for further studies of RNAP evolution, assembly and mechanism.

Laxmikanthan, G., Xu, C., Brilot, A. F., Warren, D., Steele, L., Seah, N., Tong, W., Grigorieff, N., Landy, A., and Van Duyne, G. D. Structure of a Holliday junction complex reveals mechanisms governing a highly regulated DNA transaction. Elife. 2016; 5

ABSTRACT: The molecular machinery responsible for DNA expression, recombination, and compaction has been difficult to visualize as functionally complete entities due to their

combinatorial and structural complexity. We report here the structure of the intact functional assembly responsible for regulating and executing a site-specific DNA recombination reaction. The assembly is a 240-bp Holliday junction (HJ) bound specifically by 11 protein subunits. This higher-order complex is a key intermediate in the tightly regulated pathway for the excision of bacteriophage lambda viral DNA out of the E. coli host chromosome, an extensively studied paradigmatic model system for the regulated rearrangement of DNA. Our results provide a structural basis for pre-existing data describing the excisive and integrative recombination pathways, and they help explain their regulation.

Lee, C. Y., Kim, S. J., Park, B. C., and Han, J. H. Effects of dietary supplementation of bacteriophages against enterotoxigenic Escherichia coli (ETEC) K88 on clinical symptoms of post-weaning pigs challenged with the ETEC pathogen. J.Anim Physiol Anim Nutr.(Berl). 6-8-2016;

ABSTRACT: The present study was performed to investigate the effects of dietary supplementation of bacteriophages (phages) against enterotoxigenic Escherichia coli (ETEC) K88 as a therapy against the ETEC infection in post-weaning pigs. Two groups of post-weaning pigs aged 35 days, eight animals per group, were challenged with 3.0 x 1010 colony forming units of ETEC K88, a third group given the vehicle. The unchallenged group and one challenged group were fed a basal nursery diet for 14 days while the remaining challenged group was fed the basal diet supplemented with 1.0 x 107 plaque forming units of the phage per kg. Average daily gain (ADG), goblet cell density and villous height:crypt depth (VH:CD) ratio in the intestine were less in the challenged group than in the unchallenged group within the animals fed the basal diet ($p < 0.05$); the reverse was true for rectal temperature, faecal consistency score (FCS), E. coli adhesion score (EAS) in the intestine, serum interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-alpha) concentrations and digesta pH in the stomach, caecum and colon. The ETEC infection symptom within the challenged animals was alleviated by the dietary phage supplementation ($p < 0.05$) in ADG, FCS, EAS in the jejunum, serum TNF-alpha concentration, digesta pH in the colon, goblet cell density in the ileum and colon and VH:CD ratio in the ileum. Moreover, the infection symptom tended to be alleviated ($p < 0.10$) by the phage supplementation in rectal temperature, EAS in the ileum and caecum, and VH:CD ratio in the duodenum and jejunum. However, EAS in the colon, digesta pH in the stomach and caecum, and goblet cell density in the jejunum did not change due to the dietary phage. Overall, results indicate that the phage therapy is effective for alleviation of acute ETEC K88 infection in post-weaning pigs.

Lee, H. J., Kim, W. I., Kwon, Y. C., Cha, K. E., Kim, M., and Myung, H. A newly isolated bacteriophage, PBES 02, infecting Cronobacter sakazakii. J.Microbiol.Biotechnol. 5-30-2016;

ABSTRACT: A novel bacteriophage, PBES 02, infecting Cronobacter sakazakii was isolated and characterized. It has a spherical head 90 nm in diameter and a tail 130 nm in length, and belongs to Myoviridae as observed under a transmission electron microscope. The major virion protein appears to be 38 kilodaltons (KDa) in size. The latent period of PBES 02 is 30 min and the burst size is 250. Infectivity of the phage remained intact after exposure to temperatures ranging from 4 to 55 degrees C for 1 h. It was also stable after exposure to pHs ranging from 6 to 10 for 1 h. The phage effectively removed contaminating Cronobacter sakazakii from broth infant formula. PBES 02 has a double stranded DNA genome of 149,732 bases. Its GC ratio is 50.7%. Sequence analysis

revealed that PBES 02 has 299 open reading frames (ORFs) and 14 tRNA genes. Thirty-nine ORFs were annotated including 24 related to replication and regulation functions, 10 related to structural proteins, and 5 related to DNA packaging. The genome of PBES 02 is closely related to that of two other C. sakazaki phages, CR3 and CR8. Comparison of DNA sequences of genes encoding the major capsid protein revealed a wide geographical distribution of related phages over Asia, Europe, and America.

Leon-Velarde, C. G., Happonen, L., Pajunen, M., Leskinen, K., Kropinski, A. M., Mattinen, L., Rajtor, M., Zur, J., Smith, D., Chen, S., Nawaz, A., Johnson, R. P., Odumeru, J. A., Griffiths, M. W., and Skurnik, M. Yersinia enterocolitica specific infection by bacteriophages TG1 and varphiR1-RT is dependent on temperature regulated expression of the phage host receptor OmpF. Appl.Environ.Microbiol. 6-24-2016;

ABSTRACT: Bacteriophages present huge potential both as a resource for developing novel tools for bacterial diagnostics and for use in phage therapy. This is also valid for bacteriophages specific for Yersinia enterocolitica. To increase our knowledge on Y. enterocolitica -specific phages we characterized two novel yersiniophages. The genomes of the bacteriophages vB_YenM_TG1 (TG1) and vB_YenM_varphiR1-RT (varphiR1-RT), isolated from pig manure in Canada and from sewage in Finland, consist of linear double-stranded DNA of 162,101 and 168,809 bp respectively. Their genomes encode 262 putative coding sequences and 4 tRNAs genes, and share 91% overall nucleotide identity. Based on phylogenetic analyses of their whole genome sequences and large terminase subunit protein sequences, a genus named Tg1virus within the family Myoviridae is proposed with TG1 and varphiR1-RT as member species. These bacteriophages exhibit a host range restricted to Y. enterocolitica, and display lytic activity against the epidemiologically significant serotypes O:3, O:5,27, and O:9 at and below 25 degrees C. Adsorption analyses of LPS and OmpF mutants demonstrate that these phages use both the LPS inner core heptosyl residues and the outer membrane protein OmpF as phage receptors. Based on RNA-sequencing and quantitative proteomics we also demonstrate the temperature dependent infection is due to strong repression of OmpF at 37 degrees C. In addition, varphiR1-RT was shown to be able to enter into a pseudolysogenic state. All together, this work provides further insight into phage-host cell interactions by highlighting the importance of understanding underlying factors which may affect the abundance of phage host receptors on the cell surface. IMPORTANCE: Only a small number of bacteriophages infecting Y. enterocolitica, the predominant causative agent of yersiniosis, have been previously described. Here, two newly isolated Y. enterocolitica phages were studied in detail with the aim of elucidating the host cell receptors required for infection. Our research further expands the repertoire of phages available for consideration as potential antimicrobial agents or as diagnostic tools for this important bacterial pathogen.

Leskinen, K., Blasdel, B. G., Lavigne, R., and Skurnik, M. RNA-Sequencing Reveals the Progression of Phage-Host Interactions between phiR1-37 and Yersinia enterocolitica. Viruses. 2016; 8(4):111

ABSTRACT: Despite the expanding interest in bacterial viruses (bacteriophages), insights into the intracellular development of bacteriophage and its impact on bacterial physiology are still scarce. Here we investigate during lytic infection the whole-genome transcription of the giant phage vB_YecM_phiR1-37 (phiR1-37) and its host, the gastroenteritis causing bacterium Yersinia enterocolitica. RNA sequencing reveals that

the gene expression of phiR1-37 does not follow a pattern typical observed in other lytic bacteriophages, as only selected genes could be classified as typically early, middle or late genes. The majority of the genes appear to be expressed constitutively throughout infection. Additionally, our study demonstrates that transcription occurs mainly from the positive strand, while the negative strand encodes only genes with low to medium expression levels. Interestingly, we also detected the presence of antisense RNA species, as well as one non-coding intragenic RNA species. Gene expression in the phage-infected cell is characterized by the broad replacement of host transcripts with phage transcripts. However, the host response in the late phase of infection was also characterized by up-regulation of several specific bacterial gene products known to be involved in stress response and membrane stability, including the Cpx pathway regulators, ATP-binding cassette (ABC) transporters, phage- and cold-shock proteins.

Letchumanan, V., Chan, K. G., Pusparajah, P., Saokaew, S., Duangjai, A., Goh, B. H., Ab Mutalib, N. S., and Lee, L. H. Insights into Bacteriophage Application in Controlling Vibrio Species. Front Microbiol. 2016; 7:1114

ABSTRACT: Bacterial infections from various organisms including Vibrio sp. pose a serious hazard to humans in many forms from clinical infection to affecting the yield of agriculture and aquaculture via infection of livestock. Vibrio sp. is one of the main foodborne pathogens causing human infection and is also a common cause of losses in the aquaculture industry. Prophylactic and therapeutic usage of antibiotics has become the mainstay of managing this problem, however, this in turn led to the emergence of multidrug resistant strains of bacteria in the environment; which has raised awareness of the critical need for alternative non-antibiotic based methods of preventing and treating bacterial infections. Bacteriophages - viruses that infect and result in the death of bacteria - are currently of great interest as a highly viable alternative to antibiotics. This article provides an insight into bacteriophage application in controlling Vibrio species as well underlining the advantages and drawbacks of phage therapy.

Li, E., Wei, X., Ma, Y., Yin, Z., Li, H., Lin, W., Wang, X., Li, C., Shen, Z., Zhao, R., Yang, H., Jiang, A., Yang, W., Yuan, J., and Zhao, X. Isolation and characterization of a bacteriophage phiEap-2 infecting multidrug resistant Enterobacter aerogenes. Sci.Rep. 2016; 6:28338

ABSTRACT: Enterobacter aerogenes (Enterobacteriaceae) is an important opportunistic pathogen that causes hospital-acquired pneumonia, bacteremia, and urinary tract infections. Recently, multidrug-resistant E. aerogenes have been a public health problem. To develop an effective antimicrobial agent, bacteriophage phiEap-2 was isolated from sewage and its genome was sequenced because of its ability to lyse the multidrug-resistant clinical E. aerogenes strain 3-SP. Morphological observations suggested that the phage belongs to the Siphoviridae family. Comparative genome analysis revealed that phage phiEap-2 is related to the Salmonella phage FSL SP-031 (KC139518). All of the structural gene products (except capsid protein) encoded by phiEap-2 had orthologous gene products in FSL SP-031 and Serratia phage Eta (KC460990). Here, we report the complete genome sequence of phiEap-2 and major findings from the genomic analysis. Knowledge of this phage might be helpful for developing therapeutic strategies against E. aerogenes.

Li, M., Wang, J., Zhang, Q., Lin, L., Kuang, A., Materon, L. A., Ji, X., and Wei, Y. Isolation and Characterization of the Lytic Cold-Active Bacteriophage MYSP06 from the Mingyong Glacier in China. Curr.Microbiol. 2016; 72(2):120-127.

ABSTRACT: As unique ecological systems, glaciers are characterized by low temperatures and low nutrient levels, which allow them to be considered as "living fossils" for the purpose of researching the evolution of life and the environmental evolution of the earth. Glaciers are also natural microbial "reservoirs". In this work, a lytic cold-active bacteriophage designated MYSP06 was isolated from Janthinobacterium sp. MYB06 from the Mingyong Glacier in China, and its major characteristics were determined. Electron microscopy revealed that bacteriophage MYSP06 had an isometric head (74 nm) and a long tail (10 nm in width, 210 nm in length). It was classified as a Siphoviridae with an approximate genome size of 65-70 kb. A one-step growth curve revealed that the latent and burst periods were 95 and 65 min, respectively, with an average burst size of 16 bacteriophage particles per infected cell. The bacteriophage particles (100 %) adsorbed to the host cells within 10 min after infection. Moreover, the pH value and thermal stability of bacteriophage MYSP06 were also investigated. The maximum stability of the bacteriophage was observed at the optimal pH 7.0, and the bacteriophage became completely unstable at the extremely alkaline pH 11.0; however, it was comparatively stable at the acidic alkaline pH 6.0. As MYSP06 is a cold-active bacteriophage with a lower production temperature, its characterization and its relationship with its host Janthinobacterium sp. MYB06 deserve further study.

Li, W., Bian, X., Evivie, S. E., and Huo, G. C. Comparative Analysis of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) of Streptococcus thermophilus St-I and its Bacteriophage-Insensitive Mutants (BIM) Derivatives. Curr.Microbiol. 2016; 73(3):393-400.

ABSTRACT: The CRISPR-Cas (CRISPR together with CRISPR-associated proteins) modules are the adaptive immune system, acting as an adaptive and heritable immune system in bacteria and archaea. CRISPR-based immunity acts by integrating short virus sequences in the cell's CRISPR locus, allowing the cell to remember, recognize, and clear infections. In this study, the homology of CRISPRs sequence in BIMs (bacteriophage-insensitive mutants) of Streptococcus thermophilus St-I were analyzed. Secondary structures of the repeats and the PAMs (protospacer-associated motif) of each CRISPR locus were also predicted. Results showed that CRISPR1 has 27 repeat-spacer units, 5 of them had duplicates; CRISPR2 has one repeat-spacer unit; CRISPR3 has 28 repeat-spacer units. Only BIM1 had a new spacer acquisition in CRISPR3, while BIM2 and BIM3 had no new spacers' insertion, thus indicating that while most CRISPR1 were more active than CRISPR3, new spacer acquisition occurred just in CRSPR3 in some situations. These findings will help establish the foundation for the study of CRSPR-Cas systems in lactic acid bacteria.

Li, Y., Guo, Z., Jin, L., Wang, D., Gao, Z., Su, X., Hou, H., and Dong, Y. Mechanism of the allosteric regulation of Streptococcus mutans 2'-deoxycytidylate deaminase. Acta Crystallogr.D.Struct.Biol. 7-1-2016; 72(Pt 7):883-891.

ABSTRACT: In cells, dUMP is the intermediate precursor of dTTP in its synthesis during deoxynucleotide metabolism. In Gram-positive bacteria and eukaryotes, zinc-dependent deoxycytidylate deaminases (dCDs) catalyze the conversion of dCMP to

dUMP. The activity of dCD is allosterically activated by dCTP and inhibited by dTTP. Here, the crystal structure of Streptococcus mutans dCD (SmdCD) complexed with dTTP is presented at 2.35 A resolution, thereby solving the first pair of activator-bound and inhibitor-bound structures from the same species to provide a more definitive description of the allosteric mechanism. In contrast to the dTTP-bound dCD from the bacteriophage S-TIM5 (S-TIM5-dCD), dTTP-bound SmdCD adopts an inactive conformation similar to the apo form. A structural comparison suggests that the distinct orientations of the triphosphate group in S-TIM5-dCD and SmdCD are a result of the varying protein binding environment. In addition, calorimetric data establish that the modulators bound to dCD can be mutually competitively replaced. The results reveal the mechanism underlying its regulator-specific activity and might greatly enhance the understanding of the allosteric regulation of other dCDs.

Li, Z., Li, X., Zhang, J., Wang, X., Wang, L., Cao, Z., and Xu, Y. Use of phages to control Vibrio splendidus infection in the juvenile sea cucumber Apostichopus japonicus. Fish.Shellfish.Immunol. 2016; 54:302-311.

ABSTRACT: In the present study, we isolated 3 bacteriophages with the ability to control Vibrio splendidus, a bacterium known to cause disease in the juvenile sea cucumber. These bacteriophages were designated as vB_VspS_VS-ABTNL-1 (PVS-1), vB_VspS_VS-ABTNL-2 (PVS-2) and vB_VspS_VS-ABTNL-3 (PVS-3). The ability of the 3 phages to inhibit the growth of V. splendidus VS-ABTNL was tested in vitro using each of the 3 phages individually or in the form of a cocktail of all 3 phages in the proportion of 1:1:1. All treated cultures produced a significant ($P < 0.05$) inhibition of growth of V. splendidus VS-ABTNL compared with untreated V. splendidus VS-ABTNL with the cocktail being superior to any of the 3 phages used individually. The lytic capability of the 3 phages was subsequently determined with a Spot Assay Technique performed with 4 isolates of V. splendidus, 3 other Vibrio species and 2 environmental isolates. Both PVS-1 and PVS-2 were lytic to all 4 isolates of V. splendidus while PVS-3 only inhibited the growth of 3 of them. V. splendidus VS-ABTNL was more susceptible to phage PVS-2 than the other 2 phages. In an in vivo performance trial, 360 sea cucumbers (23 +/- 2 g) were randomly assigned to 1 of 6 treatments. Each treatment was housed in 3 PVC tanks (38 cm x 54 cm x 80 cm) with 20 sea cucumbers per tank. Six diets were prepared including an unsupplemented control diet, antibiotic treatment diet, 3 diets containing 1 of the 3 phages individually and a diet containing a cocktail of all 3 phages. After 60 days of feeding, all sea cucumber were challenged with V. splendidus VS-ABTNL by immersion in sea water containing a bacterial concentration of 6 x 10(6) CFU/mL for 2 days. The survival rate of sea cucumbers during the next 10 days was 18% for the unsupplemented diet, 82% for the antibiotic treatment, 82% for the phage cocktail, 65% for phage PVS-1, 58% for phage PVS-2 and 50% for phage PVS-3. There were no significant differences in weight gain, ingestion rate or feed conversion among sea cucumber fed the 4 phage treatments compared with those fed the unsupplemented diet ($P > 0.05$). The levels of nitric oxide synthase and acid phosphatase of sea cucumbers fed phage-containing diets were significantly ($P < 0.05$) increased compared with those fed the control diet. However, no significant differences ($P > 0.05$) were detected among the 4 phage-fed treatments. An additional study was conducted in which 60 healthy sea cucumbers (23 +/- 2 g) were randomly assigned to a control, an untreated group and a test group to investigate the effects of injecting phages by coelomic injection on the survival rate and enzyme activities in the coelomic fluid of the sea cucumbers. The control was injected with 1 ml of sterilized seawater while the untreated group and the test group were injected with the same volume of V. splendidus-ABTNL culture (3 x 10(5) CFU/mL). Then,

the test group was injected with 1 ml of the 3 phage cocktail (MOI = 10). After 48 h, the activities of lysozyme, acid phosphatase and superoxide dismutase were elevated in the untreated group while the levels of these enzymes in the test group were similar to the blank control. After 10-day observation, the survival rate of the sea cucumber was 100% for the blank control, 80% for the test group and 20% for the negative control. The overall results of this experiment indicate that phage therapy increased the survival of sea cucumber infected with V. splendidus VS-ABTNL. The above results demonstrate that using phages, especially a combination of different phages, may be a feasible way to control Vibrio infection in the sea cucumber industry.

Lima-Junior, J. D., Viana-Niero, C., Conde Oliveira, D. V., Machado, G. E., Rabello, M. C., Martins-Junior, J., Martins, L. F., Digiampietri, L. A., da Silva, A. M., Setubal, J. C., Russell, D. A., Jacobs-Sera, D., Pope, W. H., Hatfull, G. F., and Leao, S. C. Characterization of mycobacteria and mycobacteriophages isolated from compost at the Sao Paulo Zoo Park Foundation in Brazil and creation of the new mycobacteriophage Cluster U. BMC.Microbiol. 2016; 16(1):111

ABSTRACT: BACKGROUND: A large collection of sequenced mycobacteriophages capable of infecting a single host strain of Mycobacterium smegmatis shows considerable genomic diversity with dozens of distinctive types (clusters) and extensive variation within those sharing evident nucleotide sequence similarity. Here we profiled the mycobacterial components of a large composting system at the Sao Paulo zoo. RESULTS: We isolated and sequenced eight mycobacteriophages using Mycobacterium smegmatis mc(2)155 as a host. None of these eight phages infected any of mycobacterial strains isolated from the same materials. The phage isolates span considerable genomic diversity, including two phages (Barriga, Nhonho) related to Subcluster A1 phages, two Cluster B phages (Pops, Subcluster B1; Godines, Subcluster B2), three Subcluster F1 phages (Florinda, Girafales, and Quico), and Madruga, a relative of phage Patience with which it constitutes the new Cluster U. Interestingly, the two Subcluster A1 phages and the three Subcluster F1 phages have genomic relationships indicating relatively recent evolution within a geographically isolated niche in the composting system. CONCLUSIONS: We predict that composting systems such as those used to obtain these mycobacteriophages will be a rich source for the isolation of additional phages that will expand our view of bacteriophage diversity and evolution.

Lin, T. Y. Characterisation data of simple sequence repeats of phages closely related to T7M. Data Brief. 2016; 8:828-835.

ABSTRACT: Coliphages T7M and T3, Yersinia phage varphiYeO3-12, and Salmonella phage varphiSG-JL2 share high homology in genomic sequences. Simple sequence repeats (SSRs) are found in their genomes and variations of SSRs among these phages are observed. Analyses on regions of sequences in T7M and T3 genomes that are likely derived from phage recombination, as well as the counterparts in varphiYeO3-12 and varphiSG-JL2, have been discussed by Lin in "Simple sequence repeat variations expedite phage divergence: mechanisms of indels and gene mutations" [1]. These regions are referred to as recombinant regions. The focus here is on SSRs in the whole genome and regions of sequences outside the recombinant regions, referred to as non-recombinant regions. This article provides SSR counts, relative abundance, relative density, and GC contents in the complete genome and non-recombinant regions of these phages. SSR period sizes and motifs in the non-recombinant regions of phage genomes are plotted.

Genomic sequence changes between T7M and T3 due to insertions, deletions, and substitutions are also illustrated. SSRs and nearby sequences of T7M in the non-recombinant regions are compared to the sequences of varphiYeO3-12 and varphiSG-JL2 in the corresponding positions. The sequence variations of SSRs due to vertical evolution are classified into four categories and tabulated: (1) insertion/deletion of SSR units, (2) expansion/contraction of SSRs without alteration of genome length, (3) changes of repeat motifs, and (4) generation/loss of repeats.

Liu, B., Xue, Q., Tang, Y., Cao, J., Guengerich, F. P., and Zhang, H. Mechanisms of mutagenesis: DNA replication in the presence of DNA damage. Mutat.Res.Rev.Mutat.Res. 2016; 768:53-67.

ABSTRACT: Environmental mutagens cause DNA damage that disturbs replication and produces mutations, leading to cancer and other diseases. We discuss mechanisms of mutagenesis resulting from DNA damage, from the level of DNA replication by a single polymerase to the complex DNA replisome of some typical model organisms (including bacteriophage T7, T4, Sulfolobus solfataricus, Escherichia coli, yeast and human). For a single DNA polymerase, DNA damage can affect replication in three major ways: reducing replication fidelity, causing frameshift mutations, and blocking replication. For the DNA replisome, protein interactions and the functions of accessory proteins can yield rather different results even with a single DNA polymerase. The mechanism of mutation during replication performed by the DNA replisome is a long-standing question. Using new methods and techniques, the replisomes of certain organisms and human cell extracts can now be investigated with regard to the bypass of DNA damage. In this review, we consider the molecular mechanism of mutagenesis resulting from DNA damage in replication at the levels of single DNA polymerases and complex DNA replisomes, including translesion DNA synthesis.

Ma, Y., Li, E., Qi, Z., Li, H., Wei, X., Lin, W., Zhao, R., Jiang, A., Yang, H., Yin, Z., Yuan, J., and Zhao, X. Isolation and molecular characterisation of Achromobacter phage phiAxp-3, an N4-like bacteriophage. Sci.Rep. 2016; 6:24776

ABSTRACT: Achromobacter xylosoxidans, an opportunistic pathogen, is responsible for various nosocomial and community-acquired infections. We isolated phiAxp-3, an N4-like bacteriophage that infects A. xylosoxidans, from hospital waste and studied its genomic and biological properties. Transmission electron microscopy revealed that, with a 67-nm diameter icosahedral head and a 20-nm non-contractile tail, phiAxp-3 has features characteristic of Podoviridae bacteriophages (order Caudovirales). With a burst size of 9000 plaque-forming units and a latent period of 80 min, phiAxp-3 had a host range limited to only four A. xylosoxidans strains of the 35 strains that were tested. The 72,825 bp phiAxp-3 DNA genome, with 416-bp terminal redundant ends, contains 80 predicted open reading frames, none of which are related to virulence or drug resistance. Genome sequence comparisons place phiAxp-3 more closely with JWAlpha and JWDelta Achromobacter phages than with other N4 viruses. Using proteomics, we identified 25 viral proteins from purified phiAxp-3 particles. Notably, investigation of the phage phiAxp-3 receptor on the surface of the host cell revealed that lipopolysaccharide serves as the receptor for the adsorption of phage phiAxp-3. Our findings advance current knowledge about A. xylosoxidans phages in an age where alternative therapies to combat antibiotic-resistant bacteria are urgently needed.

Mapes, A. C., Trautner, B. W., Liao, K. S., and Ramig, R. F. Development of expanded host range phage active on biofilms of multi-drug resistant Pseudomonas aeruginosa. Bacteriophage. 2016; 6(1):e1096995

ABSTRACT: Phage therapy is a promising treatment of multi-drug resistant (MDR) bacterial infections but is limited by the narrow host range of phage. To overcome this limitation, we developed a host range expansion (HRE) protocol that expands the host range of Pseudomonas aeruginosa-specific phage by cycles of co-incubation of phage with multiple P. aeruginosa strains. Application of the HRE protocol to a mixture of 4 phages, using 16 P. aeruginosa strains for development, resulted in undefined phage mixtures with greatly expanded host range. Individual phage clones derived from the undefined mixture had expanded host ranges but no individual clone could lyse all of the strains covered by the undefined mixture from which it was isolated. Reconstituting host range-characterized clones into cocktails produced defined cocktails with predictable and broad host ranges. The undefined mixture from the 30th cycle of the mixed-phage HRE (4varphiC30) showed a dose-dependent ability to prevent biofilm formation by, and to reduce a pre-existing biofilm of, 3 P. aeruginosa clinical isolates that produced high amounts of biofilm. A defined cocktail reconstituted from 3 host range-characterized clones had activity on high biofilm-formers susceptible to the phage. Phage therapy was superior to antibiotic therapy (levofloxacin) in a strain of P. aeruginosa that was resistant to levofloxacin. The HRE protocol establishes a rapid approach to create libraries of phage clones and phage cocktails with broad host range, defined composition and anti-biofilm activity.

Marshall, W. F. Cell Geometry: How Cells Count and Measure Size. Annu.Rev.Biophys. 7-5-2016; 45:49-64.

ABSTRACT: The cell represents a highly organized state of living matter in which numerous geometrical parameters are under dynamic regulation in order to match the form of a cell with its function. Cells appear capable of regulating not only the total quantity of their internal organelles, but also the size and number of those organelles. The regulation of three parameters, size, number, and total quantity, can in principle be accomplished by regulating the production or growth of organelles, their degradation or disassembly, and their partitioning among daughter cells during division. Any or all of these steps could in principle be under regulation. But if organelle assembly or disassembly is regulated by number or size, how would the cell know how many copies of an organelle it has, or how big they are?

Martin, T. D., Hill, E. H., Whitten, D. G., Chi, E. Y., and Evans, D. G. Oligomeric Conjugated Polyelectrolytes Display Site-Preferential Binding to MS2 Viral Capsid. Langmuir. 7-27-2016;

ABSTRACT: Opportunistic bacteria and viruses are a worldwide health threat prompting the need for developing new targeting modalities. A class of novel synthetic poly(phenylene ethynylene) (PPE) based oligomeric conjugated polyelectrolytes (OPEs) has demonstrated potent wide-spectrum biocidal activity. A subset of cationic OPEs display high antiviral activity against the MS2 bacteriophage. The oligomers have been found to inactivate the bacteriophage and perturb the morphology of the MS2 viral capsid. However, details of the initial binding and interactions between the OPEs and the

viruses are not well understood. In this study, we use a multi-scale computational approach, including random sampling, molecular dynamics, and electronic structure calculations, to gain an understanding of the molecular level interactions of a series of OPEs that vary in length, charge, and functional groups with the MS2 capsid. Our results show that OPEs strongly bind to the MS2 capsid protein assembly with binding energies of up to -30 kcal/mol. Free energy analysis shows that the binding is dominated by strong van der Waals interactions between the hydrophobic OPE backbone and the capsid surface and strong electrostatic free energy contributions between the OPE charged moieties and charged residues on the capsid surface. This knowledge provides molecular level insight of how to tailor the OPEs to optimize viral capsid disruption and increase OPE efficacy to target amphiphilic protein coats of icosahedral based viruses.

Martinez, A. J., Kim, K. L., Harmon, J. P., and Oliver, K. M. Specificity of Multi-Modal Aphid Defenses against Two Rival Parasitoids. PLoS.One. 2016; 11(5):e0154670

ABSTRACT: Insects are often attacked by multiple natural enemies, imposing dynamic selective pressures for the development and maintenance of enemy-specific resistance. Pea aphids (Acyrthosiphon pisum) have emerged as models for the study of variation in resistance against natural enemies, including parasitoid wasps. Internal defenses against their most common parasitoid wasp, Aphidius ervi, are sourced through two known mechanisms- 1) endogenously encoded resistance or 2) infection with the heritable bacterial symbiont, Hamiltonella defensa. Levels of resistance can range from nearly 0-100% against A. ervi but varies based on aphid genotype and the strain of toxin-encoding bacteriophage (called APSE) carried by Hamiltonella. Previously, other parasitoid wasps were found to commonly attack this host, but North American introductions of A. ervi have apparently displaced all other parasitoids except Praon pequodorum, a related aphidiine braconid wasp, which is still found attacking this host in natural populations. To explain P. pequodorum's persistence, multiple studies have compared direct competition between both wasps, but have not examined specificity of host defenses as an indirectly mediating factor. Using an array of experimental aphid lines, we first examined whether aphid defenses varied in effectiveness toward either wasp species. Expectedly, both types of aphid defenses were effective against A. ervi, but unexpectedly, were completely ineffective against P. pequodorum. Further examination showed that P. pequodorum wasps suffered no consistent fitness costs from developing in even highly 'resistant' aphids. Comparison of both wasps' egg-larval development revealed that P. pequodorum's eggs have thicker chorions and hatch two days later than A. ervi's, likely explaining their differing abilities to overcome aphid defenses. Overall, our results indicate that aphids resistant to A. ervi may serve as reservoirs for P. pequodorum, hence contributing to its persistence in field populations. We find that specificity of host defenses and defensive symbiont infections, may have important roles in influencing enemy compositions by indirectly mediating the interactions and abundance of rival natural enemies.

McCarville, J. L., Caminero, A., and Verdu, E. F. Novel perspectives on therapeutic modulation of the gut microbiota. Therap.Adv.Gastroenterol. 2016; 9(4):580-593.

ABSTRACT: The gut microbiota contributes to the maintenance of health and, when disrupted, may drive gastrointestinal and extragastrointestinal disease. This can occur through direct pathways such as interaction with the epithelial barrier and mucosal immune system or indirectly via production of metabolites. There is no current curative therapy for chronic inflammatory conditions such as inflammatory bowel disease, which

are complex multifactorial disorders involving genetic predisposition, and environmental triggers. Therapies are directed to suppress inflammation rather than the driver, and these approaches are not devoid of adverse effects. Therefore, there is great interest in modulation of the gut microbiota to provide protection from disease. Interventions that modulate the microbiota include diet, probiotics and more recently the emergence of experimental therapies such as fecal microbiota transplant or phage therapy. Emerging data indicate that certain bacteria can induce protective immune responses and enhance intestinal barrier function, which could be potential therapeutic targets. However, mechanistic links and specific therapeutic recommendations are still lacking. Here we provide a pathophysiological overview of potential therapeutic applications of the gut microbiota.

Melo, L. D., Veiga, P., Cerca, N., Kropinski, A. M., Almeida, C., Azeredo, J., and Sillankorva, S. Development of a Phage Cocktail to Control Proteus mirabilis Catheter-associated Urinary Tract Infections. Front Microbiol. 2016; 7:1024

ABSTRACT: Proteus mirabilis is an enterobacterium that causes catheter-associated urinary tract infections (CAUTIs) due to its ability to colonize and form crystalline biofilms on the catheters surface. CAUTIs are very difficult to treat, since biofilm structures are highly tolerant to antibiotics. Phages have been used widely to control a diversity of bacterial species, however, a limited number of phages for P. mirabilis have been isolated and studied. Here we report the isolation of two novel virulent phages, the podovirus vB_PmiP_5460 and the myovirus vB_PmiM_5461, which are able to target, respectively, 16 of the 26 and all the Proteus strains tested in this study. Both phages have been characterized thoroughly and sequencing data revealed no traces of genes associated with lysogeny. To further evaluate the phages' ability to prevent catheter's colonization by Proteus, the phages adherence to silicone surfaces was assessed. Further tests in phage-coated catheters using a dynamic biofilm model simulating CAUTIs, have shown a significant reduction of P. mirabilis biofilm formation up to 168 h of catheterization. These results highlight the potential usefulness of the two isolated phages for the prevention of surface colonization by this bacterium.

Millen, A. M. and Romero, D. A. Genetic determinants of lactococcal C2likeviruses for host infection and their role in phage evolution. J.Gen.Virol. 7-7-2016;

ABSTRACT: Lactococcus lactis is an industrial starter culture used for the production of fermented dairy products. Pip (phage infection protein) bacteriophage insensitive mutant (BIM) L. lactis DGCC11032 was isolated following challenge of parental strain DGCC7271 with C2likeviruses. Over a period of industrial use, phages infecting DGCC11032 were isolated from industrial whey samples and identified as C2likeviruses. Although Pip is reported to be the receptor for many C2likeviruses including species type phage c2, a similar cell membrane associated protein, YjaE, was recently reported as the receptor for C2likevirus bIL67. Characterization of DGCC7271 BIMs following challenge with phage capable of infecting DGCC11032 identified mutations in yjaE, confirming YjaE as necessary for infection. DGCC7271 YjaE mutants remained sensitive to the phages used to generate pip variant DGCC11032 indicating a distinction in host phage determinants. We will refer to C2likeviruses requiring Pip as c2-type and C2likeviruses that require YjaE as bIL67-type. Genomic comparisons of two c2-type phages unable to infect pip mutant DGCC11032 and four bIL67-type phages isolated on DGCC11032 confirmed the segregation of each group based on resemblance to

prototypical phages c2 and bIL67, respectively. The distinguishing feature is linked to three contiguous late expressed genes: I14-15-16 (c2) and ORF34-35-36 (bIL67). Phage recombinants in which the c2-like I14-15-16 homologue gene set was exchanged with corresponding bIL67 genes ORF34-35-36 were capable of infecting a pip mutated host. Together, these results correlate the phage genes corresponding to I14-15-16 (c2) and ORF34-35-36 (bIL67) to host lactococcal phage determinants Pip and YjaE, respectively.

Milton, M. E., Choe, J. Y., Honzatko, R. B., and Nelson, S. W. Crystal structure of the apicoplast DNA polymerase from Plasmodium falciparum: the first look at a plastidic A-family DNA polymerase. J.Mol.Biol. 7-31-2016;

ABSTRACT: Plasmodium falciparum, the primary cause of malaria, contains a non-photosynthetic plastid called the apicoplast. The apicoplast exists in most members of the phylum Apicomplexa and has its own genome along with organelle-specific enzymes for its replication. The only DNA polymerase in the apicoplast (apPOL), which was putatively acquired through horizontal gene transfer from a bacteriophage, is classified as an atypical A-family polymerase. Here we present its crystal structure at a resolution of 2.9A. apPOL, the first structural representative of a plastidic A-family polymerase, diverges from typical A-family members in two of three previously identified signature motifs and a region not implicated by sequence. Moreover, apPOL has an additional N-terminal subdomain, the absence of which severely diminishes its 3' to 5' exonuclease activity. A compound known to be toxic to Plasmodium is a potent inhibitor of apPOL, suggesting apPOL is a viable drug target. The structure provides new insights into the structural diversity of A-family polymerases and may facilitate structurally-guided antimalarial drug design.

Mimee, M., Citorik, R. J., and Lu, T. K. Microbiome therapeutics - Advances and challenges. Adv.Drug Deliv.Rev. 5-5-2016;

ABSTRACT: The microbial community that lives on and in the human body exerts a major impact on human health, from metabolism to immunity. In order to leverage the close associations between microbes and their host, development of therapeutics targeting the microbiota has surged in recent years. Here, we discuss current additive and subtractive strategies to manipulate the microbiota, focusing on bacteria engineered to produce therapeutic payloads, consortia of natural organisms and selective antimicrobials. Further, we present challenges faced by the community in the development of microbiome therapeutics, including designing microbial therapies that are adapted for specific geographies in the body, stable colonization with microbial therapies, discovery of clinically relevant biosensors, robustness of engineered synthetic gene circuits and addressing safety and biocontainment concerns. Moving forward, collaboration between basic and applied researchers and clinicians to address these challenges will poise the field to herald an age of next-generation, cellular therapies that draw on novel findings in basic research to inform directed augmentation of the human microbiota.

Morozova, V., Kozlova, Y., Shedko, E., Kurilshikov, A., Babkin, I., Tupikin, A., Yunusova, A., Chernonosov, A., Baykov, I., capital KA, Cyrillicondratov I., Kabilov, M., Ryabchikova, E., Vlassov, V., and Tikunova, N. Lytic bacteriophage PM16 specific for Proteus mirabilis: a novel member of the genus Phikmvvirus. Arch.Virol. 6-28-2016;

ABSTRACT: Lytic Proteus phage PM16, isolated from human faeces, is a novel virus that is specific for Proteus mirabilis cells. Bacteriophage PM16 is characterized by high stability, a short latency period, large burst size and the occurrence of low phage resistance. Phage PM16 was classified as a member of the genus Phikmvvirus on the basis of genome organization, gene synteny, and protein sequences similarities. Within the genus Phikmvvirus, phage PM16 is grouped with Vibrio phage VP93, Pantoea phage LIMElight, Acinetobacter phage Petty, Enterobacter phage phiKDA1, and KP34-like bacteriophages. An investigation of the phage-cell interaction demonstrated that phage PM16 attached to the cell surface, not to the bacterial flagella. The study of P. mirabilis mutant cells obtained during the phage-resistant bacterial cell assay that were resistant to phage PM16 re-infection revealed a non-swarming phenotype, changes in membrane characteristics, and the absence of flagella. Presumably, the resistance of non-swarming P. mirabilis cells to phage PM16 re-infection is determined by changes in membrane macromolecular composition and is associated with the absence of flagella and a non-swarming phenotype.

Mukai, A., Ichiraku, A., and Horikawa, K. Reliable handling of highly A/T-rich genomic DNA for efficient generation of knockin strains of Dictyostelium discoideum. BMC.Biotechnol. 2016; 16:37

ABSTRACT: BACKGROUND: Social amoeba, Dictyostelium discoideum, is a well-established model organism for studying cellular physiology and developmental pattern formation. Its haploid genome facilitates functional analysis of genes by a single round of mutagenesis including targeted disruption. Although the efficient generation of knockout strains based on an intrinsically high homologous recombination rate has been demonstrated, successful reports for knockin strains have been limited. As social amoeba has an exceptionally high adenine and thymine (A/T)-content, conventional plasmid-based vector construction has been constrained due to deleterious deletion in E. coli. RESULTS: We describe here a simple and efficient strategy to construct GFP-knockin cassettes by using a linear DNA cloning vector derived from N15 bacteriophage. This allows reliable handling of DNA fragments whose A/T-content may be as high as 85 %, and which cannot be cloned into a circular plasmid. By optimizing the length of recombination arms, we successfully generate GFP-knockin strains for five genes involved in cAMP signalling, including a triple-colour knockin strain. CONCLUSIONS: This robust strategy would be useful in handling DNA fragments with biased A/T-contents such as the genome of lower organisms and the promoter/terminator regions of higher organisms.

Munns, K. D., Zaheer, R., Xu, Y., Stanford, K., Laing, C. R., Gannon, V. P., Selinger, L. B., and McAllister, T. A. Comparative Genomic Analysis of Escherichia coli O157:H7 Isolated from Super-Shedder and Low-Shedder Cattle. PLoS.One. 2016; 11(3):e0151673

ABSTRACT: Cattle are the primary reservoir of the foodborne pathogen Escherichia coli O157:H7, with the concentration and frequency of E. coli O157:H7 shedding varying substantially among individual hosts. The term "super-shedder" has been applied to cattle that shed >/=10(4) cfu E. coli O157:H7/g of feces. Super-shedders have been reported to be responsible for the majority of E. coli O157:H7 shed into the environment. The objective of this study was to determine if there are phenotypic and/or genotypic differences between E. coli O157:H7 isolates obtained from super-shedder compared to low-shedder cattle. From a total of 784 isolates, four were selected from low-shedder

steers and six isolates from super-shedder steers (4.01-8.45 log cfu/g feces) for whole genome sequencing. Isolates were phage and clade typed, screened for substrate utilization, pH sensitivity, virulence gene profiles and Stx bacteriophage insertion (SBI) sites. A range of 89-2473 total single nucleotide polymorphisms (SNPs) were identified when sequenced strains were compared to E. coli O157:H7 strain Sakai. More non-synonymous SNP mutations were observed in low-shedder isolates. Pan-genomic and SNPs comparisons did not identify genetic segregation between super-shedder or low-shedder isolates. All super-shedder isolates and 3 of 4 of low-shedder isolates were typed as phage type 14a, SBI cluster 3 and SNP clade 2. Super-shedder isolates displayed increased utilization of galactitol, thymidine and 3-O-beta-D-galactopyranosyl-D-arabinose when compared to low-shedder isolates, but no differences in SNPs were observed in genes encoding for proteins involved in the metabolism of these substrates. While genetic traits specific to super-shedder isolates were not identified in this study, differences in the level of gene expression or genes of unknown function may still contribute to some strains of E. coli O157:H7 reaching high densities within bovine feces.

Murphy, K. C. lambda Recombination and Recombineering. EcoSal.Plus. 2016; 7(1)

ABSTRACT: The bacteriophage lambda Red homologous recombination system has been studied over the past 50 years as a model system to define the mechanistic details of how organisms exchange DNA segments that share extended regions of homology. The lambda Red system proved useful as a system to study because recombinants could be easily generated by co-infection of genetically marked phages. What emerged from these studies was the recognition that replication of phage DNA was required for substantial Red-promoted recombination in vivo, and the critical role that double-stranded DNA ends play in allowing the Red proteins access to the phage DNA chromosomes. In the past 16 years, however, the lambda Red recombination system has gained a new notoriety. When expressed independently of other lambda functions, the Red system is able to promote recombination of linear DNA containing limited regions of homology (approximately 50 bp) with the Escherichia coli chromosome, a process known as recombineering. This review explains how the Red system works during a phage infection, and how it is utilized to make chromosomal modifications of E. coli with such efficiency that it changed the nature and number of genetic manipulations possible, leading to advances in bacterial genomics, metabolic engineering, and eukaryotic genetics.

Myhrvold, C., Polka, J. K., and Silver, P. A. Synthetic Lipid-Containing Scaffolds Enhance Production by Colocalizing Enzymes. ACS Synth.Biol. 8-3-2016;

ABSTRACT: Subcellular organization is critical for isolating, concentrating, and protecting biological activities. Natural subcellular organization is often achieved using colocalization of proteins on scaffold molecules, thereby enhancing metabolic fluxes and enabling coregulation. Synthetic scaffolds extend these benefits to new biological processes and are typically constructed from proteins or nucleic acids. To expand the range of available building materials, we use a minimal set of components from the lipid-encapsulated bacteriophage varphi6 to form synthetic lipid-containing scaffolds (SLSs) in E. coli. Analysis of diffusive behavior by particle tracking in live cells indicates that SLSs are >20 nm in diameter; furthermore, density measurements demonstrate that SLSs contain a mixture of lipids and proteins. The fluorescent proteins mCitrine and mCerulean can be colocalized to SLSs. To test for effects on enzymatic production, we localized two

enzymes involved in indigo biosynthesis to SLSs. We observed a scaffold-dependent increase in indigo production, showing that SLSs can enhance the production of a commercially relevant metabolite.

Na, H., Kong, M., and Ryu, S. Characterization of LysPBC4, a novel Bacillus cereus-specific endolysin of bacteriophage PBC4. FEMS Microbiol.Lett. 2016; 363(12)

ABSTRACT: Bacillus cereus is a spore-forming, Gram-positive bacterium and is a major food-borne pathogen. A B. cereus-specific bacteriophage PBC4 was isolated from the soil of a stock farm, and its genome was analyzed. PBC4 belongs to the Siphoviridae family and has a genome consisting of 80 647-bp-long double-stranded DNA, including 123 genes and two tRNAs. LysPBC4, the endolysin of PBC4, has an enzymatically active domain (EAD) on its N-terminal region and a putative cell wall-binding domain (CBD) on its C-terminal region, respectively. Although the phage PBC4 showed a very limited host range, LysPBC4 could lyse all of the B. cereus strains tested. However, LysPBC4 did not kill other bacteria such as B. subtilis or Listeria, indicating that the endolysin has specific lytic activity against the B. cereus group species. Furthermore, LysPBC4_CBD fused with enhanced green fluorescent protein (EGFP) could decorate limited strains of B. cereus group, suggesting that the LysPBC4_CBD may be a promising material for specific detection of B. cereus.

Nagel, T. E., Chan, B. K., De, Vos D., El-Shibiny, A., Kang'ethe, E. K., Makumi, A., and Pirnay, J. P. The Developing World Urgently Needs Phages to Combat Pathogenic Bacteria. Front Microbiol. 2016; 7:882.

No abstract currently available.

Nandakumar, D. and Patel, S. S. Methods to study the coupling between replicative helicase and leading-strand DNA polymerase at the replication fork. Methods. 5-9-2016;

ABSTRACT: Replicative helicases work closely with the replicative DNA polymerases to ensure that the genomic DNA is copied in a timely and error free manner. In the replisomes of prokaryotes, mitochondria, and eukaryotes, the helicase and DNA polymerase enzymes are functionally and physically coupled at the leading strand replication fork and rely on each other for optimal DNA strand separation and synthesis activities. In this review, we describe pre-steady state kinetic methods to quantify the base pair unwinding-synthesis rate constant, a fundamental parameter to understand how the helicase and polymerase help each other during leading strand replication. We describe a robust method to measure the chemical step size of the helicase-polymerase complex that determines how the two motors are energetically coupled while tracking along the DNA. The 2-aminopurine fluorescence-based method provide structural information on the leading strand helicase-polymerase complex, such as the distance between the two enzymes, their relative positions at the replication fork, and their roles in fork junction melting. The combined information garnered from these methods informs on the mutual dependencies between the helicase and DNA polymerase enzymes, their stepping mechanism, and their individual functions at the replication fork during leading strand replication.

Novacek, J., Siborova, M., Benesik, M., Pantucek, R., Doskar, J., and Plevka, P. Structure and genome release of Twort-like Myoviridae phage with a double-layered baseplate. Proc.Natl.Acad.Sci.U.S.A. 7-28-2016;

ABSTRACT: Bacteriophages from the family Myoviridae use double-layered contractile tails to infect bacteria. Contraction of the tail sheath enables the tail tube to penetrate through the bacterial cell wall and serve as a channel for the transport of the phage genome into the cytoplasm. However, the mechanisms controlling the tail contraction and genome release of phages with "double-layered" baseplates were unknown. We used cryo-electron microscopy to show that the binding of the Twort-like phage phi812 to the Staphylococcus aureus cell wall requires a 210 degrees rotation of the heterohexameric receptor-binding and tripod protein complexes within its baseplate about an axis perpendicular to the sixfold axis of the tail. This rotation reorients the receptor-binding proteins to point away from the phage head, and also results in disruption of the interaction of the tripod proteins with the tail sheath, hence triggering its contraction. However, the tail sheath contraction of Myoviridae phages is not sufficient to induce genome ejection. We show that the end of the phi812 double-stranded DNA genome is bound to one protein subunit from a connector complex that also forms an interface between the phage head and tail. The tail sheath contraction induces conformational changes of the neck and connector that result in disruption of the DNA binding. The genome penetrates into the neck, but is stopped at a bottleneck before the tail tube. A subsequent structural change of the tail tube induced by its interaction with the S. aureus cell is required for the genome's release.

Nyambe, S., Burgess, C., Whyte, P., and Bolton, D. Survival studies of a temperate and lytic bacteriophage in bovine faeces and slurry. J.Appl.Microbiol. 7-2-2016;

ABSTRACT: AIMS: Cattle are the main reservoir of verocytotoxigenic Escherichia coli (VTEC), food-borne pathogens that express verocytotoxins (vtx) encoded by temperate bacteriophage. Bovine faeces and unturned manure heaps can support the survival of VTEC and may propagate and transmit VTEC. This study investigated the survival of a vtx2 bacteriophage, phi24B ::Kan, in bovine faeces and slurry. The survival of an anti-Escherichia coli O157:H7 lytic bacteriophage, e11/2, was examined in the same matrices, as a possible bio-control option for VTEC. METHODS AND RESULTS: Samples were inoculated with phi24B ::Kan and/or e11/2 bacteriophage at a concentration of 7-8 log10 PFU g-1 (faeces) or ml-1 (slurry), stored at 4 and 14 degrees C and examined every 2 days for 36 days. The ability of phi24B ::Kan to transduce E. coli cells was examined. Moreover, E. coli concentrations in the faeces and slurry were monitored throughout the experiment as were the pH and aw (faeces only). Both bacteriophages survived well in faeces and slurry. In addition, phi24B ::Kan was able to form lysogens. CONCLUSIONS: phi24B ::Kan and e11/2 phage can survive and remain infective in bovine faeces and slurry for at least 30 days under representative Irish temperatures. SIGNIFICANCE AND IMPACT OF THE STUDY: Bovine faeces and slurry may act as a reservoir for vtx bacteriophages. The survival of the anti-O157 phage suggests it may be a suitable bio-control option in these matrices.

Nyambe, S., Burgess, C., Whyte, P., and Bolton, D. The Survival of a Temperate vtx Bacteriophage and an Anti-Verocytotoxigenic Escherichia coli O157 Lytic Phage in Water and Soil Samples. Zoonoses.Public Health. 6-23-2016;

ABSTRACT: Verocytotoxigenic (vtx) Escherichia coli (VTEC) are zoonotic foodborne pathogens with the vtx operon encoded by lambdoid bacteriophage (phage). Despite much research on the host bacteria, similar data on the persistence of verocytotoxin converting phage and the ecological niches where transduction occurs are lacking and novel VTEC of important public health significance, have and continue to emerge. This study investigated the survival of a temperate vtx bacteriophage (24B ::kanamycinR) in water (raw farm, pasteurized farm, laboratory tap and autoclaved purified water) and soil (sandy loam and loam soil). It also examined the persistence of an anti-VTEC lytic phage (e11/2) in the same matrices as this may be one option for controlling the emergence of novel VTEC, especially in farm ecological niches where other control options, such as chemical, heat or high pressure treatments, are not feasible. Samples inoculated with 24B ::kanamycinR and e11/2 bacteriophage (8 log10 pfu/ml or pfu/g) separately were incubated at 4 degrees C and 14 degrees C, representative Irish Winter and Summer temperatures, respectively, and tested every 2 days for 40 days. The transduction of 24B ::kanamycinR was also continuously assessed. Both phages survived with reductions observed, regardless of matrix or storage temperature. Moreover, 24B ::kanamycinR was able to transduce its host E. coli strain. It was therefore concluded that aquatic and soil environments on farms may serve as a vtx phage reservoir and transduction point but anti-VTEC phage is a possible biocontrol option.

Oakley, A. J. Dynamics of Open DNA Sliding Clamps. PLoS.One. 2016; 11(5):e0154899

ABSTRACT: A range of enzymes in DNA replication and repair bind to DNA-clamps: torus-shaped proteins that encircle double-stranded DNA and act as mobile tethers. Clamps from viruses (such as gp45 from the T4 bacteriophage) and eukaryotes (PCNAs) are homotrimers, each protomer containing two repeats of the DNA-clamp motif, while bacterial clamps (pol III beta) are homodimers, each protomer containing three DNA-clamp motifs. Clamps need to be flexible enough to allow opening and loading onto primed DNA by clamp loader complexes. Equilibrium and steered molecular dynamics simulations have been used to study DNA-clamp conformation in open and closed forms. The E. coli and PCNA clamps appear to prefer closed, planar conformations. Remarkably, gp45 appears to prefer an open right-handed spiral conformation in solution, in agreement with previously reported biophysical data. The structural preferences of DNA clamps in solution have implications for understanding the duty cycle of clamp-loaders.

Ojala, V., Mattila, S., Hoikkala, V., Bamford, J. K., Hiltunen, T., and Jalasvuori, M. Scoping the effectiveness and evolutionary obstacles in using plasmid-dependent phages to fight antibiotic resistance. Future.Microbiol. 8-9-2016;

ABSTRACT: AIM: To investigate the potential evolutionary obstacles in the sustainable therapeutic use of plasmid-dependent phages to control the clinically important conjugative plasmid-mediated dissemination of antibiotic resistance genes to pathogenic bacteria. MATERIALS & METHODS: The lytic plasmid-dependent phage PRD1 and the multiresistance conferring plasmid RP4 in an Escherichia coli host were utilized to assess the genetic and phenotypic changes induced by combined phage and antibiotic selection. RESULTS & CONCLUSIONS: Resistance to PRD1 was always coupled with either completely lost or greatly reduced conjugation ability. Reversion to full conjugation efficiency was found to be rare, and it also restored the susceptibility to plasmid-dependent phages. Consequently, plasmid-dependent phages constitute an

interesting candidate for development of sustainable anticonjugation/antiresistance therapeutic applications.

Olavesen, K. K., Lindstedt, B. A., Lobersli, I., and Brandal, L. T. Expression of Shiga toxin 2 (Stx2) in highly virulent Stx-producing Escherichia coli (STEC) carrying different anti-terminator (q) genes. Microb.Pathog. 2016; 97:1-8.

ABSTRACT: Shiga toxins (Stx) are key virulence factors of Shiga toxin-producing Escherichia coli (STEC) during development of haemolytic uremic syndrome (HUS). It has been suggested that not only specific stx2 subtypes, but also the amount of Stx2 expressed might be essential for STEC pathogenicity. We aimed to investigate if various anti-terminator (q) genes might influence the expression level of Stx2 in highly virulent STEC. A multiplex PCR detecting q933, q21, and qO111 was run on 20 stx2a-positive STEC strains, of which 18 were HUS associated serotypes (HAS) and two non-HAS. Relative expression of Stx2 mRNA was assessed for all strains, both in non-induced and induced (mitomycin C) state. The HAS STEC carried either q933 (n = 8), qO111 (n = 8), or both (n = 2). In basal state, no STEC strains showed higher expression of Stx2 mRNA than the calibrator EDL933 (non-sorbitol fermenting (NSF) O157:H7carrying q933). Variations among strains were not associated with different q genes present, but rather related to specific serogroups. In induced state, O104:H4 strains (q933) showed higher Stx2 mRNA level than EDL933, whereas sorbitol fermenting (SF) O157:H- (qO111) and O121:H? (q933) STEC showed levels comparable with EDL933. An association between the presence of q933 and higher Stx2 level was seen within some HAS, but not all. Interestingly, the O103:H25 STEC strains, responsible for a HUS outbreak in Norway, carried both q933 and qO111. However, the Stx2 mRNA level in these strains was significantly lower than EDL933 in both states, indicating that other factors than the level of Stx2 might explain the aggressiveness of these bacteria. The two non-HAS STEC did not carry any of the examined q genes. In induced state, these bacteria showed the lowest Stx2 mRNA level compared to EDL933. One of the non-HAS STEC was not induced by mitomycin C, suggesting that stx2a might be located on a defect bacteriophage. No association between specific q genes and Stx2 mRNA expression level was revealed in stx2a-positive HAS STEC. Our results suggest that other factor(s) than specific q genes might influence the level of Stx2 produced in highly virulent STEC.

Olsson, A. L., Wargenau, A., and Tufenkji, N. Optimizing Bacteriophage Surface Densities for Bacterial Capture and Sensing in Quartz Crystal Microbalance with Dissipation Monitoring. ACS Appl.Mater.Interfaces. 6-8-2016; 8(22):13698-13706.

ABSTRACT: Surface immobilized bacteriophages (phages) are increasingly used as biorecognition elements on bacterial biosensors (e.g., on acoustical, electrical, or optical platforms). The phage surface density is a critical factor determining a sensor's bacterial binding efficiencies; in fact, phage surface densities that are too low or too high can result in significantly reduced bacterial binding capacities. Identifying an optimum phage surface density is thus crucial when exploiting the bacteriophages' bacterial capture capabilities in biosensing applications. Herein, we investigated surface immobilization of the Pseudomonas aeruginosa specific E79 (tailed) phage and the Salmonella Typhimurium specific PRD1 (nontailed) phage and their subsequent bacterial capture abilities using quartz crystal microbalance with dissipation monitoring (QCM-D). The QCM-D was used in two experimental setups: (i) a conventional setup and (ii) a combined setup with ellipsometry. Both setups were exploited to link the phages'

immobilization behaviors to their bacterium capture efficiency. While E79 displayed characteristic optima in both the mechanical (QCM-D) and the optical (ellipsometry) data that coincided with its specific bacterial capture optimum, no optima were observed during PRD1 immobilization. The characteristic optima suggests that the E79 phage undergoes a surface rearrangement event that changes the hydration state of the phage film, thereby impairing the E79 phage's ability to capture bacteria. However, the absence of such optima during deposition of the nontailed PRD1 phage suggests that other mechanisms may also lead to reduced bacterial capture by surface immobilized bacteriophages.

Orndorff, P. E. Use of bacteriophage to target bacterial surface structures required for virulence: a systematic search for antibiotic alternatives. Curr.Genet. 4-25-2016;

ABSTRACT: Bacteriophages (phage) that infect pathogenic bacteria often attach to surface receptors that are coincidentally required for virulence. Receptor loss or modification through mutation renders mutants both attenuated and phage resistant. Such attenuated mutants frequently have no apparent laboratory growth defects, but in the host, they fail to exhibit properties needed to produce disease such as mucosal colonization or survival within professional phagocytic cells. The connection between attenuation and phage resistance has been exploited in experimental demonstrations of phage therapy. In such experiments, phage resistant mutants that arise naturally during therapy are inconsequential because of their attenuated status. A more contemporary approach to exploiting this connection involves identifying small effector molecules, identified in high-throughput screens, that inhibit one or more of the steps needed to produce a functioning phage receptor. Since such biosynthetic steps are unique to bacteria, inhibitors can be utilized therapeutically, in lieu of antibiotics. Also, since the inhibitor is specific to a particular bacterium or group of bacteria, no off-target resistance is generated in the host's commensal bacterial population. This brief review covers examples of how mutations that confer phage resistance produce attenuation, and how this coincidental relationship can be exploited in the search for the next generation of therapeutic agents for bacterial diseases.

Paff, M. L., Nuismer, S. L., Ellington, A., Molineux, I. J., and Bull, J. J. Virus wars: using one virus to block the spread of another. PeerJ. 2016; 4:e2166

ABSTRACT: The failure of traditional interventions to block and cure HIV infections has led to novel proposals that involve treating infections with therapeutic viruses-infectious viruses that specifically inhibit HIV propagation in the host. Early efforts in evaluating these proposals have been limited chiefly to mathematical models of dynamics, for lack of suitable empirical systems. Here we propose, develop and analyze an empirical system of a therapeutic virus that protects a host cell population against a lethal virus. The empirical system uses E. coli bacteria as the host cell population, an RNA phage as the lethal virus and a filamentous phage as the therapeutic virus. Basic dynamic properties are established for each virus alone and then together. Observed dynamics broadly agree with those predicted by a computer simulation model, although some differences are noted. Two cases of dynamics are contrasted, differing in whether the therapeutic virus is introduced before the lethal virus or after the lethal virus. The therapeutic virus increases in both cases but by different mechanisms. With the therapeutic virus introduced first, it spreads infectiously without any appreciable change in host dynamics. With the therapeutic virus introduced second, host abundance is depressed at the time

therapy is applied; following an initial period of therapeutic virus spread by infection, the subsequent rise of protection is through reproduction by hosts already protected. This latter outcome is due to inheritance of the therapeutic virus state when the protected cell divides. Overall, the work establishes the feasibility and robustness to details of a viral interference using a therapeutic virus.

Pelfrene, E., Willebrand, E., Cavaleiro, Sanches A., Sebris, Z., and Cavaleri, M. Bacteriophage therapy: a regulatory perspective. J.Antimicrob.Chemother. 2016; 71(8):2071-2074.

ABSTRACT: Despite the recognized problem of antibiotic multidrug resistance, very few antibacterial agents with new mechanisms of action are under development. Bacteriophage therapy could offer one alternative strategy to mitigate this challenge. Although widely used throughout the 20th century in Eastern Europe and the former Soviet Union, this potential therapy has not yet been investigated according to rigorous scientific standards. This paper reports on a multistakeholder meeting held at the EMA, which outlined the existing regulatory framework to which such therapy should adhere and reviewed the current obstacles and shortcomings in scientific development for bacteriophage therapy.

Pelleieux, S., Mathieu, L., Block, J. C., Gantzer, C., and Bertrand, I. The effect of chlorination and hydrodynamic shear stress on the persistence of bacteriophages associated with drinking water biofilms. J.Appl.Microbiol. 7-25-2016;

ABSTRACT: AIMS: This work aimed to assess at pilot scale the effect of chlorination and water flushing on two-month-old drinking water biofilms and, above all, on biofilm-associated F-specific RNA bacteriophages MS2, GA and Qbeta. METHODS AND RESULTS: Chlorination (4 mg l-1) was applied first with a hydrodynamic shear stress of 1 Pa and second with an increase in hydrodynamic shear stress to 10 Pa. Despite a rapid decrease in the number of biofilm bacteria and associated phages, infectious phages were still detected on surfaces after completion of the 150 min cleaning procedure. The resulting sequence of phage removal was: GA > Qbeta >> MS2. CONCLUSIONS: The effect of chlorine on biofilm bacteria and biofilm-associated phages was limited to the upper layers of the biofilm and was not enhanced by an increase in hydrodynamic shear stress. A smaller decrease was observed for MS2 than for GA or Qbeta after completion of the cleaning procedure. SIGNIFICANCE AND IMPACT OF THE STUDY: The differences observed between the three phages suggest that the location of the viral particles in the biofilm, which is related to their surface properties, affects the efficiency of chlorine disinfection. This article is protected by copyright. All rights reserved.

Pena, E. J. and Heinlein, M. In Vivo RNA Visualization in Plants Using MS2 Tagging. Methods Enzymol. 2016; 572:105-122.

ABSTRACT: Intracellular trafficking and asymmetric localization of RNA molecules within cells are a prevalent process across phyla involved in developmental control and signaling and thus in the determination of cell fate. In addition to intracellular localization, plants support the trafficking of RNA molecules also between cells through plasmodesmata (PD), which has important roles in the cell-to-cell and systemic communication during plant growth and development. Viruses have developed strategies to exploit the underlying plant RNA transport mechanisms for the cell-to-cell

and systemic dissemination of infection. In vivo RNA visualization methods have revolutionized the study of RNA dynamics in living cells. However, their application in plants is still in its infancy. To gain insights into the RNA transport mechanisms in plants, we study the localization and transport of Tobacco mosaic virus RNA using MS2 tagging. This technique involves the tagging of the RNA of interest with repeats of an RNA stem-loop (SL) that is derived from the origin of assembly of the bacteriophage MS2 and recruits the MS2 coat protein (MCP). Thus, expression of MCP fused to a fluorescent marker allows the specific visualization of the SL-carrying RNA. Here we describe a detailed protocol for Agrobacterium tumefaciens-mediated transient expression and in vivo visualization of MS2-tagged mRNAs in Nicotiana benthamiana leaves.

Penner, J. C., Ferreira, J. A., Secor, P. R., Sweere, J. M., Birukova, M., Joubert, L. M., Haagensen, J. A., Garcia, O., Malkovskiy, A. V., Kaber, G., Nazik, H., Manasherob, R., Spormann, A. M., Clemons, K. V., Stevens, D. A., and Bollyky, P. L. Pf4 bacteriophage produced by Pseudomonas aeruginosa inhibits Aspergillus fumigatus metabolism via iron sequestration. Microbiology. 7-29-2016;

ABSTRACT: Pseudomonas aeruginosa (Pa) and Aspergillus fumigatus (Af) are major human pathogens known to interact in a variety of disease settings, including airway infections in cystic fibrosis (CF). We recently reported that clinical isolates of Pa inhibit the formation and growth of Af biofilms. Here we report that the bacteriophage Pf4, produced by Pa, can inhibit the metabolic activity of Af biofilms. This phage-mediated inhibition was dose-dependent, ablated by phage denaturation, and was more pronounced against preformed Af biofilm rather than biofilm formation. In contrast, planktonic conidial growth was unaffected. Two other phages, Pf1 and fd, did not inhibit Af, nor did supernatant from a Pa strain incapable of producing Pf4. Pf4, but not Pf1, attaches to Af hyphae in an avid and prolonged manner, suggesting that Pf4-mediated inhibition of Af may occur at the biofilm surface. We show Pf4 binds iron, thus denying Af a crucial resource. Consistent with this, the inhibition of Af metabolism by Pf4 could be overcome with supplemental ferric iron, with preformed biofilm more resistant to reversal. To our knowledge, this is the first report of a bacterium producing a phage that inhibits the growth of a fungus and the first description of a phage behaving as an iron chelator in a biological system.

Perez, Pulido R., Grande Burgos, M. J., Galvez, A., and Lucas, Lopez R. Application of bacteriophages in post-harvest control of human pathogenic and food spoiling bacteria. Crit Rev.Biotechnol. 2016; 36(5):851-861.

ABSTRACT: Bacteriophages have attracted great attention for application in food biopreservation. Lytic bacteriophages specific for human pathogenic bacteria can be isolated from natural sources such as animal feces or industrial wastes where the target bacteria inhabit. Lytic bacteriophages have been tested in different food systems for inactivation of main food-borne pathogens including Listeria monocytogenes, Staphylococcus aureus, Escherichia coli O157:H7, Salmonella enterica, Shigella spp., Campylobacter jejuni and Cronobacter sakazkii, and also for control of spoilage bacteria. Application of lytic bacteriophages could selectively control host populations of concern without interfering with the remaining food microbiota. Bacteriophages could also be applied for inactivation of bacteria attached to food contact surfaces or grown as biofilms. Bacteriophages may receive a generally recognized as safe status based on their lack of toxicity and other detrimental effects to human health. Phage preparations

specific for L. monocytogenes, E. coli O157:H7 and S. enterica serotypes have been commercialized and approved for application in foods or as part of surface decontamination protocols. Phage endolysins have a broader host specificity compared to lytic bacteriophages. Cloned endolysins could be used as natural preservatives, singly or in combination with other antimicrobials such as bacteriocins.

Perez, Sepulveda B., Redgwell, T., Rihtman, B., Pitt, F., Scanlan, D. J., and Millard, A. Marine phage genomics: the tip of the iceberg. FEMS Microbiol.Lett. 2016; 363(15)

ABSTRACT: Marine viruses are the most abundant biological entity in the oceans, the majority of which infect bacteria and are known as bacteriophages. Yet, the bulk of bacteriophages form part of the vast uncultured dark matter of the microbial biosphere. In spite of the paucity of cultured marine bacteriophages, it is known that marine bacteriophages have major impacts on microbial population structure and the biogeochemical cycling of key elements. Despite the ecological relevance of marine bacteriophages, there are relatively few isolates with complete genome sequences. This minireview focuses on knowledge gathered from these genomes put in the context of viral metagenomic data and highlights key advances in the field, particularly focusing on genome structure and auxiliary metabolic genes.

Perkett, M. R., Mirijanian, D. T., and Hagan, M. F. The allosteric switching mechanism in bacteriophage MS2. J.Chem.Phys. 7-21-2016; 145(3):035101

ABSTRACT: We use all-atom simulations to elucidate the mechanisms underlying conformational switching and allostery within the coat protein of the bacteriophage MS2. Assembly of most icosahedral virus capsids requires that the capsid protein adopts different conformations at precise locations within the capsid. It has been shown that a 19 nucleotide stem loop (TR) from the MS2 genome acts as an allosteric effector, guiding conformational switching of the coat protein during capsid assembly. Since the principal conformational changes occur far from the TR binding site, it is important to understand the molecular mechanism underlying this allosteric communication. To this end, we use all-atom simulations with explicit water combined with a path sampling technique to sample the MS2 coat protein conformational transition, in the presence and absence of TR-binding. The calculations find that TR binding strongly alters the transition free energy profile, leading to a switch in the favored conformation. We discuss changes in molecular interactions responsible for this shift. We then identify networks of amino acids with correlated motions to reveal the mechanism by which effects of TR binding span the protein. We find that TR binding strongly affects residues located at the 5-fold and quasi-sixfold interfaces in the assembled capsid, suggesting a mechanism by which the TR binding could direct formation of the native capsid geometry. The analysis predicts amino acids whose substitution by mutagenesis could alter populations of the conformational substates or their transition rates.

Petrenko, V. A. and Gillespie, J. W. Paradigm shift in bacteriophage-mediated delivery of anticancer drugs: from targeted 'magic bullets' to self-navigated 'magic missiles'. Expert.Opin.Drug Deliv. 8-5-2016; 1-12.

ABSTRACT: INTRODUCTION: New phage-directed nanomedicines have emerged recently as a result of the in-depth study of the genetics and structure of filamentous phage and

evolution of phage display and phage nanobiotechnology. This review focuses on the progress made in the development of the cancer-targeted nanomaterials and discusses the trends in using phage as a bioselectable molecular navigation system. AREAS COVERED: The merging of phage display technologies with nanotechnology in recent years has proved promising in different areas of medicine and technology, such as medical diagnostics, molecular imaging, vaccine development and targeted drug/gene delivery, which is the focus of this review. The authors used data obtained from their research group and sourced using Science Citation Index (Web of Science) and NCBI PubMed search resources. EXPERT OPINION: First attempts of adapting traditional concepts of direct targeting of tumor using phage-targeted nanomedicines has shown minimal improvements. With discovery and study of biological and technical barriers that prevent anti-tumor drug delivery, a paradigm shift from traditional drug targeting to nanomedicine navigation systems is required. The advanced bacteriophage-driven self-navigation systems are thought to overcome those barriers using more precise, localized phage selection methods, multi-targeting 'promiscuous' ligands and advanced multifunctional nanomedicine platforms.

Pires, D. P., Oliveira, H., Melo, L. D., Sillankorva, S., and Azeredo, J. Bacteriophage-encoded depolymerases: their diversity and biotechnological applications. Appl.Microbiol.Biotechnol. 2016; 100(5):2141-2151.

ABSTRACT: Bacteriophages (phages), natural enemies of bacteria, can encode enzymes able to degrade polymeric substances. These substances can be found in the bacterial cell surface, such as polysaccharides, or are produced by bacteria when they are living in biofilm communities, the most common bacterial lifestyle. Consequently, phages with depolymerase activity have a facilitated access to the host receptors, by degrading the capsular polysaccharides, and are believed to have a better performance against bacterial biofilms, since the degradation of extracellular polymeric substances by depolymerases might facilitate the access of phages to the cells within different biofilm layers. Since the diversity of phage depolymerases is not yet fully explored, this is the first review gathering information about all the depolymerases encoded by fully sequenced phages. Overall, in this study, 160 putative depolymerases, including sialidases, levanases, xylosidases, dextranases, hyaluronidases, peptidases as well as pectate/pectin lyases, were found in 143 phages (43 Myoviridae, 47 Siphoviridae, 37 Podoviridae, and 16 unclassified) infecting 24 genera of bacteria. We further provide information about the main applications of phage depolymerases, which can comprise areas as diverse as medical, chemical, or food-processing industry.

Pires, D. P., Cleto, S., Sillankorva, S., Azeredo, J., and Lu, T. K. Genetically Engineered Phages: a Review of Advances over the Last Decade. Microbiol.Mol.Biol.Rev. 2016; 80(3):523-543.

ABSTRACT: Soon after their discovery in the early 20th century, bacteriophages were recognized to have great potential as antimicrobial agents, a potential that has yet to be fully realized. The nascent field of phage therapy was adversely affected by inadequately controlled trials and the discovery of antibiotics. Although the study of phages as anti-infective agents slowed, phages played an important role in the development of molecular biology. In recent years, the increase in multidrug-resistant bacteria has renewed interest in the use of phages as antimicrobial agents. With the wide array of possibilities offered by genetic engineering, these bacterial viruses are being modified to precisely control and detect bacteria and to serve as new sources of

antibacterials. In applications that go beyond their antimicrobial activity, phages are also being developed as vehicles for drug delivery and vaccines, as well as for the assembly of new materials. This review highlights advances in techniques used to engineer phages for all of these purposes and discusses existing challenges and opportunities for future work.

Planamente, S., Salih, O., Manoli, E., besa-Jove, D., Freemont, P. S., and Filloux, A. TssA forms a gp6-like ring attached to the type VI secretion sheath. EMBO J. 8-1-2016; 35(15):1613-1627.

ABSTRACT: The type VI secretion system (T6SS) is a supra-molecular bacterial complex that resembles phage tails. It is a killing machine which fires toxins into target cells upon contraction of its TssBC sheath. Here, we show that TssA1 is a T6SS component forming dodecameric ring structures whose dimensions match those of the TssBC sheath and which can accommodate the inner Hcp tube. The TssA1 ring complex binds the T6SS sheath and impacts its behaviour in vivo In the phage, the first disc of the gp18 sheath sits on a baseplate wherein gp6 is a dodecameric ring. We found remarkable sequence and structural similarities between TssA1 and gp6 C-termini, and propose that TssA1 could be a baseplate component of the T6SS Furthermore, we identified similarities between TssK1 and gp8, the former interacting with TssA1 while the latter is found in the outer radius of the gp6 ring. These observations, combined with similarities between TssF and gp6N-terminus or TssG and gp53, lead us to propose a comparative model between the phage baseplate and the T6SS.

Pope, W. H., Brown, A. K., Fisher, D. J., Okwiya, N. H., Savage, K. A., German, B. A., McDonnell, J. E., Schafer, C. E., Yu, V. J., Furbee, E. C., Grubb, S. R., Warner, M. H., Montgomery, M. T., Garlena, R. A., Russell, D. A., Jacobs-Sera, D., and Hatfull, G. F. Genome Sequence of Gordonia Bacteriophage Lucky10. Genome Announc. 2016; 4(3)

ABSTRACT: Lucky10 is a newly isolated phage of Gordonia terrae 3612 that was recovered from a soil sample in Pittsburgh, PA. Lucky10 has siphoviral morphology and a double-stranded DNA (dsDNA) genome of 42,979 bp, with 70 predicted protein-coding genes. Lucky10 shows little similarity to previously reported Gordonia phages.

Pope, W. H., Bandyopadhyay, A., Carlton, M. L., Kane, M. T., Panchal, N. J., Pham, Y. C., Reynolds, Z. J., Sapienza, M. S., German, B. A., McDonnell, J. E., Schafer, C. E., Yu, V. J., Furbee, E. C., Grubb, S. R., Warner, M. H., Montgomery, M. T., Garlena, R. A., Russell, D. A., Jacobs-Sera, D., and Hatfull, G. F. Genome Sequence of Gordonia Phage Yvonnetastic. Genome Announc. 2016; 4(4)

ABSTRACT: Gordonia bacteriophage Yvonnetastic was isolated from soil in Pittsburgh, PA, using Gordonia terrae 3612 as a host. Yvonnetastic has siphoviral morphology and a genome of 98,136 bp, with 198 predicted protein-coding genes and five tRNA genes. Yvonnetastic does not share substantial sequence similarity with other sequenced bacteriophage genomes.

Prevel, R. and Dufour, N. [Potential use of bacteriophages in modern infectiology]. Rev.Med.Interne. 6-1-2016.

No abstract currently available.

Radford, D. R., Ahmadi, H., Leon-Velarde, C. G., and Balamurugan, S. Propagation method for persistent high yield of diverse Listeria phages on permissive hosts at refrigeration temperatures. Res.Microbiol. 6-7-2016;

ABSTRACT: The efficient production of a high concentration of bacteriophage in large volumes has been a limiting factor in the exploration of the true potential of these organisms for biotechnology, agriculture and medicine. Traditional methods focus on generating small volumes of highly concentrated samples as the end product of extensive mechanical and osmotic processing. To function at an industrial scale mandates extensive investment in infrastructure and input materials not feasible for many smaller facilities. To address this, we developed a novel, scalable, generic method for producing significantly higher titer psychrophilic phage (P < 2.0 x 10-6), 2- to 4-fold faster than traditional methods. We generate renewable high yields from single source cultures by propagating phage under refrigeration conditions in which Listeria, Yersinia and their phages grow in equilibrium. Diverse Yersinia and Listeria phages tested yielded averages of 3.49 x 108 to 3.36 x 1012 PFU/ml/day compared to averages of 1.28 x 105 to 1.30 x 1010 PFU/ml/day by traditional methods. Host growth and death kinetics made this method ineffective for extended propagation of mesophilic phages.

Rambags, F., Tanner, C. C., Stott, R., and Schipper, L. A. Fecal Bacteria, Bacteriophage, and Nutrient Reductions in a Full-Scale Denitrifying Woodchip Bioreactor. J.Environ.Qual. 2016; 45(3):847-854.

ABSTRACT: Denitrifying bioreactors using woodchips or other slow-release carbon sources can be an effective method for removing nitrate (NO) from wastewater and tile drainage. However, the ability of these systems to remove fecal microbes from wastewater has been largely uninvestigated. In this study, reductions in fecal indicator bacteria () and viruses (F-specific RNA bacteriophage [FRNA phage]) were analyzed by monthly sampling along a longitudinal transect within a full-scale denitrifying woodchip bioreactor receiving secondary-treated septic tank effluent. Nitrogen, phosphorus, 5-d carbonaceous biochemical oxygen demand (CBOD), and total suspended solids (TSS) reduction were also assessed. The bioreactor demonstrated consistent and substantial reduction of (2.9 log reduction) and FRNA phage (3.9 log reduction) despite receiving highly fluctuating inflow concentrations [up to 3.5 x 10 MPN (100 mL) and 1.1 x 10 plaque-forming units (100 mL) , respectively]. Most of the removal of fecal microbial contaminants occurred within the first meter of the system (1.4 log reduction for ; 1.8 log reduction for FRNA phage). The system was also efficient at removing NO (>99.9% reduction) and TSS (89% reduction). There was no evidence of consistent removal of ammonium, organic nitrogen, or phosphorus. Leaching of CBOD occurred during initial operation but decreased and stabilized at lower values (14 g O m) after 9 mo. We present strong evidence for reliable microbial contaminant removal in denitrifying bioreactors, demonstrating their broader versatility for wastewater treatment. Research on the removal mechanisms of microbial contaminants in these systems, together with the assessment of longevity of removal, is warranted.

Rasmussen, K. K., Frandsen, K. E., Boeri, Erba E., Pedersen, M., Varming, A. K., Hammer, K., Kilstrup, M., Thulstrup, P. W., Blackledge, M., Jensen, M. R., and Lo, Leggio L. Structural and dynamics studies of a truncated variant of CI repressor from bacteriophage TP901-1. Sci.Rep. 2016; 6:29574

ABSTRACT: The CI repressor from the temperate bacteriophage TP901-1 consists of two folded domains, an N-terminal helix-turn-helix DNA-binding domain (NTD) and a C-terminal oligomerization domain (CTD), which we here suggest to be further divided into CTD1 and CTD2. Full-length CI is a hexameric protein, whereas a truncated version, CI58, forms dimers. We identify the dimerization region of CI58 as CTD1 and determine its secondary structure to be helical both within the context of CI58 and in isolation. To our knowledge this is the first time that a helical dimerization domain has been found in a phage repressor. We also precisely determine the length of the flexible linker connecting the NTD to the CTD. Using electrophoretic mobility shift assays and native mass spectrometry, we show that CI58 interacts with the OL operator site as one dimer bound to both half-sites, and with much higher affinity than the isolated NTD domain thus demonstrating cooperativity between the two DNA binding domains. Finally, using small angle X-ray scattering data and state-of-the-art ensemble selection techniques, we delineate the conformational space sampled by CI58 in solution, and we discuss the possible role that the dynamics play in CI-repressor function.

Rastogi, V., Pragya, Verma, N., Mishra, A. K., Nath, G., Gaur, P. K., and Verma, A. An Overview on Bacteriophages: A Natural Nanostructured Antibacterial Agent. Curr.Drug Deliv. 4-6-2016;

ABSTRACT: BACKGROUND: Recent advances in the field of bionanomedicine make us not only to produce biomaterials but also to manipulate them at molecular level. Viruses particularly bacteriophages are a promising nanomaterial that can be functionalized with great precision. Bacteriophages are the natural antimicrobial agents that fi ght against antibiotic resistant bacteria which causes infections in animals, in humans, or in crops of agricultural value. OBJECTIVE: The idea of utilizing bacteriophages as therapeutic agents is due to their ability to kill bacteria at the end of the infectious cycle. This paper reviewed on the general biology of bacteriophages, presence of receptors on the bacteria which are necessary for the recognition and adsorption of bacteriophages. Pharmacokinetics and therapeutic potential of bacteriophages administered through various routes in treating diverse bacterial infections is also reviewed along with the problems associated with bacteriophage therapy. CONCLUSION: By engineering the phages or by making a cocktail of phages it would become easy to treat various bacterial infections which are as such resistant to the current generations of antibiotics available in the market. Among various routes of administration parenteral route is found to be the most thriving route for the treatment of systemic infections whereas oral route is meant to treat gastrointestinal infections whereas; local delivery (skin, nasal, ears) of phages has proven their potency to treat topical infections.

Regeimbal, J. M., Jacobs, A. C., Corey, B. W., Henry, M. S., Thompson, M. G., Pavlicek, R. L., Quinones, J., Hannah, R. M., Ghebremedhin, M., Crane, N. J., Zurawski, D. V., Teneza-Mora, N. C., Biswas, B., and Hall, E. R. Personalized therapeutic cocktail of wild environmental phages rescues mice from A. baumannii wound infections. Antimicrob.Agents Chemother. 7-18-2016;

ABSTRACT: Multidrug resistant bacterial pathogens are an increasing threat to public health, and lytic bacteriophages have reemerged as a potential therapeutic option. In this work we isolated and assembled a five member cocktail of wild phages against A. baumannii and demonstrated therapeutic efficacy in a mouse full-thickness dorsal infected wound model. The cocktail lowers the bioburden in the wound, prevents the spread of infection and necrosis to surrounding tissue, and decreases infection-associated morbidity. Interestingly, this effective cocktail is composed of four phages that do not kill the parent strain of the infection, and one phage that simply delays bacterial growth in vitro via a strong but incomplete selection event. The cocktail here appears to function in a combinatorial manner, as one constituent phage targets capsulated A. baumannii and selects for loss of receptor, shifting the population to an uncapsulated state that is then sensitized to the remaining four phages in the cocktail. Additionally, capsule is a known virulence factor for A. baumannii, and we demonstrated that the emergent uncapsulated bacteria are avirulent in a G. mellonella model. These results highlight the importance of anticipating population changes during phage therapy and designing intelligent cocktails to control emergent strains, as well as the benefits of using phages that target virulence factors. Because of the efficacy of this cocktail isolated from a limited environmental pool, we have established a pipeline for developing new phage therapeutics against additional clinically relevant multidrug resistant pathogens using environmental phages sourced from around the globe.

Reveille, A. M., Eldridge, K. A., and Temple, L. M. Complete Genome Sequence of Bacillus megaterium Bacteriophage Eldridge. Genome Announc. 2016; 4(2)

ABSTRACT: In this study the complete genome sequence of the unique bacteriophage Eldridge, isolated from soil using ITALIC! Bacillus megateriumas the host organism, was determined. Eldridge is a myovirus with a genome consisting of 242 genes and is unique when compared to phage sequences in GenBank.

Rihtman, B., Meaden, S., Clokie, M. R., Koskella, B., and Millard, A. D. Assessing Illumina technology for the high-throughput sequencing of bacteriophage genomes. PeerJ. 2016; 4:e2055

ABSTRACT: Bacteriophages are the most abundant biological entities on the planet, playing crucial roles in the shaping of bacterial populations. Phages have smaller genomes than their bacterial hosts, yet there are currently fewer fully sequenced phage than bacterial genomes. We assessed the suitability of Illumina technology for high-throughput sequencing and subsequent assembly of phage genomes. In silico datasets reveal that 30x coverage is sufficient to correctly assemble the complete genome of ~98.5% of known phages, with experimental data confirming that the majority of phage genomes can be assembled at 30x coverage. Furthermore, in silico data demonstrate it is possible to co-sequence multiple phages from different hosts, without introducing assembly errors.

Roces, C., Campelo, A. B., Escobedo, S., Wegmann, U., Garcia, P., Rodriguez, A., and Martinez, B. Reduced Binding of the Endolysin LysTP712 to Lactococcus lactis DeltaftsH Contributes to Phage Resistance. Front Microbiol. 2016; 7:138

ABSTRACT: Absence of the membrane protease FtsH in Lactococcus lactis hinders release of the bacteriophage TP712. In this work we have analyzed the mechanism responsible for the non-lytic phenotype of L. lactis DeltaftsH after phage infection. The lytic cassette of TP712 contains a putative antiholin-pinholin system and a modular endolysin (LysTP712). Inducible expression of the holin gene demonstrated the presence of a dual start motif which is functional in both wildtype and L. lactis DeltaftsH cells. Moreover, simulating holin activity with ionophores accelerated lysis of wildtype cells but not L. lactis DeltaftsH cells, suggesting inhibition of the endolysin rather than a role of FtsH in holin activation. However, zymograms revealed the synthesis of an active endolysin in both wildtype and L. lactis DeltaftsH TP712 lysogens. A reporter protein was generated by fusing the cell wall binding domain of LysTP712 to the fluorescent mCherry protein. Binding of this reporter protein took place at the septa of both wildtype and L. lactis DeltaftsH cells as shown by fluorescence microscopy. Nonetheless, fluorescence spectroscopy demonstrated that mutant cells bound 40% less protein. In conclusion, the non-lytic phenotype of L. lactis DeltaftsH is not due to direct action of the FtsH protease on the phage lytic proteins but rather to a putative function of FtsH in modulating the architecture of the L. lactis cell envelope that results in a lower affinity of the phage endolysin to its substrate.

Rodriguez-Rubio, L., Gerstmans, H., Thorpe, S., Mesnage, S., Lavigne, R., and Briers, Y. DUF3380 Domain from a Salmonella Phage Endolysin Shows Potent N-Acetylmuramidase Activity. Appl.Environ.Microbiol. 8-15-2016; 82(16):4975-4981.

ABSTRACT: Bacteriophage-encoded endolysins are highly diverse enzymes that cleave the bacterial peptidoglycan layer. Current research focuses on their potential applications in medicine, in food conservation, and as biotechnological tools. Despite the wealth of applications relying on the use of endolysin, little is known about the enzymatic properties of these enzymes, especially in the case of endolysins of bacteriophages infecting Gram-negative species. Automated genome annotations therefore remain to be confirmed. Here, we report the biochemical analysis and cleavage site determination of a novel Salmonella bacteriophage endolysin, Gp110, which comprises an uncharacterized domain of unknown function (DUF3380; pfam11860) in its C terminus and shows a higher specific activity (34,240 U/muM) than that of 14 previously characterized endolysins active against peptidoglycan from Gram-negative bacteria (corresponding to 1.7- to 364-fold higher activity). Gp110 is a modular endolysin with an optimal pH of enzymatic activity of pH 8 and elevated thermal resistance. Reverse-phase high-performance liquid chromatography (RP-HPLC) analysis coupled to mass spectrometry showed that DUF3380 has N-acetylmuramidase (lysozyme) activity cleaving the beta-(1,4) glycosidic bond between N-acetylmuramic acid and N-acetylglucosamine residues. Gp110 is active against directly cross-linked peptidoglycans with various peptide stem compositions, making it an attractive enzyme for developing novel antimicrobial agents. IMPORTANCE: We report the functional and biochemical characterization of the Salmonella phage endolysin Gp110. This endolysin has a modular structure with an enzymatically active domain and a cell wall binding domain. The enzymatic activity of this endolysin exceeds that of all other endolysins previously characterized using the same methods. A domain of unknown function (DUF3380) is responsible for this high enzymatic activity. We report that DUF3380 has N-acetylmuramidase activity against directly cross-linked peptidoglycans with various peptide stem compositions. This experimentally verified activity allows better classification and understanding of the enzymatic activities of endolysins, which mostly are inferred by sequence similarities. Three-dimensional structure predictions for Gp110 suggest a fold

that is completely different from that of known structures of enzymes with the same peptidoglycan cleavage specificity, making this endolysin quite unique. All of these features, combined with increased thermal resistance, make Gp110 an attractive candidate for engineering novel endolysin-based antibacterials.

Salas, M. and de, Vega M. Protein-Primed Replication of Bacteriophage Phi29 DNA. Enzymes. 2016; 39:137-167.

ABSTRACT: The requirement of DNA polymerases for a 3'-hydroxyl (3'-OH) group to prime DNA synthesis raised the question about how the ends of linear chromosomes could be replicated. Among the strategies that have evolved to handle the end replication problem, a group of linear phages and eukaryotic and archaeal viruses, among others, make use of a protein (terminal protein, TP) that primes DNA synthesis from the end of their genomes. The replicative DNA polymerase recognizes the OH group of a specific residue in the TP to initiate replication that is guided by an internal 3' nucleotide of the template strand. By a sliding-back mechanism or variants of it the terminal nucleotide(s) is(are) recovered and the TP becomes covalently attached to the genome ends. Bacillus subtilis phage varphi29 is the organism in which such a mechanism has been studied more extensively, having allowed to lay the foundations of the so-called protein-primed replication mechanism. Here we focus on the main biochemical and structural features of the two main proteins responsible for the protein-primed initiation step: the DNA polymerase and the TP. Thus, we will discuss the structural determinants of the DNA polymerase responsible for its ability to use sequentially a TP and a DNA as primers, as well as for its inherent capacity to couple high processive synthesis to strand displacement. On the other hand, we will review how TP primes initiation followed by a transition step for further DNA-primed replication by the same polymerase molecule. Finally, we will review how replication is compartmentalized in vivo.

Sangsanont, J., The, Dan D., Thi Viet, Nga T., Katayama, H., and Furumai, H. Detection of pepper mild mottle virus as an indicator for drinking water quality in Hanoi, Vietnam, in large volume of water after household treatment. J.Environ.Sci.Health A Tox.Hazard.Subst.Environ.Eng. 7-15-2016; 1-7.

ABSTRACT: The aims of this study were to examine the removal of bacteria and viruses by household point-of-use (POU) treatments and to apply a previously developed large-volume virus concentration method (approximately 20 L). First, the removal of microbes by household POU treatment was investigated in the laboratory. Second, the prevalence of viruses in drinking water sources for households and the removal efficiency of microbes by POU treatments in two suburban communities in Hanoi, Vietnam, were investigated. Indigenous pepper mild mottle virus (PMMoV) was used as the main target together with adenovirus, Aichi virus, enterovirus, F-specific bacteriophage genogroup 1, and Escherichia coli to investigate the removal efficiency of household treatments. The results from laboratory and field survey were compared. From the laboratory study, ceramic membranes were not effective for removing viruses and bacteria from water; pathogen reduction was less than 1.5 log10. By contrast, reverse osmosis (RO) devices reduced microbes by 3 to > 5 log10. In a field study, PMMoV was found to be the most prevalent waterborne virus. Household sand filtration was ineffective for removing E. coli, total coliforms and PMMoV; the reduction was less than 1 order of magnitude. Boiling the water and then filtering it with a ceramic membrane reduced E. coli by 3 orders of magnitude, but this was not effective for removing PMMoV. RO filtration was one of the

promising methods for removing E. coli, total coliforms and PMMoV to below their detection limits in most of the samples studied. The removal of E. coli, total coliforms and PMMoV was >2.3, >4 and >3 log10, respectively. The laboratory results of virus removal efficiency by POU devices agreed with the field study. Due to the prevalence and characteristics of PMMoV, it is a strong candidate for an indigenous indicator to investigate the viral removal efficiency of household POU treatments.

Sarker, S. A. and Brussow, H. From bench to bed and back again: phage therapy of childhood Escherichia coli diarrhea. Ann.N.Y.Acad.Sci. 2016; 1372(1):42-52.

ABSTRACT: Over the last 20 years, the Nestle Research Center in Switzerland and the International Center for Diarrhoeal Diseases Research in Bangladesh have explored the efficacy of alternative biological agents for the treatment of diarrheal diseases. This paper reviews the work of this collaborative effort, particularly on Escherichia coli phage therapy (PT), and discusses the development of the project, starting with the isolation of T4-like coliphages from the stool of diarrhea patients, their pilot plant amplification and purification, and the constitution and testing of a cocktail of T4-like phages in mice. A series of phase I clinical trials has demonstrated the safety of PT. Oral phage given without protection survived gastric passage and was recovered in the feces. Oral T4 phage cocktail was then tested in parallel to a commercial phage product in a phase II randomized, placebo-controlled single-center trial in Bangladeshi children hospitalized with acute E. coli diarrhea. It was found that oral phage did not perform better than the current standard of care by oral rehydration/zinc treatment. Furthermore, fecal E. coli pathogen titers were low and mixed infections were found to be frequent. Microbiota analysis showed a correlation between diarrhea and increased levels of Streptococcus, which raises fundamental questions on the causative agent of diarrhea that may explain PT clinical failure.

Sawant, A. A., Mukherjee, P. P., Jangid, R. K., Galande, S., and Srivatsan, S. G. A clickable UTP analog for the posttranscriptional chemical labeling and imaging of RNA. Org.Biomol.Chem. 6-28-2016; 14(24):5832-5842.

ABSTRACT: The development of robust tools and practical RNA labeling strategies that would facilitate the biophysical analysis of RNA in both cell-free and cellular systems will have profound implications in the discovery of new RNA diagnostic tools and therapeutic strategies. In this context, we describe the development of a new alkyne-modified UTP analog, 5-(1,7-octadinyl)uridine triphosphate (ODUTP), which serves as an efficient substrate for the introduction of a clickable alkyne label into RNA transcripts by bacteriophage T7 RNA polymerase and mammalian cellular RNA polymerases. The ODU-labeled RNA is effectively used by reverse transcriptase to produce cDNA, a property which could be utilized in expanding the chemical space of a RNA library in the aptamer selection scheme. Further, the alkyne label on RNA provides a convenient tool for the posttranscriptional chemical functionalization with a variety of biophysical tags (fluorescent, affinity, amino acid and sugar) by using alkyne-azide cycloaddition reaction. Importantly, the ability of endogenous RNA polymerases to specifically incorporate ODUTP into cellular RNA transcripts enabled the visualization of newly transcribing RNA in cells by microscopy using click reactions. In addition to a clickable alkyne group, ODU contains a Raman scattering label (internal disubstituted alkyne), which exhibits characteristic Raman shifts that fall in the Raman-silent region of cells. Our results indicate that an ODU label could potentially facilitate two-channel visualization of

RNA in cells by using click chemistry and Raman spectroscopy. Taken together, ODU represents a multipurpose ribonucleoside tool, which is expected to provide new avenues to study RNA in cell-free and cellular systems.

Schijven, J. F., Sadeghi, G., and Hassanizadeh, S. M. Long-term inactivation of bacteriophage PRD1 as a function of temperature, pH, sodium and calcium concentration. Water Res. 7-13-2016; 103:66-73.

ABSTRACT: The two most significant processes controlling virus mobility in the subsurface environment are virus attachment and inactivation. In particular, models that predict subsurface virus transport are highly sensitive to inactivation. Virus inactivation is known to depend on temperature as well as hydrochemical conditions. The aim of the current work was to study the effects of temperature and hydrochemical conditions on the inactivation of bacteriophage PRD1 as a model virus, and to develop a quantitative relation for these effects. Series of batch experiments under controlled temperature were conducted, for a range of conditions: 9.5 degrees C and 12 degrees C, pH4 - pH8, sodium concentrations of 1, 10 and 20 mM, and calcium concentrations of 0.5, 1.5, and 3 mM. By multivariate regression analysis, a joint log-square model was developed that describes the inactivation rate of PRD1 as a function of these hydrochemical conditions. This model approximates two rate and Weibull models and accounts for the observed non-linear inactivation at increased pH and salt concentrations. Model predictions are within +/-0.4 log10 (0.4-2.5 times) virus concentration reduction. The nature of the log-square model does not allow extrapolation of virus inactivation beyond the experimental conditions. Inactivation rate of PRD1 was found to increase with increasing temperature and increasing sodium and calcium concentrations, and to be lowest between pH 6.5 and pH 7.5. Within the studied conditions, the developed log-square model may be applied at field scale for predicting inactivation during subsurface transport of viruses.

Semenyuk, P. I., Orlov, V. N., Sokolova, O. S., and Kurochkina, L. P. New GroEL-like chaperonin of bacteriophage OBP Pseudomonas fluorescens suppresses thermal protein aggregation in an ATP-dependent manner. Biochem.J. 8-1-2016; 473(15):2383-2393.

ABSTRACT: Recently, we discovered and studied the first virus-encoded chaperonin of bacteriophage EL Pseudomonas aeruginosa, gene product (gp) 146. In the present study, we performed bioinformatics analysis of currently predicted GroEL-like proteins encoded by phage genomes in comparison with cellular and mitochondrial chaperonins. Putative phage chaperonins share a low similarity and do not form a monophyletic group; nevertheless, they are closer to bacterial chaperonins in the phylogenetic tree. Experimental investigation of putative GroEL-like chaperonin proteins has been continued by physicochemical and functional characterization of gp246 encoded by the genome of Pseudomonas fluorescens bacteriophage OBP. Unlike the more usual double-ring architecture of chaperonins, including the EL gp146, the recombinant gp246 produced by Escherichia coli cells has been purified as a single heptameric ring. It possesses ATPase activity and does not require a co-chaperonin for its function. In vitro experiments demonstrated that gp246 is able to suppress the thermal protein inactivation and aggregation in an ATP-dependent manner, thus indicating chaperonin function. Single-particle electron microscopy analysis revealed the different conformational states of OBP chaperonin, depending on the bound nucleotide.

Seo, J., Seo, D. J., Oh, H., Jeon, S. B., Oh, M. H., and Choi, C. Inhibiting the Growth of Escherichia coli O157:H7 in Beef, Pork, and Chicken Meat using a Bacteriophage. Korean J.Food Sci.Anim Resour. 2016; 36(2):186-193.

ABSTRACT: This study aimed to inhibit Escherichia coli (E. coli) O157:H7 artificially contaminated in fresh meat using bacteriophage. Among 14 bacteriophages, the highly lytic bacteriophage BPECO19 strain was selected to inhibit E. coli O157:H7 in artificially contaminated meat samples. Bacteriophage BPECO19 significantly reduced E. coli O157:H7 bacterial load in vitro in a multiplicity of infection (MOI)-dependent manner. E. coli O157:H7 was completely inhibited only in 10 min in vitro by the treatment of 10,000 MOI BPECO19. The treatment of BPECO19 at 100,000 MOI completely reduced 5 Log CFU/cm(2) E. coli O157:H7 bacterial load in beef and pork at 4 and 8h, respectively. In chicken meat, a 4.65 log reduction of E. coli O157:H7 was observed at 4 h by 100,000 MOI. The treatment of single bacteriophage BPECO19 was an effective method to control E. coli O157:H7 in meat samples.

Servick, K. DRUG DEVELOPMENT. Beleaguered phage therapy trial presses on. Science. 6-24-2016; 352(6293):1506.

No abstract available at this time.

Shapiro, J. W., Williams, E. S., and Turner, P. E. Evolution of parasitism and mutualism between filamentous phage M13 and Escherichia coli. PeerJ. 2016; 4:e2060

ABSTRACT: Background. How host-symbiont interactions coevolve between mutualism and parasitism depends on the ecology of the system and on the genetic and physiological constraints of the organisms involved. Theory often predicts that greater reliance on horizontal transmission favors increased costs of infection and may result in more virulent parasites or less beneficial mutualists. We set out to understand transitions between parasitism and mutualism by evolving the filamentous bacteriophage M13 and its host Escherichia coli. Results. The effect of phage M13 on bacterial fitness depends on the growth environment, and initial assays revealed that infected bacteria reproduce faster and to higher density than uninfected bacteria in 96-well microplates. These data suggested that M13 is, in fact, a facultative mutualist of E. coli. We then allowed E. coli and M13 to evolve in replicated environments, which varied in the relative opportunity for horizontal and vertical transmission of phage in order to assess the evolutionary stability of this mutualism. After 20 experimental passages, infected bacteria from treatments with both vertical and horizontal transmission of phage had evolved the fastest growth rates. At the same time, phage from these treatments no longer benefited the ancestral bacteria. Conclusions. These data suggest a positive correlation between the positive effects of M13 on E. coli hosts from the same culture and the negative effects of the same phage toward the ancestral bacterial genotype. The results also expose flaws in applying concepts from the virulence-transmission tradeoff hypothesis to mutualism evolution. We discuss the data in the context of more recent theory on how horizontal transmission affects mutualisms and explore how these effects influence phages encoding virulence factors in pathogenic bacteria.

Shavrina, M. S., Zimin, A. A., Molochkov, N. V., Chernyshov, S. V., Machulin, A. V., and Mikoulinskaia, G. V. In vitro study of the antibacterial effect of the bacteriophage T5 thermostable endolysin on Escherichia coli cells. J.Appl.Microbiol. 8-8-2016;

ABSTRACT: AIMS: This study aimed to evaluate lysis of Escherichia coli stationary cell cultures induced by the combined action of bacteriophage T5 endolysin (l-alanyl-d-glutamate peptidase) and low doses of various cationic agents permeabilizing the outer membrane of Gram-negative bacteria (polymyxin B, gramicidin D, poly-l-lysine, chlorhexidine and miramistin). METHODS AND RESULTS: The enzyme activity was assayed with the turbidimetric method. Antimicrobial activity was assessed through the number of colony-forming units (CFUs); the results of calculation were represented as logarithmic units. The optical microscopy examination of bacterial cells was conducted in the phase-contrast mode. The use of bacteriophage T5 endolysin in combination with polymyxin B (0.4 mug ml-1) or chlorhexidine (0.5 mug ml-1) made it possible to reduce the number of colony-forming units by five orders of magnitude; and in combination with poly-l-lysine (80 mug ml-1) by four orders, as compared to control. The endolysin was found to be a thermostable protein: it retained ~65% of its initial activity after heating for 30-min at 90 degrees C. Examining the curves of its thermal denaturation revealed the half-transition temperature to be 56.3 +/- 1.0 degrees C. Circular dichroism spectra showed that after recooling the protein restored up to 80% of its native structure. CONCLUSIONS: A substantial synergistic effect of the bacteriophage T5 endolysin and membrane-permeabilizing compounds was demonstrated. SIGNIFICANCE AND IMPACT OF THE STUDY: The study of thermal stability of the bacteriophage T5 endolysin and the quantitative assessment of its antimicrobial activity have been done for the first time. The approach examined lays foundations for designing a two-component preparation which would effectively lyse cells of Gram-negative pathogens from outside. This article is protected by copyright. All rights reserved.

Shen, X., Zhang, J., Xu, J., Du, P., Pang, B., Li, J., and Kan, B. The Resistance of Vibrio cholerae O1 El Tor Strains to the Typing Phage 919TP, a Member of K139 Phage Family. Front Microbiol. 2016; 7:726

ABSTRACT: Bacteriophage 919TP is a temperate phage of Vibrio cholerae serogroup O1 El Tor and is used as a subtyping phage in the phage-biotyping scheme in cholera surveillance in China. In this study, sequencing of the 919TP genome showed that it belonged to the Vibrio phage K139 family. The mechanisms conferring resistance to 919TP infection of El Tor strains were explored to help understand the subtyping basis of phage 919TP and mutations related to 919TP resistance. Among the test strains resistant to phage 919TP, most contained the temperate 919TP phage genome, which facilitated superinfection exclusion to 919TP. Our data suggested that this immunity to Vibrio phage 919TP occurred after absorption of the phage onto the bacteria. Other strains contained LPS receptor synthesis gene mutations that disable adsorption of phage 919TP. Several strains resistant to 919TP infection possessed unknown resistance mechanisms, since they did not contain LPS receptor mutations or temperate K139 phage genome. Further research is required to elucidate the phage infection steps involved in the resistance of these strains to phage infection.

Shin, J. E., Lin, C., and Lim, H. N. Horizontal transfer of DNA methylation patterns into bacterial chromosomes. Nucleic Acids Res. 5-19-2016; 44(9):4460-4471.

ABSTRACT: Horizontal gene transfer (HGT) is the non-inherited acquisition of novel DNA sequences. HGT is common and important in bacteria because it enables the rapid generation of new phenotypes such as antibiotic resistance. Here we show that in vivo

and in vitro DNA methylation patterns can be horizontally transferred into bacterial chromosomes to program cell phenotypes. The experiments were performed using a synthetic system in Escherichia coli where different DNA methylation patterns within the cis-regulatory sequence of the agn43 gene turn on or off a fluorescent reporter (CFP). With this system we demonstrated that DNA methylation patterns not only accompany the horizontal transfer of genes into the bacterial cytoplasm but can be transferred into chromosomes by: (i) bacteriophage P1 transduction; and (ii) transformation of extracellular synthetic DNA. We also modified the experimental system by replacing CFP with the SgrS small RNA, which regulates glucose and methyl alpha-D-glucoside uptake, and showed that horizontally acquired DNA methylation patterns can increase or decrease cell fitness. That is, horizontally acquired DNA methylation patterns can result in the selection for and against cells that have HGT. Findings from these proof-of-concept experiments have applications in synthetic biology and potentially broad implications for bacterial adaptation and evolution.

Shirasaki, N., Matsushita, T., Matsui, Y., Marubayashi, T., and Murai, K. Investigation of enteric adenovirus and poliovirus removal by coagulation processes and suitability of bacteriophages MS2 and phiX174 as surrogates for those viruses. Sci.Total Environ. 9-1-2016; 563-564:29-39.

ABSTRACT: We evaluated the removal of enteric adenovirus (AdV) type 40 and poliovirus (PV) type 1 by coagulation, using water samples from 13 water sources for drinking water treatment plants in Japan. The behaviors of two widely accepted enteric virus surrogates, bacteriophages MS2 and phiX174, were compared with the behaviors of AdV and PV. Coagulation with polyaluminum chloride (PACl, basicity 1.5) removed AdV and PV from virus-spiked source waters: the infectious AdV and PV removal ratios evaluated by means of a plaque-forming-unit method were 0.1-1.4-log10 and 0.5-2.4-log10, respectively. A nonsulfated high-basicity PACl (basicity 2.1) removed infectious AdV and PV more efficiently than did other commercially available PACls (basicity 1.5-2.1), alum, and ferric chloride. The MS2 removal ratios tended to be larger than those of AdV and PV, partly because of differences in the hydrophobicities of the virus particles and the sensitivity of the virus to the virucidal activity of PACl; the differences in removal ratios were not due to differences in the surface charges of the virus particles. MS2, which was more hydrophobic than the other viruses, was inactivated during coagulation with PACl. Therefore, MS2 does not appear to be an appropriate surrogate for AdV and PV during coagulation. In contrast, because phiX174, like AdV and PV, was not inactivated during coagulation, and because the hydrophobicity of phiX174 was similar to or somewhat lower than the hydrophobicities of AdV and PV, the phiX174 removal ratios tended to be similar to or somewhat smaller than those of the enteric viruses. Therefore, phiX174 is a potential conservative surrogate for AdV and PV during coagulation. In summary, the surface hydrophobicity of virus particles and the sensitivity of the virus to the virucidal activity of the coagulant are probably important determinants of the efficiency of virus removal during coagulation.

Siddiqui, R., Kulsoom, H., Lalani, S., and Khan, N. A. Isolation of Balamuthia mandrillaris-specific antibody fragments from a bacteriophage antibody display library. Exp.Parasitol. 2016; 166:94-96.

ABSTRACT: Balamuthia mandrillaris is a protist pathogen that can cause encephalitis with a mortality rate of more than 95%. Early diagnosis followed by aggressive treatment is a

pre-requisite for successful prognosis. Current methods for identifying this organism rely on culture and microscopy, antibody-based methods using animals, or involve the use of molecular tools that are expensive. Here, we describe the isolation of antibody fragments that can be used for the unequivocal identification of B. mandrillaris. B. mandrillaris-specific antibody fragments were isolated from a bacteriophage antibody display library. Individual clones were studied by enzyme-linked immunosorbent assay, and immunofluorescence. Four antibody clones showed specific binding to B. mandrillaris. The usefulness of phage antibody display technology as a diagnostic tool for isolating antibody fragments against B. mandrillaris antigens and studying their biological role(s) is discussed further.

Simpkin, A. J. and Rigden, D. J. GP0.4 from bacteriophage T7: in silico characterisation of its structure and interaction with E. coli FtsZ. BMC.Res.Notes. 2016; 9(1):343

ABSTRACT: BACKGROUND: Proteins produced by bacteriophages can have potent antimicrobial activity. The study of phage-host interactions can therefore inform small molecule drug discovery by revealing and characterising new drug targets. Here we characterise in silico the predicted interaction of gene protein 0.4 (GP0.4) from the Escherichia coli (E. coli) phage T7 with E. coli filamenting temperature-sensitive mutant Z division protein (FtsZ). FtsZ is a tubulin homolog which plays a key role in bacterial cell division and that has been proposed as a drug target. RESULTS: Using ab initio, fragment assembly structure modelling, we predicted the structure of GP0.4 with two programs. A structure similarity-based network was used to identify a U-shaped helix-turn-helix candidate fold as being favoured. ClusPro was used to dock this structure prediction to a homology model of E. coli FtsZ resulting in a favourable predicted interaction mode. Alternative docking methods supported the proposed mode which offered an immediate explanation for the anti-filamenting activity of GP0.4. Importantly, further strong support derived from a previously characterised insertion mutation, known to abolish GP0.4 activity, that is positioned in close proximity to the proposed GP0.4/FtsZ interface. CONCLUSIONS: The mode of interaction predicted by bioinformatics techniques strongly suggests a mechanism through which GP0.4 inhibits FtsZ and further establishes the latter's druggable intrafilament interface as a potential drug target.

Singh, P. and Pande, R. DNA Folding Transition in Presence of Naphthylhydroxamic Acids as Revealed by Fluorescence Microscopic Single Molecule Observation Method. J.Fluoresc. 2016; 26(1):67-73.

ABSTRACT: Fluorescence microscopy is a field of growing applications in various fields as it can be used to study immunofluorescence,fluorescent proteins techniques, live-cell imaging and many more. The present investigation is based on this single molecule observation technique to observe the effect of N-arylhydroxamic acids on lambda plasmid DNA and linear Bacteriophage T7 DNA. The compounds under present investigation include N-1-naphthyl-o-methylbenzohydroxamic acid,N-1-naphthyl-p-methylbenzohydroxamic acid, N-1-naphthyl ethoxy benzo hydroxamic acid, N-1-naphthylphenylacetohydroxamic acid and N-1-naphthyl valero hydroxamic acid. The hydrodynamic radius, RH of lambda DNA and long-axis length, l of T7 DNA were determined from the direct observation of Brownian motion of the DNA molecules in the absence and presence of hydroxamic acids. Folding transition was observed for lambda DNA as well as T7 DNA in the presence of naphthyl hydroxamic acids. N-1-naphthylvalerohydroxamic acid was found to be most effective.

Singla, S., Harjai, K., Raza, K., Wadhwa, S., Katare, O. P., and Chhibber, S. Phospholipid vesicles encapsulated bacteriophage: A novel approach to enhance phage biodistribution. J.Virol.Methods. 7-5-2016; 236:68-76.

ABSTRACT: Phage therapy has been at the centre of attraction for combating multi-drug resistant strains. However, less stability and rapid clearance of phage by mononuclear phagocytic system (MPS) restricts its use in humans. In the present study, aim was to develop a liposomal delivery system for bacteriophage that can assure efficient phage delivery and retention at the site of infection. Different ratios of cholesterol, lipids and surfactant along with different charge inducers were employed to prepare liposomes. Phage was then entrapped in the liposomes and characterized on the basis of morphology, size, entrapment efficiency and stability. Further, in vivo biodistribution of free phage and liposome entrapped phage was compared in different organs of mice. A cationic liposomal formulation showed maximum encapsulation efficiency of 92%. Transmission electron microscopy (TEM) confirmed the entrapment of phages in liposomes. Liposome preparation was found to be most stable at 4 degrees C during storage. Liposome entrapped bacteriophage was retained for longer duration in different organs i.e. upto day 4 in blood, day 6 in liver, lungs and kidney, 14days in spleen of mice as compared to free phage that became undetectable by 36th h in blood as well as lungs and by 48th h in all other organs.

Singla, S., Harjai, K., Katare, O. P., and Chhibber, S. Encapsulation of Bacteriophage in Liposome Accentuates Its Entry in to Macrophage and Shields It from Neutralizing Antibodies. PLoS.One. 2016; 11(4):e0153777

ABSTRACT: Phage therapy has been a centre of attraction for biomedical scientists to treat infections caused by drug resistant strains. However, ability of phage to act only on extracellular bacteria and probability of interference by anti-phage antibodies in vivo is considered as a important limitation of bacteriophage therapy. To overcome these hurdles, liposome were used as delivery vehicle for phage in this study. Anti-phage antibodies were raised in mice and pooled serum was evaluated for its ability to neutralize free and liposome entrapped phage. Further, ability of phage and liposome-entrapped phage to enter mouse peritoneal macrophages and kill intracellular Klebsiella pneumoniae was compared. Also, an attempt to compare the efficacy of free phage and liposome entrapped phage, alone or in conjunction with amikacin in eradicating mature biofilm was made. The entrapment of phage in liposome provided 100% protection to phage from neutralizing antibody. On the contrary un-entrapped phage got neutralized within 3 h of its interaction with antibody. Compared to the inability of free phage to enter macrophages, the liposome were able to deliver entrapped phage inside macrophages and cause 94.6% killing of intracellular K. pneumoniae. Liposome entrapped phage showed synergistic activity along with amikacin to eradicate mature biofilm of K. pneumoniae. Our study reinforces the growing interest in using phage therapy as a means of targeting multidrug resistant bacterial infections as liposome entrapment of phage makes them highly effective in vitro as well as in vivo by overcoming the majority of the hurdles related to clinical use of phage.

Skurnik, M. and Kiljunen, S. [Possibilities of bacteriophage therapy]. Duodecim. 2016; 132(8):712-719.

ABSTRACT: Antibiotic resistance of bacterial pathogens has increased, and new therapies are urgently needed. Bacteriophages (phages), viruses infecting and killing bacteria, are the most abundant organisms on earth. In nature there are several specific phages for every bacterium, controlling bacterial numbers and maintaining ecological balance. Phage therapy, i.e., treating bacterial infections with phages, offers an alternative complementary to antibiotics as phages infect and kill also multi-resistant bacteria. Phages possess narrow host specificity, each phage infecting only a few bacterial species or strains. Thereby phages do not harm the normal microbiota as antibiotics do. We aim to begin clinical trials of phage therapy in Finland.

Snyder, A. B., Perry, J. J., and Yousef, A. E. Developing and optimizing bacteriophage treatment to control enterohemorrhagic Escherichia coli on fresh produce. Int.J.Food Microbiol. 7-16-2016; 236:90-97.

ABSTRACT: Bacteriophages are potentially useful in controlling foodborne pathogens on minimally processed products since phage application is a non-destructive treatment. The purpose of this study was to evaluate the efficacy of a newly isolated environmental bacteriophage against enterohemorrhagic Escherichia coli on fresh produce, and optimize the treatment with consideration for potential application. Seven anti E. coli O157:H7 EDL933 bacteriophages were isolated from various sources; the most promising was isolated from municipal wastewater. This isolate (designated as E. coli phage OSY-SP) was propagated with the host, in a growth medium, to a titer of 108 PFU/ml. Before inoculation into fresh produce, E. coli phage OSY-SP was incubated with the host bacterium, spent medium was filter-sterilized, and the resulting crude lysate was used as a source of phage inocula for preliminary experiments. For optimized testing, phage in the crude lysate was purified by ultra-centrifugation and resuspension in phosphate-buffered saline. Efficacy of phage treatments was determined as a function of fresh produce type (cut green pepper or spinach leaves), treatment time (2 or 5min rinsing), and temperature of holding treated produce (4 degrees C, 25 degrees , or a combination of both temperatures). Cut green pepper was treated with UV light, to eliminate background microbiota, then spot-inoculated with E. coli O157:H7 EDL933 on cut edges, and the inoculum was allowed to dry. Because of its susceptibility to damage, baby spinach leaves were not subjected to a decontamination treatment. These leaves were inoculated with the green fluorescent protein-labeled E. coli O157:H7 B6-914 to facilitate inoculum enumeration in the presence of background microbiota. Phage suspension was applied to the inoculated fresh produce that was subsequently held for three days under variable storage conditions. The optimized phage treatment decreased the populations of pathogenic E. coli by 2.4-3.0logCFU/g on cut green pepper (5-min rinse) and 3.4-3.5logCFU/g on spinach leaves (2-min rinse), during 72h storage. The majority of this decline was caused by the antimicrobial action of the phage. These findings suggest the utility of bacteriophage to selectively control pathogens on fresh produce.

Stockley, P. G., White, S. J., Dykeman, E., Manfield, I., Rolfsson, O., Patel, N., Bingham, R., Barker, A., Wroblewski, E., Chandler-Bostock, R., Weiss, E. U., Ranson, N. A., Tuma, R., and Twarock, R. Bacteriophage MS2 genomic RNA encodes an assembly instruction manual for its capsid. Bacteriophage. 2016; 6(1):e1157666

ABSTRACT: Using RNA-coat protein crosslinking we have shown that the principal RNA recognition surface on the interior of infectious MS2 virions overlaps with the known peptides that bind the high affinity translational operator, TR, within the phage genome. The data also reveal the sequences of genomic fragments in contact with the coat protein shell. These show remarkable overlap with previous predictions based on the hypothesis that virion assembly is mediated by multiple sequences-specific contacts at RNA sites termed Packaging Signals (PSs). These PSs are variations on the TR stem-loop sequence and secondary structure. They act co-operatively to regulate the dominant assembly pathway and ensure cognate RNA encapsidation. In MS2, they also trigger conformational change in the dimeric capsomere creating the A/B quasi-conformer, 60 of which are needed to complete the T=3 capsid. This is the most compelling demonstration to date that this ssRNA virus, and by implications potentially very many of them, assemble via a PS-mediated assembly mechanism.

Stodola, J. L., Stith, C. M., and Burgers, P. M. Proficient Replication of the Yeast Genome by a Viral DNA Polymerase. J.Biol.Chem. 5-27-2016; 291(22):11698-11705.

ABSTRACT: DNA replication in eukaryotic cells requires minimally three B-family DNA polymerases: Pol alpha, Pol delta, and Pol . Pol delta replicates and matures Okazaki fragments on the lagging strand of the replication fork. Saccharomyces cerevisiae Pol delta is a three-subunit enzyme (Pol3-Pol31-Pol32). A small C-terminal domain of the catalytic subunit Pol3 carries both iron-sulfur cluster and zinc-binding motifs, which mediate interactions with Pol31, and processive replication with the replication clamp proliferating cell nuclear antigen (PCNA), respectively. We show that the entire N-terminal domain of Pol3, containing polymerase and proofreading activities, could be effectively replaced by those from bacteriophage RB69, and could carry out chromosomal DNA replication in yeast with remarkable high fidelity, provided that adaptive mutations in the replication clamp PCNA were introduced. This result is consistent with the model that all essential interactions for DNA replication in yeast are mediated through the small C-terminal domain of Pol3. The chimeric polymerase carries out processive replication with PCNA in vitro; however, in yeast, it requires an increased involvement of the mutagenic translesion DNA polymerase zeta during DNA replication.

Sun, Y., Sun, Y., Zhao, R., and Gao, K. Intracellular delivery of messenger RNA by recombinant PP7 virus-like particles carrying low molecular weight protamine. BMC.Biotechnol. 2016; 16(1):46

ABSTRACT: BACKGROUND: Cell-penetrating peptides (CPPs) have been widely used as carriers to transport different molecules into living cells, whereas messenger RNAs (mRNAs) have been utilized as target molecules for the prevention and treatment of various diseases. However, the instability of CPPs and mRNAs has limited their application. Bacteriophage PP7 virus-like particles (VLPs) may protect peptides and RNAs from degradation through displaying foreign peptides on their surface and encapsidating RNA linked with the pac site. RESULTS: In this study, the cDNA of the PP7 coat protein single-chain dimer carrying low molecular weight protamine (LMWP) and the cDNA of green fluorescent protein (GFP) were inserted into two multiple cloning sites of pETDuet-1, respectively. PP7 VLPs carrying the LMWP peptide and GFP mRNA were subsequently expressed in Escherichia coli BL21 (DE3) with high yield and thermal stability, and were easily purified. The VLPs were also non-replicative, non-infectious, and non-toxic. Moreover, they penetrated the mouse prostate cancer cells RM-1 after 24 h incubation.

Last, PP7 VLPs carrying the LMWP could encapsidate the GFP mRNA, which was translated into mature protein in mammalian cells. CONCLUSIONS: Recombinant PP7 VLPs can be used simultaneously as a targeted delivery vector for both peptides and mRNA due to their abilities to package RNA and display peptides.

Swift, B. M., Convery, T. W., and Rees, C. E. Evidence of Mycobacterium tuberculosis complex bacteraemia in intradermal skin test positive cattle detected using phage-RPA. Virulence. 5-19-2016; 1-10.

ABSTRACT: Bovine tuberculosis is a zoonotic infectious disease caused by Mycobacterium bovis that affects cattle and can cause tuberculosis in a range of wildlife animals. A bacteriophage-based method combined with PCR (phage-PCR) has been recently used to detect and identify viable pathogenic mycobacteria in the peripheral blood mononuclear cells (PBMCs) of animals suffering from paratuberculosis. To adapt this method for the detection of M. bovis in blood, a new isothermal DNA amplification protocol using Recombinase Polymerase Amplification (RPA) was developed and was found to be able to detect M. bovis BCG within 48 h, with a limit of detection of approximately 10 cells per ml of blood for artificially inoculated blood samples. When blood samples (2 ml) from a Single Comparative Cervical Intradermal Tuberculin (SCCIT)-negative beef herd were tested, Mycobacterium tuberculosis complex (MTC) cells were not detected from any (45) of the blood samples. However when blood samples from SCCIT-positive animals were tested, viable MTC bacteria were detected in 66 % (27/41) of samples. Of these 41 animals sampled, 32 % (13) had visible lesions. In the visible lesion (VL) group, 85 % (11/13) had detectable levels of MTC whereas only 57 % (16/28) of animals which had no visible lesions (NVL) were found to have detectable mycobacteraemia. These results indicated that this simple, rapid method can be applied for the study of M. bovis infections. The frequency with which viable mycobacteria were detected in the peripheral blood of SCCIT-positive animals changes the paradigm of this disease.

Swift, B. M., Huxley, J. N., Plain, K. M., Begg, D. J., de, Silva K., Purdie, A. C., Whittington, R. J., and Rees, C. E. Evaluation of the limitations and methods to improve rapid phage-based detection of viable Mycobacterium avium subsp. paratuberculosis in the blood of experimentally infected cattle. BMC.Vet.Res. 2016; 12(1):115

ABSTRACT: BACKGROUND: Disseminated infection and bacteraemia is an underreported and under-researched aspect of Johne's disease. This is mainly due to the time it takes for Mycobacterium avium subsp. paratuberculosis (MAP) to grow and lack of sensitivity of culture. Viable MAP cells can be detected in the blood of cattle suffering from Johne's disease within 48 h using peptide-mediated magnetic separation (PMMS) followed by bacteriophage amplification. The aim of this study was to demonstrate the first detection of MAP in the blood of experimentally exposed cattle using the PMMS-bacteriophage assay and to compare these results with the immune response of the animal based on serum ELISA and shedding of MAP by faecal culture. RESULTS: Using the PMMS-phage assay, seven out of the 19 (37 %) MAP-exposed animals that were tested were positive for viable MAP cells although very low numbers of MAP were detected. Two of these animals were positive by faecal culture and one was positive by serum ELISA. There was no correlation between PMMS-phage assay results and the faecal and serum ELISA results. None of the control animals (10) were positive for MAP using any of the four detection methods. Investigations carried out into the efficiency of the assay; found that

the PMMS step was the limiting factor reducing the sensitivity of the phage assay. A modified method using the phage assay directly on isolated peripheral blood mononuclear cells (without PMMS) was found to be superior to the PMMS isolation step. CONCLUSIONS: This proof of concept study has shown that viable MAP cells are present in the blood of MAP-exposed cattle prior to the onset of clinical signs. Although only one time point was tested, the ability to detect viable MAP in the blood of subclinically infected animals by the rapid phage-based method has the potential to increase the understanding of the pathogenesis of Johne's disease progression by warranting further research on the presence of MAP in blood.

Sybesma, W., Zbinden, R., Chanishvili, N., Kutateladze, M., Chkhotua, A., Ujmajuridze, A., Mehnert, U., and Kessler, T. M. Bacteriophages as Potential Treatment for Urinary Tract Infections. Front Microbiol. 2016; 7:465

ABSTRACT: BACKGROUND: Urinary tract infections (UTIs) are among the most prevalent microbial diseases and their financial burden on society is substantial. The continuing increase of antibiotic resistance worldwide is alarming so that well-tolerated, highly effective therapeutic alternatives are urgently needed. OBJECTIVE: To investigate the effect of bacteriophages on Escherichia coli and Klebsiella pneumoniae strains isolated from the urine of patients suffering from UTIs. MATERIAL AND METHODS: Forty-one E. coli and 9 K. pneumoniae strains, isolated from the urine of patients suffering from UTIs, were tested in vitro for their susceptibility toward bacteriophages. The bacteriophages originated from either commercially available bacteriophage cocktails registered in Georgia or from the bacteriophage collection of the George Eliava Institute of Bacteriophage, Microbiology and Virology. In vitro screening of bacterial strains was performed by use of the spot-test method. The experiments were implemented three times by different groups of scientists. RESULTS: The lytic activity of the commercial bacteriophage cocktails on the 41 E. coli strains varied between 66% (Pyo bacteriophage) and 93% (Enko bacteriophage). After bacteriophage adaptation of the Pyo bacteriophage cocktail, its lytic activity was increased from 66 to 93% and only one E. coli strain remained resistant. One bacteriophage of the Eliava collection could lyse all 9 K. pneumoniae strains. CONCLUSIONS: Based on the high lytic activity and the potential of resistance optimization by direct adaption of bacteriophages as reported in this study, and in view of the continuing increase of antibiotic resistance worldwide, bacteriophage therapy is a promising treatment option for UTIs highly warranting randomized controlled trials.

Talbert, J. N., Alcaine, S. D., and Nugen, S. R. Engineering bacteriophage for a pragmatic low-resource setting bacterial diagnostic platform. Bioengineered. 2016; 7(3):132-136.

ABSTRACT: Bacteriophages represent multifaceted building blocks that can be incorporated as substitutes for, or in unison with other detection methods, to create powerful new diagnostics for the detection of bacteria. The ease of phage manipulation, production, and detection speed clearly highlights that there remains unrealized opportunities to leverage these phage-based components in diagnostics amenable to resource-limited settings. The passage of regulations like the Food Safety Modernization act, and the ever increasing extent of global trade and travel, will create further demand for these types of diagnostics. While phage-based diagnostics have begun to entering the market place, further research is needed to ensure the potential benefits of phage-based technologies for public health are fully realized. We are just

beginning to explore the possibilities that phage-based detection can offer us in the future. The combination of engineered phages as well as engineered enzymes could result in ultrasensitive detection systems for low-resource settings. Because the reporter enzyme is synthesized in vivo, we need to consider the options outside of normal enzyme reporters. In this case, common enzyme issues such as purification and long-term stability are less important. Phage-based diagnostics were conceptualized from out-of-the box thinking and the evolution of these systems should be as well.

Tang, S. S., Carlin, N. I., Talukder, K. A., Cam, P. D., and Verma, N. K. Shigella flexneri serotype 1c derived from serotype 1a by acquisition of gtrIC gene cluster via a bacteriophage. BMC.Microbiol. 2016; 16(1):127

ABSTRACT: BACKGROUND: Shigella spp. are the primary causative agents of bacillary dysentery. Since its emergence in the late 1980s, the S. flexneri serotype 1c remains poorly understood, particularly with regard to its origin and genetic evolution. This article provides a molecular insight into this novel serotype and the gtrIC gene cluster that determines its unique immune recognition. RESULTS: A PCR of the gtrIC cluster showed that serotype 1c isolates from different geographical origins were genetically conserved. An analysis of sequences flanking the gtrIC cluster revealed remnants of a prophage genome, in particular integrase and tRNA(Pro) genes. Meanwhile, Southern blot analyses on serotype 1c, 1a and 1b strains indicated that all the tested serotype 1c strains may have had a common origin that has since remained distinct from the closely related 1a and 1b serotypes. The identification of prophage genes upstream of the gtrIC cluster is consistent with the notion of bacteriophage-mediated integration of the gtrIC cluster into a pre-existing serotype. CONCLUSIONS: This is the first study to show that serotype 1c isolates from different geographical origins share an identical pattern of genetic arrangement, suggesting that serotype 1c strains may have originated from a single parental strain. Analysis of the sequence around the gtrIC cluster revealed a new site for the integration of the serotype converting phages of S. flexneri. Understanding the origin of new pathogenic serotypes and the molecular basis of serotype conversion in S. flexneri would provide information for developing cross-reactive Shigella vaccines.

Tao, P., Mahalingam, M., and Rao, V. B. Highly Effective Soluble and Bacteriophage T4 Nanoparticle Plague Vaccines Against Yersinia pestis. Methods Mol.Biol. 2016; 1403:499-518.

ABSTRACT: Plague caused by Yersinia pestis is an ancient disease, responsible for millions of deaths in human history. Unfortunately, there is no FDA-approved vaccine available. Recombinant subunit vaccines based on two major antigens, Caf 1 (F1) and LcrV (V), have been under investigation and showed promise. However, there are two main problems associated with these vaccines. First, the Yersinia capsular protein F1 has high propensity to aggregate, particularly when expressed in heterologous systems such as Escherichia coli, thus affecting vaccine quality and efficacy. Second, the subunit vaccines do not induce adequate cell-mediated immune responses that also appear to be essential for optimal protection against plague. We have developed two basic approaches, structure-based immunogen design and phage T4 nanoparticle delivery, to construct new plague vaccines that may overcome these problems. First, by engineering F1 protein, we generated a monomeric and soluble F1V mutant (F1mutV) which has similar immunogenicity as wild-type F1V. The NH2-terminal beta-strand of F1 was transplanted to the COOH-terminus and the sequence flanking the beta-strand was

duplicated to retain a key CD4(+) T cell epitope. Second, we generated a nanoparticle plague vaccine that can induce balanced antibody- and cell-mediated immune responses. This was done by arraying the F1mutV on phage T4 via the small outer capsid (Soc) protein which binds to T4 capsid at nanomolar affinity. Preparation of these vaccines is described in detail and we hope that these would be considered as candidates for licensing a next-generation plague vaccine.

Taylor, N. M., Prokhorov, N. S., Guerrero-Ferreira, R. C., Shneider, M. M., Browning, C., Goldie, K. N., Stahlberg, H., and Leiman, P. G. Structure of the T4 baseplate and its function in triggering sheath contraction. Nature. 5-19-2016; 533(7603):346-352.

ABSTRACT: Several systems, including contractile tail bacteriophages, the type VI secretion system and R-type pyocins, use a multiprotein tubular apparatus to attach to and penetrate host cell membranes. This macromolecular machine resembles a stretched, coiled spring (or sheath) wound around a rigid tube with a spike-shaped protein at its tip. A baseplate structure, which is arguably the most complex part of this assembly, relays the contraction signal to the sheath. Here we present the atomic structure of the approximately 6-megadalton bacteriophage T4 baseplate in its pre- and post-host attachment states and explain the events that lead to sheath contraction in atomic detail. We establish the identity and function of a minimal set of components that is conserved in all contractile injection systems and show that the triggering mechanism is universally conserved.

Taylor, V. L., Hoage, J. F., Thrane, S. W., Huszczynski, S. M., Jelsbak, L., and Lam, J. S. A Bacteriophage-Acquired O-Antigen Polymerase (Wzybeta) from P. aeruginosa Serotype O16 Performs a Varied Mechanism Compared to Its Cognate Wzyalpha. Front Microbiol. 2016; 7:393

ABSTRACT: Pseudomonas aeruginosa is a Gram-negative bacterium that produces highly varied lipopolysaccharide (LPS) structures. The O antigen (O-Ag) in the LPS is synthesized through the Wzx/Wzy-dependent pathway where lipid-linked O-Ag repeats are polymerized by Wzy. Horizontal-gene transfer has been associated with O-Ag diversity. The O-Ag present on the surface of serotypes O5 and O16, differ in the intra-molecular bonds, alpha and beta, respectively; the latter arose from the action of three genes in a serotype converting unit acquired from bacteriophage D3, including a beta-polymerase (Wzybeta). To further our understanding of O-polymerases, the inner membrane (IM) topology of Wzybeta was determined using a dual phoA-lacZalpha reporter system wherein random 3' gene truncations were localized to specific loci with respect to the IM by normalized reporter activities as determined through the ratio of alkaline phosphatase activity to beta-galactosidase activity. The topology of Wzybeta developed through this approach was shown to contain two predominant periplasmic loops, PL3 (containing an RX10G motif) and PL4 (having an O-Ag ligase superfamily motif), associated with inverting glycosyltransferase reaction. Through site-directed mutagenesis and complementation assays, residues Arg(254), Arg(270), Arg(272), and His(300) were found to be essential for Wzybeta function. Additionally, like-charge substitutions, R254K and R270K, could not complement the wzy beta knockout, highlighting the essential guanidium side group of Arg residues. The O-Ag ligase domain is conserved among heterologous Wzy proteins that produce beta-linked O-Ag repeat units. Taking advantage of the recently obtained whole-genome sequence of serotype O16 a candidate promoter was identified. Wzy beta under its native promoter was integrated in

the PAO1 genome, which resulted in simultaneous production of alpha- and beta-linked O-Ag. These observations established that members of Wzy-like family consistently exhibit a dual-periplasmic loops topology, and identifies motifs that are plausible to be involved in enzymatic activities. Based on these results, the phage-derived Wzybeta utilizes a different reaction mechanism in the P. aeruginosa host to avoid self-inhibition during serotype conversion.

Telesmanich, N. R., Goncharenko, E. V., Chaika, S. O., Chaika, I. A., and Telicheva, V. O. [POSSIBILITIES OF APPLICATION OF MALDI-TOF MASS-SPECTROMETRY FOR STUDY OF CARBOHYDRATE-SPECIFIC RECEPTORS FOR DIAGNOSTIC BACTERIOPHAGE EL TOR]. Zh.Mikrobiol.Epidemiol.Immunobiol. 2016; (2):85-90.

ABSTRACT: AIM: Study mechanisms of interaction of diagnostic bacteriophage El Tor with sensitive strain Vibrio cholerae El Tor 18507 using direct protein profiling, identification of constant and variable proteins, taking part in interaction of the phage and cell, as well as carbohydrate-specific phage receptors. MATERIALS AND METHODS: . A commercial preparation of cholera diagnostic bacteriophage El Tor, strain V. cholerae El Tor 18507 were used. Effect of carbohydrates on bacteriophage activity was determined in experiments with phage by a classic and modified by us method. Protein profiles of the studied objects were studied using MSP-analysis method. RESULTS: Sucrose was shown to inhibit lytic activity of bacteriophage. Proteome profiles of El Tor bacteriophage and sensitive indicator strains were studied, identification of constant and variable proteins of the studied objects by MSP Peak-list program was carried out. CONCLUSION: Analysis of changes of profiles of phage and microbial cell during interaction with sucrose gave a basis for assuming, that sucrose in the mixture of culture-phage enters interaction namely with phage protein receptors, blocking receptors specific for cholera vibrio, that subsequently manifests in a sharp decrease of phage activity against the sensitive strain.

Tetz, G. and Tetz, V. Bacteriophage infections of microbiota can lead to leaky gut in an experimental rodent model. Gut Pathog. 2016; 8:33

ABSTRACT: Increased intestinal permeability and translocation of gut microbiota from the intestinal lumen to the systemic circulation predispose patients to various diseases and may be one of the main triggers thereof. The role of microbiota in increased intestinal permeability is under intensive investigation. Here, we studied alterations in the host and increased intestinal permeability as a direct effect of treatment with a bacteriophage cocktail. After 10 days of challenge, the rats showed weight loss, messy hair, and decreased activity. Additionally, they displayed a significantly elevated lactulose:mannitol ratio and the level of circulating immune complexes. To our knowledge, this study demonstrates for the first time that increased intestinal permeability may be induced by bacteriophages that affect the microbiota.

Tinoco, J. M., Buttaro, B., Zhang, H., Liss, N., Sassone, L., and Stevens, R. Effect of a genetically engineered bacteriophage on Enterococcus faecalis biofilms. Arch.Oral Biol. 7-6-2016; 71:80-86.

ABSTRACT: OBJECTIVE: Enterococcus faecalis is a Gram-positive, facultative anaerobic bacterium that is associated with failed endodontic cases and nosocomial infections. E. faecalis can form biofilms, penetrate dentinal tubules and survive in root canals with

scarce nutritional supplies. These properties can make E. faecalis resistant to conventional endodontic disinfection therapy. Furthermore, treatment may be complicated by the fact that many E. faecalis strains are resistant to antibiotics. A potential alternative to antibiotic therapy is phage therapy. varphiEf11 is a temperate phage that infects strains of E. faecalis. It was previously sequenced and genetically engineered to modify its properties in order to render it useful as a therapeutic agent in phage therapy. In the current study, we have further genetically modified the phage to create phage varphiEf11/varphiFL1C(Delta36)PnisA. The aim of this study was to evaluate the efficacy of bacteriophage varphiEf11/varphiFL1C(Delta36)PnisA, to disrupt biofilms of two Enterococcus faecalis strains: JH2-2 (vancomycin-sensitive) and V583 (vancomycin-resistant). METHODS: 24h static biofilms of E. faecalis strains JH2-2(pMSP3535 nisR/K) and V583 (pMSP3535nisR/K), formed on cover slips, were inoculated with bacteriophage varphiEf11/varphiFL1C(Delta36)PnisA. After 24 and 48h incubation, the bacterial biomass was imaged by confocal microscopy and viable cells were quantified by colony forming unit measurement. RESULTS: The results showed a 10-100-fold decrease in viable cells (CFU/biofilm) after phage treatment, which was consistent with comparisons of treated and untreated biofilm images visualized as max projections of the Z-series. CONCLUSION: The biomass of both vancomycin-sensitive and vancomycin-resistant E. faecalis biofilms is markedly reduced following infection by bacteriophage varphiEf11/varphiFL1C(Delta36)PnisA.

Topham, C. M., Barbe, S., and Andre, I. An Atomistic Statistically Effective Energy Function for Computational Protein Design. J.Chem.Theory.Comput. 8-9-2016; 12(8):4146-4168.

ABSTRACT: Shortcomings in the definition of effective free-energy surfaces of proteins are recognized to be a major contributory factor responsible for the low success rates of existing automated methods for computational protein design (CPD). The formulation of an atomistic statistically effective energy function (SEEF) suitable for a wide range of CPD applications and its derivation from structural data extracted from protein domains and protein-ligand complexes are described here. The proposed energy function comprises nonlocal atom-based and local residue-based SEEFs, which are coupled using a novel atom connectivity number factor to scale short-range, pairwise, nonbonded atomic interaction energies and a surface-area-dependent cavity energy term. This energy function was used to derive additional SEEFs describing the unfolded-state ensemble of any given residue sequence based on computed average energies for partially or fully solvent-exposed fragments in regions of irregular structure in native proteins. Relative thermal stabilities of 97 T4 bacteriophage lysozyme mutants were predicted from calculated energy differences for folded and unfolded states with an average unsigned error (AUE) of 0.84 kcal mol(-1) when compared to experiment. To demonstrate the utility of the energy function for CPD, further validation was carried out in tests of its capacity to recover cognate protein sequences and to discriminate native and near-native protein folds, loop conformers, and small-molecule ligand binding poses from non-native benchmark decoys. Experimental ligand binding free energies for a diverse set of 80 protein complexes could be predicted with an AUE of 2.4 kcal mol(-1) using an additional energy term to account for the loss in ligand configurational entropy upon binding. The atomistic SEEF is expected to improve the accuracy of residue-based coarse-grained SEEFs currently used in CPD and to extend the range of applications of extant atom-based protein statistical potentials.

Torres-Barcelo, C., Franzon, B., Vasse, M., and Hochberg, M. E. Long-term effects of single and combined introductions of antibiotics and bacteriophages on populations of Pseudomonas aeruginosa. Evol.Appl. 2016; 9(4):583-595.

ABSTRACT: With escalating resistance to antibiotics, there is an urgent need to develop alternative therapies against bacterial pathogens and pests. One of the most promising is the employment of bacteriophages (phages), which may be highly specific and evolve to counter antiphage resistance. Despite an increased understanding of how phages interact with bacteria, we know very little about how their interactions may be modified in antibiotic environments and, reciprocally, how phage may affect the evolution of antibiotic resistance. We experimentally evaluated the impacts of single and combined applications of antibiotics (different doses and different types) and phages on in vitro evolving populations of the opportunistic pathogen Pseudomonas aeruginosa PAO1. We also assessed the effects of past treatments on bacterial virulence in vivo, employing larvae of Galleria mellonella to survey the treatment consequences for the pathogen. We find a strong synergistic effect of combining antibiotics and phages on bacterial population density and in limiting their recovery rate. Our long-term study establishes that antibiotic dose is important, but that effects are relatively insensitive to antibiotic type. From an applied perspective, our results indicate that phages can contribute to managing antibiotic resistance levels, with limited consequences for the evolution of bacterial virulence.

Tsafa, E., Al-Bahrani, M., Bentayebi, K., Przystal, J., Suwan, K., and Hajitou, A. The natural dietary genistein boosts bacteriophage-mediated cancer cell killing by improving phage-targeted tumor cell transduction. Oncotarget. 7-18-2016;

ABSTRACT: Gene therapy has long been regarded as a promising treatment for cancer. However, cancer gene therapy is still facing the challenge of targeting gene delivery vectors specifically to tumors when administered via clinically acceptable non-invasive systemic routes (i.e. intravenous). The bacteria virus, bacteriophage (phage), represents a new generation of promising vectors in systemic gene delivery since their targeting can be achieved through phage capsid display ligands, which enable them to home to specific tumor receptors without the need to ablate any native eukaryotic tropism. We have previously reported a tumor specific bacteriophage vector named adeno-associated virus/phage, or AAVP, in which gene expression is under a recombinant human rAAV2 virus genome targeted to tumors via a ligand-directed phage capsid. However, cancer gene therapy with this tumor-targeted vector achieved variable outcomes ranging from tumor regression to no effect in both experimental and natural preclinical models. Herein, we hypothesized that combining the natural dietary genistein, with proven anticancer activity, would improve bacteriophage anticancer safe therapy. We show that combination treatment with genistein and AAVP increased targeted cancer cell killing by AAVP carrying the gene for Herpes simplex virus thymidine kinase (HSVtk) in 2D tissue cultures and 3D tumor spheroids. We found this increased tumor cell killing was associated with enhanced AAVP-mediated gene expression. Next, we established that genistein protects AAVP against proteasome degradation and enhances vector genome accumulation in the nucleus. Combination of genistein and phage-guided virotherapy is a safe and promising strategy that should be considered in anticancer therapy with AAVP.

Uchiyama, J., Suzuki, M., Nishifuji, K., Kato, S., Miyata, R., Nasukawa, T., Yamaguchi, K., Takemura-Uchiyama, I., Ujihara, T., Shimakura, H., Murakami, H., Okamoto, N., Sakaguchi, Y., Shibayama, K., Sakaguchi, M., and Matsuzaki, S. Analyses of Short-Term Antagonistic Evolution of Pseudomonas aeruginosa Strain PAO1 and Phage KPP22 (Myoviridae Family, PB1-Like Virus Genus). Appl.Environ.Microbiol. 8-1-2016; 82(15):4482-4491.

ABSTRACT: Pseudomonas aeruginosa causes serious intractable infections in humans and animals. Bacteriophage (phage) therapy has been applied to treat P. aeruginosa infections, and phages belonging to the PB1-like virus genus in the Myoviridae family have been used as therapeutic phages. To achieve safer and more effective phage therapy, the use of preadapted phages is proposed. To understand in detail such phage preadaptation, the short-term antagonistic evolution of bacteria and phages should be studied. In this study, the short-term antagonistic evolution of bacteria and PB1-like phage was examined by studying phage-resistant clones of P. aeruginosa strain PAO1 and mutant PB1-like phages that had recovered their infectivity. First, phage KPP22 was isolated and characterized; it was classified as belonging to the PB1-like virus genus in the Myoviridae family. Subsequently, three KPP22-resistant PAO1 clones and three KPP22 mutant phages capable of infecting these clones were isolated in three sets of in vitro experiments. It was shown that the bacterial resistance to phage KPP22 was caused by significant decreases in phage adsorption and that the improved infectivity of KPP22 mutant phages was caused by significant increases in phage adsorption. The KPP22-resistant PAO1 clones and the KPP22 mutant phages were then analyzed genetically. All three KPP22-resistant PAO1 clones, which were deficient for the O5 antigen, had a common nonsense mutation in the wzy gene. All the KPP22 mutant phage genomes showed the same four missense mutations in the open reading frames orf060, orf065, and orf086 The information obtained in this study should be useful for further development of safe and efficient phage therapy. IMPORTANCE: Pseudomonas aeruginosa causes serious intractable infections in humans and animals; bacteriophage (phage) therapy has been utilized to treat P. aeruginosa infections, and phages that belong to the PB1-like virus genus in the family Myoviridae have been used as therapeutic phages. The preadapted phage is trained in advance through the antagonistic evolution of bacteria and phage and is proposed to be used to achieve safer and more effective phage therapy. In this study, to understand the phage preadaptation, the in vitro short-term antagonistic evolution was studied using P. aeruginosa strain PAO1 and the newly isolated PB1-like phage KPP22. Phage KPP22 was characterized, and the molecular framework regarding the phage preadaptation of KPP22 was elucidated. The importance of study of antagonistic evolution of bacteria and phage in phage therapy is discussed.

Van den, Bossche A., Hardwick, S. W., Ceyssens, P. J., Hendrix, H., Voet, M., Dendooven, T., Bandyra, K. J., De, Maeyer M., Aertsen, A., Noben, J. P., Luisi, B. F., and Lavigne, R. Structural elucidation of a novel mechanism for the bacteriophage-based inhibition of the RNA degradosome. Elife. 7-22-2016; 5

ABSTRACT: In all domains of life, the catalysed degradation of RNA facilitates rapid adaptation to changing environmental conditions, while destruction of foreign RNA is an important mechanism to prevent host infection. We have identified a virus-encoded protein termed gp37/Dip, which directly binds and inhibits the RNA degradation machinery of its bacterial host. Encoded by giant phage PhiKZ, this protein associates with two RNA binding sites of the RNase E component of the Pseudomonas aeruginosa

RNA degradosome, occluding them from substrates and resulting in effective inhibition of RNA degradation and processing. The 2.2 A crystal structure reveals that this novel homo-dimeric protein has no identifiable structural homologues. Our biochemical data indicate that acidic patches on the convex outer surface bind RNase E. Through the activity of Dip, PhiKZ has evolved a unique mechanism to down regulate a key metabolic process of its host to allow accumulation of viral RNA in infected cells.

van, Houte S., Buckling, A., and Westra, E. R. Evolutionary Ecology of Prokaryotic Immune Mechanisms. Microbiol.Mol.Biol.Rev. 2016; 80(3):745-763.

ABSTRACT: Bacteria have a range of distinct immune strategies that provide protection against bacteriophage (phage) infections. While much has been learned about the mechanism of action of these defense strategies, it is less clear why such diversity in defense strategies has evolved. In this review, we discuss the short- and long-term costs and benefits of the different resistance strategies and, hence, the ecological conditions that are likely to favor the different strategies alone and in combination. Finally, we discuss some of the broader consequences, beyond resistance to phage and other genetic elements, resulting from the operation of different immune strategies.

Verstappen, K. M., Tulinski, P., Duim, B., Fluit, A. C., Carney, J., van, Nes A., and Wagenaar, J. A. The Effectiveness of Bacteriophages against Methicillin-Resistant Staphylococcus aureus ST398 Nasal Colonization in Pigs. PLoS.One. 2016; 11(8):e0160242

ABSTRACT: Methicillin-resistant Staphylococcus aureus (MRSA) is an important colonizer in animals and an opportunistic pathogen in humans. In humans, MRSA can cause infections that might be difficult to treat because of antimicrobial resistance. The use of bacteriophages has been suggested as a potential approach for the control of MRSA colonization to minimize the-often occupational-exposure of humans. The aim of this study was to assess the efficacy of bacteriophage treatment on porcine nasal colonization with MRSA in vitro, in vivo, and ex vivo. The effectiveness of a bacteriophage combination of phage K*710 and P68 was assessed in vitro by incubating them with MRSA V0608892/1 (ST398) measuring the OD600 hourly. To study the in vivo effect, bacteriophages were administered in a gel developed for human application, which contain 109 plaque-forming units (pfu)/mL (K and P68 in a 19.25:1 ratio) for 5 days to piglets (N = 8) that were experimentally colonized with the MRSA strain. Eight piglets experimentally colonized were used as a negative control. The MRSA strain was also used to colonize porcine nasal mucosa explants and bacteriophages were applied to assess the ex vivo efficacy of treatment. Bacteriophages were effective in vitro. In vivo, sixteen piglets were colonized with MRSA but the number of CFU recovered after the application of the bacteriophages in 8 piglets was not reduced compared to the control animals (approx. 105 CFU/swab). In the ex vivo model, 108 CFU were used to establish colonization with MRSA; a reduction of colonization was not observed after application of bacteriophages. However, application of mupirocin both in vivo and ex vivo resulted in a near eradication of MRSA. IN CONCLUSION: i) The MRSA strain was killed in the presence of the bacteriophages phage K*710 and P68 in vitro. ii) Bacteriophages did not reduce porcine nasal colonization in vivo or ex vivo. Physiological in vivo and ex vivo conditions may explain these observations. Efficacy in the ex vivo model matched that of the in vivo system.

Wainwright, S. R., Barha, C. K., Hamson, D. K., Epp, J. R., Chow, C., Lieblich, S. E., Rutishauser, U., and Galea, L. A. Enzymatic Depletion of the Polysialic Acid Moiety Associated with the Neural Cell Adhesion Molecule Inhibits Antidepressant Efficacy. Neuropsychopharmacology. 2016; 41(6):1670-1680.

ABSTRACT: Antidepressant drugs are too often ineffective, the exact mechanism of efficacy is still ambiguous, and there has been a paucity of novel targets for pharmacotherapy. In an attempt to understand the pathogenesis of depression and subsequently develop more efficacious antidepressant drugs, multiple theories have been proposed, including the modulation of neurotransmission, the upregulation of neurogenesis and neurotrophic factors, normalizing hypothalamic-pituitary-adrenal reactivity, and the reduction of neuroinflammation; all of which have supporting lines of evidence. Therefore, an ideal molecular target for novel pharmaceutical intervention would function at the confluence of these theories. The polysialylated form of the neural cell adhesion molecule (PSA-NCAM) functions broadly, serving to mediate synaptic plasticity, neurogenesis, neurotrophic factor signaling, and inflammatory signaling throughout the brain; all of which are associated with the pathophysiology and treatment of depression. Moreover, the expression of PSA-NCAM is reduced by depression, and conversely enhanced by antidepressant treatment, particularly within the hippocampus. Here we demonstrate that selectively cleaving the polysialic acid moiety, using the bacteriophage-derived enzyme endoneuraminidase N, completely inhibits the antidepressant efficacy of the selective-serotonin reuptake inhibitor fluoxetine (FLX) in a chronic unpredictable stress model of depression. We also observe a corresponding attenuation of FLX-induced hippocampal neuroplasticity, including decreased hippocampal neurogenesis, synaptic density, and neural activation. These data indicate that PSA-NCAM-mediated neuroplasticity is necessary for antidepressant action; therefore PSA-NCAM represents an interesting, and novel, target for pharmacotherapy.

Wan, H., Otsuka, Y., Gao, Z. Q., Wei, Y., Chen, Z., Masuda, M., Yonesaki, T., Zhang, H., and Dong, Y. H. Structural insights into the inhibition mechanism of bacterial toxin LsoA by bacteriophage antitoxin Dmd. Mol.Microbiol. 5-12-2016;

ABSTRACT: Bacteria have obtained a variety of resistance mechanisms including toxin-antitoxin (TA) systems against bacteriophages (phages), whereas phages have also evolved to overcome bacterial anti-phage mechanisms. Dmd from T4 phage can suppress the toxicities of homologous toxins LsoA and RnlA from Escherichia coli, representing the first example of a phage antitoxin against multiple bacterial toxins in known TA systems. Here, the crystal structure of LsoA-Dmd complex showed Dmd is inserted into the deep groove between the N-terminal repeated domain (NRD) and the Dmd-binding domain (DBD) of LsoA. The NRD shifts significantly from a "closed" to an "open" conformation upon Dmd binding. Site-directed mutagenesis of Dmd revealed the conserved residues (W31 and N40) are necessary for LsoA binding and the toxicity suppression as determined by pull-down and cell toxicity assays. Further mutagenesis identified the conserved Dmd-binding residues (R243, E246 and R305) of LsoA are vital for its toxicity, and suggested Dmd and LsoB may possess different inhibitory mechanisms against LsoA toxicity. Our structure-function studies demonstrate Dmd can recognize LsoA and inhibit its toxicity by occupying the active site possibly via substrate mimicry. These findings have provided unique insights into the defense and counter-defense mechanisms between bacteria and phages in their co-evolution. This article is protected by copyright. All rights reserved.

Wang, D. B., Li, Y., Sun, M. Q., Huang, J. P., Shao, H. B., Xin, Q. L., and Wang, M. Complete Genome of a Novel Pseudoalteromonas Phage PHq0. Curr.Microbiol. 2016; 72(1):81-87.

ABSTRACT: We isolated and purified a novel virulent Pseudoalteromonas bacteriophage PHq0 and the host bacterium Pseudoalteromonas BQ0 from seawater collected in a coastal area of the Yellow Sea of China. (36 degrees 06'N, 120 degrees 32'E). Transmission electron microscopy revealed that the phage had an icosahedral head of 50 nm in diameter with a long tail of 100 nm. The one-step growth curve showed the latent period of about 15 min, a rise period of 15 min, and a burst size of about 363 virions. The genome of phage PHq0 was found to consist of a linear, double-stranded 33,399-bp DNA molecule with a GC content of 40.29 % and 56 putative open reading frames (ORFs). Among these genes, 23 conserved domains were detected by BLASTP, 17 were functionally known, leaving 39 unknown putative genes, BLASTP results show that 57.14 % of the 56 predicted ORFs were not found to have any matches of putative functions or conserved domains in the BLASTP database which should be classified as a new member of the Siphoviridae family. The phage PHq0 genome adds a new Siphoviridae-family phage genome for marine bacteriophages which will provide useful basic information for further molecular research on interaction mechanism between bacteriophages and their hosts.

Wang, G., Jia, T., Xu, X., Chang, L., Zhang, R., Fu, Y., Li, Y., Yang, X., Zhang, K., Lin, G., Han, Y., and Li, J. Novel miR-122 delivery system based on MS2 virus like particle surface displaying cell-penetrating peptide TAT for hepatocellular carcinoma. Oncotarget. 7-18-2016;

ABSTRACT: Current treatments for hepatocellular carcinoma (HCC) have shown inadequate. MicroRNA-122 (miR-122) mediated RNA interference brings new prospects. A safe, efficient miRNA delivery system is an indispensable assurance. Previously, we developed an MS2 bacteriophage virus-like particle (VLP)-based microRNA delivery system crosslinked with the HIV TAT peptide, which served as an effective inhibitor in the treatments of systemic lupus erythematosus and osteoporosis. However, defects, such as low crosslinking efficiency, high cost, and potential toxicity of the crosslinking agent, needed to be confronted. Therefore, TAT peptide was designed to display on the surface of MS2 VLPs, instead of being chemically crosslinked, using the platform of phage surface display. The results reflected that MS2 VLPs displaying TAT could effectively penetrate the cytomembrane and deliver miR-122. Additionally, its inhibitory effects on HCC were significant in Hep3B, HepG2, and Huh7 cells and Hep3B related animal models. Thus, we have established a novel miR-122 delivery system based on MS2 VLPs surface displaying TAT peptide, which could effectively perform the function of penetrating cytomembrane and the inhibition of HCC.

Wang, W., Li, M., Lin, H., Wang, J., and Mao, X. The Vibrio parahaemolyticus-infecting bacteriophage qdvp001: genome sequence and endolysin with a modular structure. Arch.Virol. 7-4-2016;

ABSTRACT: Vibrio parahaemolyticus, a marine pathogen, is a causative agent of gastroenteritis in humans after consumption of contaminated seafood. In recent years, infections with V. parahaemolyticus have become an increasingly frequent factor in microbial food poisoning; therefore, it is urgent to figure out ways to control Vibrio

parahaemolyticus. Endolysins, lytic enzymes encoded by bacteriophages, have been regarded as a therapeutic alternative to antibiotics in control of bacterial growth and have been successfully utilized in various areas. Here, we report the full genome sequence of the novel phage qdvp001, which lyses Vibrio parahaemolyticus 17802. The qdvp001 genome consists of a 134,742-bp DNA with a G+C content of 35.35 % and 227 putative open reading frames. Analysis revealed that the qdvp001 open reading frames encoded various putative functional proteins with a putative endolysin gene (ORF 60). No holin genes were identified in qdvp001. ORF 60 was cloned and expressed. The results showed that the purified endolysin Lysqdvp001 had a high hydrolytic activity toward Vibrio parahaemolyticus and a broader spectrum compared to that of the parental bacteriophage qdvp001. Thus, purified endolysin Lysqdvp001 has a potential to be used as an antibacterial agent in the future.

Wang, X., Yao, D., Xu, J. G., Li, A. R., Xu, J., Fu, P., Zhou, Y., and Zhu, Y. Structural basis of Cas3 inhibition by the bacteriophage protein AcrF3. Nat.Struct.Mol.Biol. 7-25-2016;

ABSTRACT: Bacteriophages express proteins that inactivate the CRISPR-Cas bacterial immune system. Here we report the crystal structure of the anti-CRISPR protein AcrF3 in complex with Pseudomonas aeruginosa Cas3 (PaCas3). AcrF3 forms a homodimer that locks PaCas3 in an ADP-bound form, blocks the entrance of the DNA-binding tunnel in the helicase domain, and masks the linker region and C-terminal domain of PaCas3, thereby preventing recruitment by Cascade and inhibiting the type I-F CRISPR-Cas system.

Wang, Z., Wang, D., Kinchla, A. J., Sela, D. A., and Nugen, S. R. Rapid screening of waterborne pathogens using phage-mediated separation coupled with real-time PCR detection. Anal.Bioanal.Chem. 2016; 408(15):4169-4178.

ABSTRACT: Escherichia coli O157:H7 is a ubiquitous pathogen which can be linked to foodborne outbreaks worldwide. In addition to the significant illnesses, hospitalizations, and deaths resulting from the outbreaks, there can be severe economic consequences to farmers, food manufacturers, and municipalities. A rapid detection assay which can validate sanitation and water quality would prove beneficial to these situations. Here, we report a novel bacteriophage-mediated detection of E. coli O157:H7 which utilizes the specific recognition between phages and their host cell as well as the natural lysis component of the infection cycle for DNA release. Carboxylic acid-functionalized magnetic beads were conjugated with bacteriophage and used to separate and concentrate E. coli O157:H7. The effects of bead incubation time, salinity, pH, and temperature on the bio-magnetic separation were investigated and compared to an antibody-based counterpart. The conditions of 0.01 M PBS, pH 7.0, and 20 min of reaction at 37 degrees C were found to be optimal. The capture efficiency of the coupled assay was approximately 20 % higher than that of antibody-based separation under extreme conditions. The resulting bead-phage-bacteria complexes were quantitatively detected by real-time PCR (qPCR). Our results demonstrated that the use of phage-based magnetic separation coupled with qPCR improved the sensitivity of detection by 2 orders of magnitude compared that without phage-based pre-concentration. Specificity and selectivity of the assay system was evaluated, and no cross-reactivity occurred when Salmonella typhimurium, Staphylococcus aureus, and Pseudomonas aeruginosa were tested. The total assay time was less than 2 h.

Wang, Z., Wang, D., Chen, J., Sela, D. A., and Nugen, S. R. Development of a novel bacteriophage based biomagnetic separation method as an aid for sensitive detection of viable Escherichia coli. Analyst. 2-7-2016; 141(3):1009-1016.

ABSTRACT: The application of bacteriophage combined with the use of magnetic separation techniques has emerged as a valuable tool for the sensitive identification and detection of bacteria. In this study, bacteriophage T7 labelled magnetic beads were developed for the detection of viable bacterial cells. Fusion of the biotin acceptor peptide (BAP) with the phage capsid protein gene and the insertion of the biotin ligase (BirA) gene enabled the display of the BAP ligand and the expression protein BirA during the replication cycle of phage infection. The replicated Escherichia coli specific bacteriophage was biotinylated in vivo and coated on magnetic beads via streptavidin-biotin interaction. Immobilization efficiency of the recombinant phage was investigated on magnetic beads and the phage-bead complex was evaluated by detecting E. coli from inoculated broth. When compared to the wild type phage, the recombinant phage T7birA-bap had a high immobilization density on streptavidin-coated magnetic beads and could capture 86.2% of E. coli cells from broth within 20 min. As this phage-based biomagnetic detection approach provided a low detection limit of 10(2) CFU mL(-1) without pre-enrichment, we believe this assay could be further developed to detect other bacteria of interest by applying host-specific phages. This would be of particular use in detecting bacteria which are difficult to grow or replicate slowly in culture.

Wang, Z., Zheng, P., Ji, W., Fu, Q., Wang, H., Yan, Y., and Sun, J. SLPW: A Virulent Bacteriophage Targeting Methicillin-Resistant Staphylococcus aureus In vitro and In vivo. Front Microbiol. 2016; 7:934

ABSTRACT: Staphylococcus aureus (S. aureus) is a Gram-positive pathogen causing a variety of infections in humans and animals. Extensive use of antibiotics has led to the emergence of methicillin-resistant S. aureus (MRSA). As an alternative antibacterial agent against drug-resistant S. aureus, a lytic phage, designated SLPW, was isolated from fecal sewage in a pig farm. The SLPW was morphologically classified under Podoviridae and contains a double-stranded DNA genome. The genome of SLPW was 17,861 bp (29.35% G+C) containing 20 open reading frames and lacked regions encoding lysogeny-related integrase gene and cI repressor gene. Phage SLPW showed a broad host range and high efficiency of plating against various types of S. aureus. One-step growth curve showed a short latency period (10 min) and a long lytic period (120 min). Phage SLPW remained stable under a wide range of temperatures or pH and was almost unaffected in chloroform or ultraviolet light. Further, it efficiently lysed MRSA strains in vitro and in vivo. Intraperitoneal phage administration at 1 h post-infection cured the mice and reduced the bacterial expression of inflammatory cytokines in mice. Specifically, the phage SLPW displayed a wide antibacterial spectrum. It was therapeutically effective against intra-abdominal infection in mice harboring different multilocus sequence typing (MLST) types of S. aureus strains. Therefore, phage SLPW is a potential therapeutic agent against MRSA infections.

Washizaki, A., Yonesaki, T., and Otsuka, Y. Characterization of the interactions between Escherichia coli receptors, LPS and OmpC, and bacteriophage T4 long tail fibers. Microbiologyopen. 6-6-2016;

ABSTRACT: Bacteriophages have strict host specificity and the step of adsorption is one of key factors for determining host specificity. Here, we systematically examined the interaction between the Escherichia coli receptors lipopolysaccharide (LPS) and outer membrane protein C (OmpC), and the long tail fibers of bacteriophage T4. Using a variety of LPS mutants, we demonstrated that T4 has no specificity for the sugar sequence of the outer core (one of three LPS regions) in the presence of OmpC but, in the absence of OmpC, can adsorb to a specific LPS which has only one or two glucose residues without a branch. These results strengthen the idea that T4 adsorbs to E. coli via two distinct modes, OmpC-dependent and OmpC-independent, suggested by previous reports (Prehm et al. 1976; Yu and Mizushima 1982). Isolation and characterization of the T4 mutants Nik (No infection to K-12 strain), Nib (No infection to B strain), and Arl (altered recognition of LPS) identified amino acids of the long tail fiber that play important roles in the interaction with OmpC or LPS, suggesting that the top surface of the distal tip head domain of T4 long tail fibers interacts with LPS and its lateral surface interacts with OmpC.

Waters, J. T., Kim, H. D., Gumbart, J. C., Lu, X. J., and Harvey, S. C. DNA Scrunching in the Packaging of Viral Genomes. J.Phys.Chem.B. 7-7-2016; 120(26):6200-6207.

ABSTRACT: The motors that drive double-stranded DNA (dsDNA) genomes into viral capsids are among the strongest of all biological motors for which forces have been measured, but it is not known how they generate force. We previously proposed that the DNA is not a passive substrate but that it plays an active role in force generation. This "scrunchworm hypothesis" holds that the motor proteins repeatedly dehydrate and rehydrate the DNA, which then undergoes cyclic shortening and lengthening motions. These are captured by a coupled protein-DNA grip-and-release cycle to rectify the motion and translocate the DNA into the capsid. In this study, we examined the interactions of dsDNA with the dodecameric connector protein of bacteriophage varphi29, using molecular dynamics simulations on four different DNA sequences, starting from two different conformations (A-DNA and B-DNA). In all four simulations starting with the protein equilibrated with A-DNA in the channel, we observed transitions to a common, metastable, highly scrunched conformation, designated A*. This conformation is very similar to one recently reported by Kumar and Grubmuller in much longer MD simulations on B-DNA docked into the varphi29 connector. These results are significant for four reasons. First, the scrunched conformations occur spontaneously, without requiring lever-like protein motions often believed to be necessary for DNA translocation. Second, the transition takes place within the connector, providing the location of the putative "dehydrator". Third, the protein has more contacts with one strand of the DNA than with the other; the former was identified in single-molecule laser tweezer experiments as the "load-bearing strand". Finally, the spontaneity of the DNA-protein interaction suggests that it may play a role in the initial docking of DNA in motors like that of T4 that can load and package any sequence.

Winstel, V., Kuhner, P., Rohde, H., and Peschel, A. Genetic engineering of untransformable coagulase-negative staphylococcal pathogens. Nat.Protoc. 2016; 11(5):949-959.

ABSTRACT: Coagulase-negative staphylococci (CoNS) are recognized as significant opportunistic pathogens. However, current knowledge of virulence mechanisms is very limited because a significant proportion of CoNS are refractory to available techniques for DNA transformation. We describe an efficient protocol for plasmid transfer using

bacteriophage Phi187, which can transduce plasmid DNA to a wide range of CoNS from a unique, engineered Staphylococcus aureus strain. The use of a restriction-deficient, modification-proficient S. aureus PS187 mutant, which has a CoNS-type bacteriophage surface receptor, allows plasmid transfer to CoNS even when they are refractory to electroporation. Once the Phi187 titer reaches 10(9) plaque-forming units per milliliter, plasmid transfer can be accomplished within 1-2 d. Thus, our protocol is a major technical advance offering attractive opportunities for research on CoNS-mediated infections.

Wittekind, M. and Schuch, R. Cell wall hydrolases and antibiotics: exploiting synergy to create efficacious new antimicrobial treatments. Curr.Opin.Microbiol. 5-31-2016; 33:18-24.

ABSTRACT: Cell wall hydrolases (CWH) are enzymes that build, remodel and degrade peptidoglycan within bacterial cell walls and serve essential roles in cell-wall metabolism, bacteriophage adsorption and bacteriolysis, environmental niche expansion, as well as eukaryotic innate immune defense against bacterial infection. Some CWHs, when tested as recombinant purified proteins, have been shown to have bactericidal activities both as single agents and in combinations with other antimicrobials, displaying synergies in vitro and potent activities in animal models of infection greater than the single agents alone. We summarize in vitro, in vivo, and mechanistic studies that illustrate ACWH synergy with antibiotics, antimicrobial peptides, and other ACWHs, underscoring the overall synergistic potential of the ACWH class.

Wu, L., Song, Y., Luan, T., Ma, L., Su, L., Wang, S., and Yan, X. Specific detection of live Escherichia coli O157:H7 using tetracysteine-tagged PP01 bacteriophage. Biosens.Bioelectron. 6-15-2016; 86:102-108.

ABSTRACT: Sensitive and rapid detection of Escherichia coli O157:H7, one of the most notorious bacterial pathogens, is urgently needed for public health protection. Yet, the existing methods are either lack of speed or limited in discriminating viable and dead cells. Using a recombinant bacteriophage, here we report the development of a rapid and sensitive method for live E. coli O157:H7 detection. First, the wild-type PP01 phage was engineered with a tetracysteine (TC)-tag fused with the small outer capsid (SOC) protein. Then, this PP01-TC phage was used to inoculate bacterial sample for 30min. Specific infection and rapid replication of PP01-TC phage in viable E. coli O157:H7 host cell yields a large number of progeny phages with capsids displaying TC tags that can be fluorescently labeled by a membrane permeable biarsenical dye (FlAsH). The bright green fluorescence of single E. coli O157:H7 cells can be readily detected by flow cytometry (FCM) and fluorescence microscopy. High specificity of the assay was verified with seven other bacterial strains. Practical application in E. coli O157:H7 detection in drinks was successfully demonstrated with artificially contaminated 100% apple juice. In less than three hours (including sample preconcentration) and with 40mL of sample volume, as low as 1cfu/mL E. coli O157:H7 can be detected in the presence of large excess of other nontarget bacteria via fluorescence microscopic measurement. The as-developed TC-PP01-FlAsH approach shows a great potential in the safeguard of liquid food products by providing rapid, sensitive, and specific detection of live E. coli O157:H7.

Xu, J., Gui, M., Wang, D., and Xiang, Y. The bacteriophage varphi29 tail possesses a pore-forming loop for cell membrane penetration. Nature. 6-23-2016; 534(7608):544-547.

ABSTRACT: Most bacteriophages are tailed bacteriophages with an isometric or a prolate head attached to a long contractile, long non-contractile, or short non-contractile tail. The tail is a complex machine that plays a central role in host cell recognition and attachment, cell wall and membrane penetration, and viral genome ejection. The mechanisms involved in the penetration of the inner host cell membrane by bacteriophage tails are not well understood. Here we describe structural and functional studies of the bacteriophage varphi29 tail knob protein gene product 9 (gp9). The 2.0 A crystal structure of gp9 shows that six gp9 molecules form a hexameric tube structure with six flexible hydrophobic loops blocking one end of the tube before DNA ejection. Sequence and structural analyses suggest that the loops in the tube could be membrane active. Further biochemical assays and electron microscopy structural analyses show that the six hydrophobic loops in the tube exit upon DNA ejection and form a channel that spans the lipid bilayer of the membrane and allows the release of the bacteriophage genomic DNA, suggesting that cell membrane penetration involves a pore-forming mechanism similar to that of certain non-enveloped eukaryotic viruses. A search of other phage tail proteins identified similar hydrophobic loops, which indicates that a common mechanism might be used for membrane penetration by prokaryotic viruses. These findings suggest that although prokaryotic and eukaryotic viruses use apparently very different mechanisms for infection, they have evolved similar mechanisms for breaching the cell membrane.

Xu, J., Chen, M., He, L., Zhang, S., Ding, T., Yao, H., Lu, C., and Zhang, W. Isolation and characterization of a T4-like phage with a relatively wide host range within Escherichia coli. J.Basic Microbiol. 2016; 56(4):405-421.

ABSTRACT: Avian pathogenic Escherichia coli (APEC) causes colibacillosis in poultry, resulting in severe economic losses worldwide. Coliphages represent alternative antibacterial substitutes based on high lytic efficiency and few side-effects. However, the complete genome sequences information of APEC phages are limited, and knowledge of undesired genes and the narrow host range restrict their applications. In this study, we isolated a virulent phage QL01, with a relatively broad lytic spectrum (41 of 78 APEC strains). Transmission electron micrography showed it belonged to the family Myoviridae with an elongated head and a contractile tail. Whole genome sequencing revealed a linear double-stranded DNA (170,527 kb; GC content, 39.6%) with 275 possible ORFs. Comparative genome analysis revealed high homology between QL01 and other T4-like phages. However, it also showed some unique features, for example, ORF142 and ORF143, which encode IP9 and IP8, respectively, and may counteract host resistance only exist in a few T4-like phages such as IME08 and vB_EcoM_VR5. Furthermore, phage therapy in artificially infected ducks showed a 26.67% decrease in mortality compared with the untreated group. Our study indicates the potential antibacterial function of phage QL01 against APEC infections and highlights unique molecular features underlying the relatively broad host range.

Xu, X., Tao, Y., Gao, X., Zhang, L., Li, X., Zou, W., Ruan, K., Wang, F., Xu, G. L., and Hu, R. A CRISPR-based approach for targeted DNA demethylation. Cell Discov. 2016; 2:16009

ABSTRACT: In mammalian cells, DNA methylation critically regulates gene expression and thus has pivotal roles in myriad of physiological and pathological processes. Here we report a novel method for targeted DNA demethylation using the widely used clustered

regularly interspaced short palindromic repeat (CRISPR)-Cas system. Initially, modified single guide RNAs (sgRNAs) (sgRNA2.0) were constructed by inserting two copies of bacteriophage MS2 RNA elements into the conventional sgRNAs, which would facilitate the tethering of the Tet1 catalytic domain (Tet-CD), in fusion with dCas9 or MS2 coat proteins, to the targeted gene loci. Subsequently, such system was shown to significantly upregulate transcription of the target genes, including RANKL, MAGEB2 or MMP2, which was in close correlation to DNA demethylation of their neighboring CpGs in the promoters. In addition, the dCas9/sgRNA2.0-directed demethylation system appeared to afford efficient demethylation of the target genes with tenuous off-target effects. Applications of this system would not only help us understand mechanistically how DNA methylation might regulate gene expression in specific contexts, but also enable control of gene expression and functionality with potential clinical benefits.

Yan, S., Xu, M., Duan, X., Yu, Z., Li, Q., Xie, L., Fan, X., and Xie, J. Mycobacteriophage putative GTPase-activating protein can potentiate antibiotics. Appl.Microbiol.Biotechnol. 6-27-2016;

ABSTRACT: The soaring incidences of infection by antimicrobial resistant (AR) pathogens and shortage of effective antibiotics with new mechanisms of action have renewed interest in phage therapy. This scenario is exemplified by resistant tuberculosis (TB), caused by resistant Mycobacterium tuberculosis. Mycobacteriophage SWU1 A321_gp67 encodes a putative GTPase-activating protein. Mycobacterium smegmatis with gp67 overexpression showed changed colony formation and biofilm morphology and supports the efficacy of streptomycin and capreomycin against Mycobacterium. gp67 down-regulated the transcription of genes involved in cell wall and biofilm development. To our knowledge, this is the first report to show that phage protein in addition to lysin or recombination components can synergize with existing antibiotics. Phage components might represent a promising new clue for better antibiotic potentiators.

Yan, Y., Zhang, M., Moon, C. H., Su, H. C., Myung, N. V., and Haberer, E. D. Viral-templated gold/polypyrrole nanopeapods for an ammonia gas sensor. Nanotechnology. 8-12-2016; 27(32):325502

ABSTRACT: One-dimensional gold/polypyrrole (Au/PPy) nanopeapods were fabricated using a viral template: M13 bacteriophage. The genetically modified filamentous virus displayed gold-binding peptides along its length, allowing selective attachment of gold nanoparticles (Au NPs) under ambient conditions. A PPy shell was electropolymerized on the viral-templated Au NP chains forming nanopeapod structures. The PPy shell morphology and thickness were controlled through electrodeposition potential and time, resulting in an ultra-thin conductive polymer shell of 17.4 +/- 3.3 nm. A post-electrodeposition acid treatment was used to modify the electrical properties of these hybrid materials. The electrical resistance of the nanopeapods was monitored at each assembly step. Chemiresistive ammonia (NH3) gas sensors were developed from networks of the hybrid Au/PPy nanostructures. Room temperature sensing performance was evaluated from 5 to 50 ppmv and a mixture of reversible and irreversible chemiresistive behavior was observed. A sensitivity of 0.30%/ppmv was found for NH3 concentrations of 10 ppmv or less, and a lowest detection limit (LDL) of 0.007 ppmv was calculated. Furthermore, acid-treated devices exhibited an enhanced sensitivity of 1.26%/ppmv within the same concentration range and a calculated LDL of 0.005 ppmv.

Yosef, I., Manor, M., and Qimron, U. Counteracting selection for antibiotic-resistant bacteria. Bacteriophage. 2016; 6(1):e1096996

ABSTRACT: The occurrence of antibiotic-resistant bacterial pathogens is on the rise because antibiotics exert selection pressure that kills only the antibiotic-sensitive pathogens. Sanitation and cleansing of hospital surfaces and the skin of medical personnel do not counteract this selective pressure, but rather indiscriminately reduce total pathogens on treated surfaces. Here, we discuss two recently introduced genetic strategies, based on temperate bacteriophages as DNA-delivery vehicles, that aim to sensitize bacteria to antibiotics and selectively kill the antibiotic-resistant ones. Outlooks for rendering one such approach more efficient and applicable are proposed. We believe that using an end product designed according to the provided principles on hospital surfaces and in hand-sanitizers will facilitate substitution of antibiotic-resistant pathogens with sensitive ones.

Yosef, I., Edgar, R., and Qimron, U. Phenotypic heterogeneity in a bacteriophage population only appears as stress-induced mutagenesis. Curr.Genet. 4-28-2016;

ABSTRACT: Stress-induced mutagenesis has been studied in cancer cells, yeast, bacteria, and archaea, but not in viruses. In a recent publication, we present a bacteriophage model showing an apparent stress-induced mutagenesis. We show that the stress does not drive the mutagenesis, but only selects the fittest mutants. The mechanism underlying the observed phenomenon is a phenotypic heterogeneity that resembles persistence of the viral population. The new findings, the background for the ongoing debate on stress-induced mutagenesis, and the phenotypic heterogeneity underlying a novel phage infection strategy are discussed in this short manuscript.

Yoshimura, H., Edwards, E., Uchida, M., McCoy, K., Roychoudhury, R., Schwarz, B., Patterson, D., and Douglas, T. Two-Dimensional Crystallization of P22 Virus-Like Particles. J.Phys.Chem.B. 7-7-2016; 120(26):5938-5944.

ABSTRACT: Virus-like particles (VLPs) are well established platforms for constructing functional biomimetic materials. The VLP from the bacteriophage P22 can be used as a nanocontainer to sequester active enzymes, at high concentration, within its cavity through a process of directed self-assembly. Construction of ordered 2D assemblies of these catalytic VLPs can be envisioned as a functional membrane. To achieve this, it is important to establish methods to fabricate densely packed monolayers of VLPs. Highly ordered assemblies of P22 can also be utilized as a two-dimensional (2D) crystal for electron crystallography to get precise structural information on the VLP. Here we report 2D crystallization of different P22 morphologies: P22 procapsid (PC), enzyme encapsulated PC (beta-glycosidase and enhanced green fluorescent protein), empty shell (PC without scaffold proteins, ES), the expanded form of P22 (EX), and enzyme encapsulated EX (NADH oxidase). The 2D crystals of P22 VLPs were formed on a positively charged lipid monolayer at the water-air interface with a subphase containing 1% trehalose. A P22 solution, injected underneath the lipid monolayer, floated to the surface because of the density difference between the subphase and protein solution. The lipid monolayer, with adsorbed P22, was transferred to a holey carbon grid and was examined by electron microscopy. 2D crystals were obtained from a subphase containing 100 mM NaCl, 10 mM MES (pH 5.0), and 1% trehalose. The diffraction spots

from the transferred film extended to the sixth order in negatively stained samples and the 10th order in cryo-electron microscopy samples.

Yost, D. G., Tsourkas, P., and Amy, P. S. Experimental bacteriophage treatment of honeybees (Apis mellifera) infected with Paenibacillus larvae, the causative agent of American Foulbrood Disease. Bacteriophage. 2016; 6(1):e1122698

ABSTRACT: American Foulbrood Disease (AFB) is an infection of honeybees caused by the bacterium Paenibacillus larvae. One potential remedy involves using biocontrol, such as bacteriophages (phages) to lyse P. larvae. Therefore, bacteriophages specific for P. larvae were isolated to determine their efficacy in lysing P. larvae cells. Samples from soil, beehive materials, cosmetics, and lysogenized P. larvae strains were screened; of 157 total samples, 28 were positive for at least one P. larvae bacteriophage, with a total of 30. Newly isolated bacteriophages were tested for the ability to lyse each of 11 P. larvae strains. Electron microscopy demonstrated that the phage isolates were from the family Siphoviridae. Seven phages with the broadest host ranges were combined into a cocktail for use in experimental treatments of infected bee larvae; both prophylactic and post-infection treatments were conducted. Results indicated that although both pre- and post-treatments were effective, prophylactic administration of the phages increased the survival of larvae more than post-treatment experiments. These preliminary experiments demonstrate the likelihood that phage therapy could be an effective method to control AFB.

Young, P., Buchanan, N., and Fallowfield, H. J. Inactivation of indicator organisms in wastewater treated by a high rate algal pond system. J.Appl.Microbiol. 2016; 121(2):577-586.

ABSTRACT: AIMS: High rate algal ponds (HRAPs) have been suggested as replacements for waste stabilization ponds (WSPs) in Community Wastewater Management Systems (CWMS) used in rural South Australian (SA) towns. Treated effluent from CWMS is reused for irrigation. To manage the risk of human exposure to pathogens, the disinfection performance of HRAPs was validated using the common indicators Escherichia coli and F-RNA bacteriophage; aerobic spore-forming bacteria (ASFB) were used as indicators for protozoa. METHODS AND RESULTS: Using standard culture methods, the removal of the indicator organisms F-RNA bacteriophage, E. coli and ASFB by a HRAP at Kingston-on-Murray, SA, was measured. The mean log10 reduction values achieved for the F-RNA bacteriophage was 1.59 +/- 0.82 log10 PFU 100 ml(-1) and for E. coli it was 2.13 +/- 0.55 log10 E. coli MPN 100 ml(-1) . ASFB numbers in the treated pond effluent often exceeded those of the influent. CONCLUSIONS: The results show that HRAPs are able to remove viral and bacterial indicators to levels acceptable for subsurface irrigation of nonfood crops. Additionally, it was concluded that alternate environmental sources and the potential for regrowth made ASFB unsuitable indicators for pathogenic protozoa in natural pond systems. SIGNIFICANCE AND IMPACT OF THE STUDY: This study shows HRAPs would be suitable replacements for WSPs in CWMS schemes in regard to pathogen disinfection. Such demonstration of the treatment efficacy of HRAPs, together with their smaller land area requirements relative to WSPs, should facilitate their wider adoption in rural and remote communities.

Yu, J. G., Lim, J. A., Song, Y. R., Heu, S., Kim, G. H., Koh, Y. J., and Oh, C. S. Isolation and Characterization of Bacteriophages Against Pseudomonas syringae pv. actinidiae Causing Bacterial Canker Disease in Kiwifruit. J.Microbiol.Biotechnol. 2016; 26(2):385-393.

ABSTRACT: Pseudomonas syringae pv. actinidiae causes bacterial canker disease in kiwifruit. Owing to the prohibition of agricultural antibiotic use in major kiwifruit-cultivating countries, alternative methods need to be developed to manage this disease. Bacteriophages are viruses that specifically infect target bacteria and have recently been reconsidered as potential biological control agents for bacterial pathogens owing to their specificity in terms of host range. In this study, we isolated bacteriophages against P. syringae pv. actinidiae from soils collected from kiwifruit orchards in Korea and selected seven bacteriophages for further characterization based on restriction enzyme digestion patterns of genomic DNA. Among the studied bacteriophages, two belong to the Myoviridae family and three belong to the Podoviridae family, based on morphology observed by transmission electron microscopy. The host range of the selected bacteriophages was confirmed using 18 strains of P. syringae pv. actinidiae, including the Psa2 and Psa3 groups, and some were also effective against other P. syringae pathovars. Lytic activity of the selected bacteriophages was sustained in vitro until 80 h, and their activity remained stable up to 50 degrees C, at pH 11, and under UV-B light. These results indicate that the isolated bacteriophages are specific to P. syringae species and are resistant to various environmental factors, implying their potential use in control of bacterial canker disease in kiwifruits.

Yuan, Y. and Gao, M. Proteomic Analysis of a Novel Bacillus Jumbo Phage Revealing Glycoside Hydrolase As Structural Component. Front Microbiol. 2016; 7:745

ABSTRACT: Tailed phages with genomes of larger than 200 kbp are classified as Jumbo phages and exhibited extremely high uncharted diversity. The genomic annotation of Jumbo phage is often disappointing because most of the predicted proteins, including structural proteins, failed to make good hits to the sequences in the databases. In this study, 23 proteins of a novel Bacillus Jumbo phage, vB_BpuM_BpSp, were identified as phage structural proteins by the structural proteome analysis, including 14 proteins of unknown function, 5 proteins with predicted function as structural proteins, a glycoside hydrolase, a Holliday junction resolvase, a RNA-polymerase beta-subunit, and a host-coding portal protein, which might be hijacked from the host strain during phage virion assembly. The glycoside hydrolase (Gp255) was identified as phage virion component and was found to interact with the phage baseplate protein. Gp255 shows specific lytic activity against the phage host strain GR8 and has high temperature tolerance. In situ peptidoglycan-hydrolyzing activities analysis revealed that the expressed Gp255 and phage structural proteome exhibited glycoside hydrolysis activity against the tested GR8 cell extracts. This study identified the first functional individual structural glycoside hydrolase in phage virion. The presence of activated glycoside hydrolase in phage virions might facilitate the injection of the phage genome during infection by forming pores on the bacterial cell wall.

Zelechowska, K., Karczewska-Golec, J., Karczewski, J., Los, M., Klonkowski, A. M., Wegrzyn, G., and Golec, P. Phage-directed synthesis of photoluminescent zinc oxide nanoparticles under benign conditions. Bioconjug.Chem. 8-1-2016;

ABSTRACT: Biological systems, especially bacteriophages and peptides, are an attractive green alternative to other known methods of nanoparticle synthesis. In this work, for the first time, bacteriophages were employed to identify and synthesize specific peptide, capable of producing nanoparticles (NPs). Derivatives of M13 bacteriophage exposing a ZnO-binding peptide (TMGANLGLKWPV) on either pIII or pVIII phage coat protein were constructed and used as a bio-template. The exposition of the ZnO-binding peptide, synthesized by phages during their propagation in bacteria, on M13 virions provided a groundwork for growing ZnO nanostructures. Depending on the recombinant phage type used (M13-pIII-ZnO or M13-pVIII-ZnO), well separated ZnO NPs or complex 3D structures of ZnO NPs of ca. 20-40 nm were synthesized at room temperature. The synthesized ZnO nanoparticles served as a luminescent material that emitted light near the short wavelength end of the visible region (at ca. 400 nm). The next very low intensity emission band at 530 nm demonstrated that the ZnO material obtained is characterized by a low concentration of surface defects.

Zha, T., Liang, J., Xiao, Y., and Jing, H. [Detection of Yersinia Enterocolitica Bacteriophage PhiYe-F10 Lysis Spectrum and Analysis of the Relationship between Lysis Ability and Virulence Gene of Yersinia Enterocolitica]. Bing.Du Xue.Bao. 2016; 32(2):185-189.

ABSTRACT: To determine the lysis spectrum of Yersinia enterocolitica bacteriophage phiYe-F10 and to analyze the relationship between the lysis ability of phiYe-F10 and the virulence gene of Yersinia enterocolitica. To observe the lysis ability of the phage phiYe-F10 to the different Yersinia strains with the double-layer technique. The strains used in this study including 213 of Yersinia enterocolitica and 36 of Yersinia pseudotuberculosis and 1 of Yersinia pestis. The virulence genes of these Yersinia enterocolitica (attachment invasion locus (ail) and enterotoxin (ystA, ystB) and yersinia adhesin A (yadA), virulence factor (virF), specific gene for lipopolysaccharide O-side chain of serotype O : 3 (rfbc) were all detected. Among the 213 Yersinia enterocolitica, 84 strains were O : 3 serotype (78 strains with rfbc gene), 10 were serotype O : 5, 13 were serotype O : 8, 34 were serotype O : 9 and 72 were other serotypes. Of these, 77 were typical pathogenic Yersinia enterocolitica harboring with virulence plasmid (ail+, ystA+, ystB-, yadA+, virF+), and 15 were pathogenic bacterial strains deficiency virulence plasmid (ail+, ystA+, ystB-, yadA-, virF-) and the rest 121 were non pathogenic genotype strains. PhiYe-F10 lysed the 71 serotype O : 3 Yersinia enterocolitica strains which were all carried with rfbc+, including 52 pathogenic Yersinia enterocolitica, 19 nonpathogenic Y. enterocolitica. The phiYe-F10 can not lysed serotype O : 5, O : 9 and other serotype Y. enterocolitica, the lysis rate of serotype O : 3 was as high as 84.5%. The phiYe-F10 can not lysed Yersinia pseudotuberculosis and Yersinia pestis. Yersinia phage phiYe-F10 is highly specific for serotype O : 3 Yersinia enterocolitic at 25 degrees C, which showed a typical narrow lysis spectrum. Phage phiYe-F10 can lysed much more pathogenic Y. enterocolitica than nonpathogenic Y. enterocolitica.

Zhan, Y., Huang, S., Voget, S., Simon, M., and Chen, F. A novel roseobacter phage possesses features of podoviruses, siphoviruses, prophages and gene transfer agents. Sci.Rep. 2016; 6:30372

ABSTRACT: Bacteria in the Roseobacter lineage have been studied extensively due to their significant biogeochemical roles in the marine ecosystem. However, our knowledge on bacteriophage which infects the Roseobacter clade is still very limited. Here, we report a new bacteriophage, phage DSS3Phi8, which infects marine roseobacter

Ruegeria pomeroyi DSS-3. DSS3Phi8 is a lytic siphovirus. Genomic analysis showed that DSS3Phi8 is most closely related to a group of siphoviruses, CbK-like phages, which infect freshwater bacterium Caulobacter crescentus. DSS3Phi8 contains a smaller capsid and has a reduced genome size (146 kb) compared to the CbK-like phages (205-279 kb). DSS3Phi8 contains the DNA polymerase gene which is closely related to T7-like podoviruses. DSS3Phi8 also contains the integrase and repressor genes, indicating its potential to involve in lysogenic cycle. In addition, four GTA (gene transfer agent) genes were identified in the DSS3Phi8 genome. Genomic analysis suggests that DSS3Phi8 is a highly mosaic phage that inherits the genetic features from siphoviruses, podoviruses, prophages and GTAs. This is the first report of CbK-like phages infecting marine bacteria. We believe phage isolation is still a powerful tool that can lead to discovery of new phages and help interpret the overwhelming unknown sequences in the viral metagenomics.

Zhang, H., Li, L., Zhao, Z., Peng, D., and Zhou, X. Polar flagella rotation in Vibrio parahaemolyticus confers resistance to bacteriophage infection. Sci.Rep. 2016; 6:26147

ABSTRACT: Bacteriophage has been recognized as a novel approach to treat bacterial infectious diseases. However, phage resistance may reduce the efficacy of phage therapy. Here, we described a mechanism of bacterial resistance to phage infections. In Gram-negative enteric pathogen Vibrio parahaemolyticus, we found that polar flagella can reduce the phage infectivity. Deletion of polar flagella, but not the lateral flagella, can dramatically promote the adsorption of phage to the bacteria and enhances the phage infectivity to V. parahaemolyticus, indicating that polar flagella play an inhibitory role in the phage infection. Notably, it is the rotation, not the physical presence, of polar flagella that inhibits the phage infection of V. parahaemolyticus. Strikingly, phage dramatically reduces the virulence of V. parahaemolyticus only when polar flagella were absent both in vitro and in vivo. These results indicated that polar flagella rotation is a previously unidentified mechanism that confers bacteriophage resistance.

Zhang, L., Huang, Y., Xu, D., Yang, L., Qian, K., Chang, G., Gong, Y., Zhou, X., and Ma, K. Biochemical characterization of a thermostable HNH endonuclease from deep-sea thermophilic bacteriophage GVE2. Appl.Microbiol.Biotechnol. 4-30-2016;

ABSTRACT: His-Asn-His (HNH) proteins are a very common family of small nucleic acid-binding proteins that are generally associated with endonuclease activity and are found in all kingdoms of life. Although HNH endonucleases from mesophiles have been widely investigated, the biochemical functions of HNH endonucleases from thermophilic bacteriophages remain unknown. Here, we characterized the biochemical properties of a thermostable HNH endonuclease from deep-sea thermophilic bacteriophage GVE2. The recombinant GVE2 HNH endonuclease exhibited non-specific cleavage activity at high temperature. The optimal temperature of the GVE2 HNH endonuclease for cleaving DNA was 60-65 degrees C, and the enzyme retained its DNA cleavage activity even after heating at 100 degrees C for 30 min, suggesting the enzyme is a thermostable endonuclease. The GVE2 HNH endonuclease cleaved DNA over a wide pH spectrum, ranging from 5.5 to 9.0, and the optimal pH for the enzyme activity was 8.0-9.0. Furthermore, the GVE2 HNH endonuclease activity was dependent on a divalent metal ion. While the enzyme is inactive in the presence of Cu2+, the GVE2 HNH endonuclease displayed cleavage activity of varied efficiency with Mn2+, Mg2+, Ca2+, Fe2+, Co2+, Zn2+, and Ni2+. The GVE2 HNH endonuclease activity was inhibited by NaCl. This study

provides the basis for determining the role of this endonuclease in life cycle of the bacteriophage GVE2 and suggests the potential application of the enzyme in molecular biology and biotechnology.

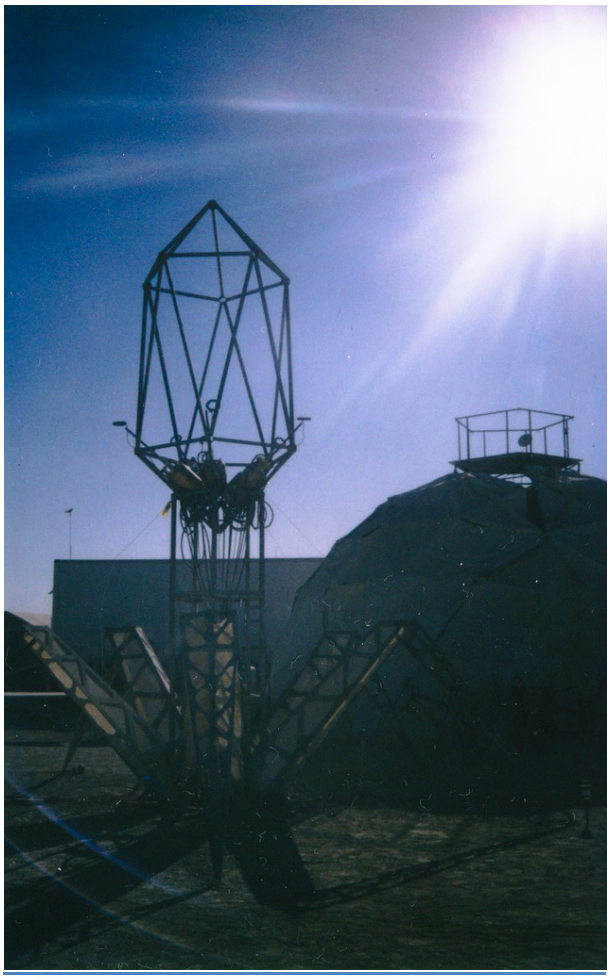
Zhao, Z., De-Donatis, G. M., Schwartz, C., Fang, H., Li, J., and Guo, P. Arginine finger regulates sequential action of asymmetrical hexameric ATPase in dsDNA translocation motor. Mol.Cell Biol. 7-25-2016;

ABSTRACT: Biological motors are ubiquitous in living systems. Currently, how the motor component coordinates the unidirectional motion is elusive in most cases. Here we report that the sequential action of the ATPase ring in the DNA packaging motor of bacteriophage phi29 is regulated by an arginine finger that extends from one ATPase subunit to the adjacent unit to promote noncovalent dimer formation. Mutation of the arginine finger resulted in the interruption of ATPase oligomerization, ATP binding/hydrolysis, and DNA translocation. Dimer formation re-appeared when arginine mutants were mixed with other ATPase subunits that can offer the arginine to promote their interaction. Ultracentrifugation and virion assembly assays indicated that the ATPase was presenting as monomers and dimer mixtures. The isolated dimer alone was inactive in DNA translocation, but addition of monomer could resume the activity, suggesting that the hexameric ATPase ring contained both dimer and monomers. Moreover, ATP binding or hydrolysis resulted in conformation and entropy changes of the ATPase with high or low DNA affinity. Taken together, it is concluded that the arginine finger regulates sequential action of the motor ATPase subunit by promoting the formation of the dimer inside the hexamer. The finding of asymmetrical hexameric organization is supported by structural evidences of many other ATPase systems showing the presence of one noncovalent dimer and four monomer subunits. All these provide clues for why the asymmetrical hexameric ATPase gp16 of phi29 was previously reported as pentameric configuration by cryo-EM. Since the contact by the arginine figure renders two adjacent ATPase subunits closer than other subunits. Thus the asymmetrical hexamer would appear as a pentamer by cryo-EM, a technology that acquires the average of many images.

Zhu, X., Wang, J., Peng, B., and Shete, S. Empirical estimation of sequencing error rates using smoothing splines. BMC.Bioinformatics. 2016; 17:177

ABSTRACT: BACKGROUND: Next-generation sequencing has been used by investigators to address a diverse range of biological problems through, for example, polymorphism and mutation discovery and microRNA profiling. However, compared to conventional sequencing, the error rates for next-generation sequencing are often higher, which impacts the downstream genomic analysis. Recently, Wang et al. (BMC Bioinformatics 13:185, 2012) proposed a shadow regression approach to estimate the error rates for next-generation sequencing data based on the assumption of a linear relationship between the number of reads sequenced and the number of reads containing errors (denoted as shadows). However, this linear read-shadow relationship may not be appropriate for all types of sequence data. Therefore, it is necessary to estimate the error rates in a more reliable way without assuming linearity. We proposed an empirical error rate estimation approach that employs cubic and robust smoothing splines to model the relationship between the number of reads sequenced and the number of shadows. RESULTS: We performed simulation studies using a frequency-based approach to generate the read and shadow counts directly, which can mimic the real sequence counts data structure. Using simulation, we investigated the performance of the

proposed approach and compared it to that of shadow linear regression. The proposed approach provided more accurate error rate estimations than the shadow linear regression approach for all the scenarios tested. We also applied the proposed approach to assess the error rates for the sequence data from the MicroArray Quality Control project, a mutation screening study, the Encyclopedia of DNA Elements project, and bacteriophage PhiX DNA samples. CONCLUSIONS: The proposed empirical error rate estimation approach does not assume a linear relationship between the error-free read and shadow counts and provides more accurate estimations of error rates for next-generation, short-read sequencing data.



Ian Norman, Phage Camp, September 7 2011, Creative Commons License

I. Probiotics & Bacteriotherapy

Abhari, K., Shekarforoush, S. S., Hosseinzadeh, S., Nazifi, S., Sajedianfard, J., and Eskandari, M. H. The effects of orally administered Bacillus coagulans and inulin on prevention and progression of rheumatoid arthritis in rats. Food Nutr.Res. 2016; 60:30876

ABSTRACT: BACKGROUND: Probiotics have been considered as an approach to addressing the consequences of different inflammatory disorders. The spore-forming probiotic strain Bacillus coagulans has demonstrated anti-inflammatory and immune-modulating effects in both animals and humans. The prebiotic inulin also potentially affects the immune system as a result of the change in the composition or fermentation profile of the gastrointestinal microbiota. OBJECTIVE: In the present study, an in vivo model was conducted to investigate the possible influences of probiotic B. coagulans and prebiotic inulin, both in combination and/or separately, on the downregulation of immune responses and the progression of rheumatoid arthritis (RA), using arthritis-induced rat model. DESIGN: Forty-eight healthy male Wistar rats were randomly categorized into six experimental groups as follows: 1) control: normal healthy rats fed with standard diet, 2) disease control (RA): arthritis-induced rats fed with standard diet, 3) prebiotic (PRE): RA+ 5% w/w long-chain inulin, 4) probiotic (PRO): RA+ 10(9) spores/day B. coagulans by orogastric gavage, 5) synbiotic (SYN): RA+ 5% w/w long-chain inulin and 10(9) spores/day B. coagulans, and 6) treatment control: (INDO): RA+ 3 mg/kg/day indomethacin by orogastric gavage. Feeding with the listed diets started on day 0 and continued to the end of study. On day 14, rats were injected with complete Freund's adjuvant (CFA) to induce arthritis. Arthritis activity was evaluated by the biochemical parameters and paw thickness. Biochemical assay for fibrinogen (Fn), serum amyloid A (SAA), and TNF-alpha and alpha-1-acid glycoprotein (alpha1AGp) was performed on day 21, 28, and 35 (7, 14 and 21 days post RA induction), respectively. RESULTS: Pretreatment with PRE, PRO, and SYN diets significantly inhibits SAA and Fn production in arthritic rats ($P < 0.001$). A significant decrease in the production of pro-inflammatory cytokines, such as TNF-alpha, was seen in the PRE, PRO, and SYN groups ($P < 0.001$), which was similar to the anti-inflammatory effect of indomethacin. Furthermore, no significant anti-inflammatory effects were observed following different treatments using alpha1 AGp as an RA indicator. Pretreatment with all supplied diets significantly inhibited the development of paw swelling induced by CFA ($P < 0.001$). CONCLUSION: The results of this study indicate that the oral intake of probiotic B. coagulans and prebiotic inulin can improve the biochemical and clinical parameters of induced RA in rat.

Aceti, A., Gori, D., Barone, G., Callegari, M. L., Fantini, M. P., Indrio, F., Maggio, L., Meneghin, F., Morelli, L., Zuccotti, G., and Corvaglia, L. Probiotics and Time to Achieve Full Enteral Feeding in Human Milk-Fed and Formula-Fed Preterm Infants: Systematic Review and Meta-Analysis. Nutrients. 2016; 8(8)

ABSTRACT: Probiotics have been linked to a reduction in the incidence of necrotizing enterocolitis and late-onset sepsis in preterm infants. Recently, probiotics have also proved to reduce time to achieve full enteral feeding (FEF). However, the relationship between FEF achievement and type of feeding in infants treated with probiotics has not been explored yet. The aim of this systematic review and meta-analysis was to evaluate the effect of probiotics in reducing time to achieve FEF in preterm infants, according to type of feeding (exclusive human milk (HM) vs. formula). Randomized-controlled trials involving preterm infants receiving probiotics, and reporting on time to reach FEF were

included in the systematic review. Trials reporting on outcome according to type of feeding (exclusive HM vs. formula) were included in the meta-analysis. Fixed-effect or random-effects models were used as appropriate. Results were expressed as mean difference (MD) with 95% confidence interval (CI). Twenty-five studies were included in the systematic review. In the five studies recruiting exclusively HM-fed preterm infants, those treated with probiotics reached FEF approximately 3 days before controls (MD -3.15 days (95% CI -5.25/-1.05), p = 0.003). None of the two studies reporting on exclusively formula-fed infants showed any difference between infants receiving probiotics and controls in terms of FEF achievement. The limited number of included studies did not allow testing for other subgroup differences between HM and formula-fed infants. However, if confirmed in further studies, the 3-days reduction in time to achieve FEF in exclusively HM-fed preterm infants might have significant implications for their clinical management.

Agnello, A., Bevilacqua, L., Ariviello, R., Bandieramonte, G., Peroni, M., Simoncini, E., Verdi, P., and Zanardi, C. Infezioni virali in ginecologia: un problema risolto? Minerva Ginecol. 2016; 68(3):388-391.

ABSTRACT: The aim of this observational study was to evaluate the effectiveness of a dietary integrator containing methionine, zinc, Echinacea angustifolia and E. purpurea, probiotics, and antioxidant factors (Immuno Gin) in the treatment of mild cervical dysplasia associated with human papillomavirus (HPV) infection. The study sample was 95 women (age range, 31-55 years) resident in various cities in Italy. Initial Pap test results showed abnormal changes in cervical cells described as atypical squamous cells of undetermined significance (ASC-US) and HPV infection in 23/95 women, 3 of which received the study product. Follow-up repeat Pap testing at 6 months returned normal test results in all 3. In 12 of the 20 women who did not receive treatment with the study product, the repeat Pap test at 6 months showed normal results, whereas persistence of lesions was observed in the other 8 women, with progression to low-grade squamous intraepithelial lesion (LSIL) in one case. Forty-five women presented initially with abnormal changes in cervical cells described as LSIL and HPV infection. Twenty received treatment with the study product; the repeat Pap test at 6 months showed normal results in 15 and no change in lesions in the other 5. Among the 25 women who did not receive treatment with the study product, the repeat Pap test at 6 months showed normal results in 13, whereas persistence of lesions was noted in the other 12, with progression to high-grade squamous intraepithelial lesion - moderate cervical intraepithelial lesion 2 (H.

Agha-Jaffar, R., Oliver, N., Johnston, D., and Robinson, S. Gestational diabetes mellitus: does an effective prevention strategy exist? Nat.Rev.Endocrinol. 2016; 12(9):533-546.

ABSTRACT: The overall incidence of gestational diabetes mellitus (GDM) is increasing worldwide. Preventing pathological hyperglycaemia during pregnancy could have several benefits: a reduction in the immediate adverse outcomes during pregnancy, a reduced risk of long-term sequelae and a decrease in the economic burden to healthcare systems. In this Review we examine the evidence supporting lifestyle modification strategies in women with and without risk factors for GDM, and the efficacy of dietary supplementation and pharmacological approaches to prevent this disease. A high degree of heterogeneity exists between trials so a generalised recommendation is problematic. In population studies of dietary or combined lifestyle measures, risk of developing GDM is not improved and those involving a physical activity intervention

have yielded conflicting results. In pregnant women with obesity, dietary modification might reduce fetal macrosomia but in these patients, low compliance and no significant reduction in the incidence of GDM has been observed in trials investigating physical activity. Supplementation with probiotics or myoinositol have reduced the incidence of GDM but confirmatory studies are still needed. In randomized controlled trials, metformin does not prevent GDM in certain at-risk groups. Given the considerable potential for reducing disease burden, further research is needed to identify strategies that can be easily and effectively implemented on a population level.

Ahl, D., Liu, H., Schreiber, O., Roos, S., Phillipson, M., and Holm, L. Lactobacillus reuteri increases mucus thickness and ameliorates dextran sulphate sodium-induced colitis in mice. Acta Physiol (Oxf). 2016; 217(4):300-310.

ABSTRACT: AIM: The aim of this study was to investigate whether two Lactobacillus reuteri strains (rat-derived R2LC and human-derived ATCC PTA 4659 (4659)) could protect mice against colitis, as well as delineate the mechanisms behind this protection. METHODS: Mice were given L. reuteri R2LC or 4659 by gavage once daily for 14 days, and colitis was induced by addition of 3% DSS (dextran sulphate sodium) to drinking water for the last 7 days of this period. The severity of disease was assessed through clinical observations, histological evaluation and ELISA measurements of myeloperoxidase (MPO) and pro-inflammatory cytokines from colonic samples. Mucus thickness was measured in vivo with micropipettes, and tight junction protein expression was assessed using immunohistochemistry. RESULTS: Colitis severity was significantly reduced by L. reuteri R2LC or 4659 when evaluated both clinically and histologically. The inflammation markers MPO, IL-1beta, IL-6 and mKC (mouse keratinocyte chemoattractant) were increased by DSS and significantly reduced by the L. reuteri strains. The firmly adherent mucus thickness was reduced by DSS, but significantly increased by L. reuteri in both control and DSS-treated mice. Expression of the tight junction proteins occludin and ZO-1 was significantly increased in the bottom of the colonic crypts by L. reuteri R2LC. CONCLUSION: These results demonstrate that each of the two different L. reuteri strains, one human-derived and one-rat-derived, protects against colitis in mice. Mechanisms behind this protection could at least partly be explained by the increased mucus thickness as well as a tightened epithelium in the stem cell area of the crypts.

Aktas, B., De Wolfe, T. J., Safdar, N., Darien, B. J., and Steele, J. L. The Impact of Lactobacillus casei on the Composition of the Cecal Microbiota and Innate Immune System Is Strain Specific. PLoS.One. 2016; 11(5):e0156374

ABSTRACT: The probiotic function to impact human health is thought to be related to their ability to alter the composition of the gut microbiota and modulate the human innate immune system. The ability to function as a probiotic is believed to be strain specific. Strains of Lactobacillus casei are commonly utilized as probiotics that when consumed alter the composition of the gut microbiota and modulate the host immune response. L. casei strains are known to differ significantly in gene content. The objective of this study was to investigate seven different L. casei strains for their ability to alter the murine gut microbiota and modulate the murine immune system. C57BL/6 mice were fed L. casei strains at a dose of 108 CFU/day/mouse for seven days and sacrificed 3.5h after the last administration. The cecal content and the ileum tissue were collected for microbiota analysis and immune profiling, respectively. While 5 of the L. casei strains altered the gut microbiota in a strain specific manner, two of the strains did not alter the

overall cecal microbiota composition. The observed changes cluster into three groups containing between 1 and 2 strains. Two strains that did not affect the gut microbiota composition cluster together with the control in their impact on pattern recognition receptors (PRRs) expression, suggesting that the ability to alter the cecal microbiota correlates with the ability to alter PRR expression. They also cluster together in their impact on the expression of intestinal antimicrobial peptides (AMPs). This result suggests that a relationship exists between the capability of a L. casei strains to alter the composition of the gut microbiota, PRR regulation, and AMP regulation.

Al, Khodor S. and Shatat, I. F. Gut microbiome and kidney disease: a bidirectional relationship. Pediatr.Nephrol. 4-29-2016;

ABSTRACT: Recent technological advances and efforts, including powerful metagenomic and metatranscriptomic analyses, have led to a tremendous growth in our understanding of microbial communities. Changes in microbial abundance or composition of human microbial communities impact human health or disease state. However, explorations into the mechanisms underlying host-microbe interactions in health and disease are still in their infancy. Although changes in the gut microbiota have been described in patients with kidney disease, the relationships between pathogenesis, mechanisms of disease progression, and the gut microbiome are still evolving. Here, we review changes in the host-microbiome symbiotic relationship in an attempt to explore the bidirectional relationship in which alterations in the microbiome affect kidney disease progression and how kidney disease may disrupt a balanced microbiome. We also discuss potential targeted interventions that may help re-establish this symbiosis and propose more effective ways to deploy traditional treatments in patients with kidney disease.

Alard, J., Lehrter, V., Rhimi, M., Mangin, I., Peucelle, V., Abraham, A. L., Mariadassou, M., Maguin, E., Waligora-Dupriet, A. J., Pot, B., Wolowczuk, I., and Grangette, C. Beneficial metabolic effects of selected probiotics on diet-induced obesity and insulin resistance in mice are associated with improvement of dysbiotic gut microbiota. Environ.Microbiol. 2016; 18(5):1484-1497.

ABSTRACT: Alterations in gut microbiota composition and diversity were suggested to play a role in the development of obesity, a chronic subclinical inflammatory condition. We here evaluated the impact of oral consumption of a monostrain or multi-strain probiotic preparation in high-fat diet-induced obese mice. We observed a strain-specific effect and reported dissociation between the capacity of probiotics to dampen adipose tissue inflammation and to limit body weight gain. A multi-strain mixture was able to improve adiposity, insulin resistance and dyslipidemia through adipose tissue immune cell-remodelling, mainly affecting macrophages. At the gut level, the mixture modified the uptake of fatty acids and restored the expression level of the short-chain fatty acid receptor GPR43. These beneficial effects were associated with changes in the microbiota composition, such as the restoration of the abundance of Akkermansia muciniphila and Rikenellaceae and the decrease of other taxa like Lactobacillaceae. Using an in vitro gut model, we further showed that the probiotic mixture favours the production of butyrate and propionate. Our findings provide crucial clues for the design and use of more efficient probiotic preparations in obesity management and may bring new insights into the mechanisms by which host-microbe interactions govern such protective effects.

Alizadeh, M., Munyaka, P., Yitbarek, A., Echeverry, H., and Rodriguez-Lecompte, J. C. Maternal antibody decay and antibody-mediated immune responses in chicken pullets fed prebiotics and synbiotics. Poult.Sci. 7-18-2016;

ABSTRACT: Three experiments were conducted to evaluate the effect of yeast-derived carbohydrates (YDC), and a blend of probiotics and YDC (synbiotic, SNB) on serum IgG concentration, maternal-derived antibody (MDA) decay, and specific antibody-mediated immune response in chick pullets following immunization with T-cell dependent antigens. A total of 300 day-old pullet chicks were randomly assigned to 3 dietary treatments including: a basal diet (Control), and diets containing YDC, and SNB (Lactobacillus acidophilus, L. casei, Streptococcus faecium, and Bacillus subtilis, and YDC). In experiment one, on d 1 and wk 3, 4, 5, and 6, blood samples were collected and serum were analyzed by ELISA for total IgG (Y), and MDA against Newcastle disease virus (NDV) and infectious bursal disease virus (IBDV). The second experiment examined the specific antibody against infectious bronchitis virus (IBV) in pullet chicks following vaccination against IBV at d 1. Finally, in experiment 3, on d 21 and 28 posthatch, 10 birds per treatment were immunized intramuscularly with both sheep red blood cells (SRBC) and bovine serum albumin (BSA), and 11 after immunization serum samples were analyzed by hemagglutination assay for antibody response to SRBC, and by ELISA for serum IgM and IgG response to BSA. The results demonstrated that diet containing SNB increased serum IgG at wk 3 posthatch. However, the decay rate of MDA against NDV and IBDV were not affected by dietary treatments. Birds fed YDC showed higher specific antibody response against IBV in wk 4, while both diets containing YDC and SNB decreased antibody response to IBV in wk 6. In addition, specific antibody response against SRBC and BSA was not affected by diets. In conclusion, supplementation of diet with SNB improved humoral immunity by increasing IgG concentration in serum, and modulated the adaptive antibody-mediated immune response against IBV.

Allaert, F. A., Courau, S., and Forestier, A. Effect of magnesium, probiotic, and vitamin food supplementation in healthy subjects with psychological stress and evaluation of a persistent effect after discontinuing intake. Panminerva Med. 6-16-2016;

ABSTRACT: BACKGROUND: To describe the changes in subjects' psychological stress intensity under the effect of dietary supplements of magnesium, probiotics, and vitamins after one month of intake. METHODS: Observational cohort study of subject complaining of psychological stress defined by a Perceived Stress Scale (PSS 10) score of more than 21. RESULTS: The study covered 242 healthy volunteers, 38.6 +/- 13.6 years old, among whom 79.8% were women. Under the effect of the supplementation of magnesium, probiotics, and vitamins, the psychological stress of the subjects decreased significantly from 34.1 +/- 4.5 to 26.2 +/- 6.1 ($p<0.0001$), which corresponds to an average reduction of 22.7 +/- 16.0%. Fatigue decreased even more significantly from 16.8 +/- 6.4 to 8.7 +/- 6.2 ($p<0.0001$), which corresponds to an average reduction of 45.0% +/- 38.1%. Analysis showed that the psychological stress level was strictly similar one month after the treatment was discontinued and therefore clearly demonstrated that the psychological benefit was maintained over time. CONCLUSIONS: Stress and fatigue are significantly reduced by the intake of a food supplement with probiotics, magnesium, vitamins, and minerals and this effect is fully maintained one month after discontinuing the food supplement intake.

Allain, T., Mansour, N. M., Bahr, M. M., Martin, R., Florent, I., Langella, P., and Bermudez-Humaran, L. G. A new lactobacilli in vivo expression system for the production and delivery of heterologous proteins at mucosal surfaces. FEMS Microbiol.Lett. 2016; 363(13)

ABSTRACT: Food-grade lactic acid bacteria, such as lactobacilli, represent good candidates for the development of mucosal vectors. Indeed, they are generally recognized as safe microorganisms and some strains display beneficial effects (probiotics). In this study, we described a new lactobacilli in vivo expression (LIVE) system for the production and delivery of therapeutic molecules at mucosal surfaces. The versatility and functionality of this system was successfully validated in several lactobacilli species; furthermore, we assessed in vivo LIVE system in two different mouse models of human pathologies: (i) a model of therapy against intestinal inflammation (inflammatory bowel diseases) and (ii) a model of vaccination against dental caries. We demonstrated that Lactobacillus gasseri expressing the anti-inflammatory cytokine IL-10 under LIVE system efficiently delivered the recombinant protein at mucosal surfaces and display anti-inflammatory effects. In the vaccination model against caries, LIVE system allowed the heterologous expression of Streptococcus mutans antigen GbpB by L. gasseri, leading to a stimulation of the host immune response.

Alvarez-Calatayud, G. and Margolles, A. Dual-coated lactic acid bacteria: an emerging innovative technology in the field of probiotics. Future.Microbiol. 2016; 11(3):467-475.

ABSTRACT: Probiotics are living micro-organisms that do not naturally have shelf life, and normally are weakly protected against the digestive action of the GI tract. A new dual coating technology has been developed in an effort to maximize survival, that is, to be able to reach the intestine alive and in sufficient numbers to confer the beneficial health effects on the host. Dual-coating of lactic acid bacteria (LAB) is the result of fourth-generation coating technology for the protection of these bacteria at least 100-fold or greater than the uncoated LAB. This innovative technique involves a first pH-dependent protein layer that protects bacteria from gastric acid and bile salt, and a second polysaccharide matrix that protects bacteria from external factors, such as humidity, temperature and pressure, as well as the digestive action during the passage through the GI tract. Dual-coated probiotic formulation is applicable to different therapeutic areas, including irritable bowel syndrome, atopic dermatitis, acute diarrhea, chronic constipation, Helicobacter pylori eradication, and prevention of antibiotic-associated diarrhea. An updated review of the efficacy of doubly coated probiotic strains for improving bacterial survival in the intestinal tract and its consequent clinical benefits in humans is here presented.

Ambalam, P., Raman, M., Purama, R. K., and Doble, M. Probiotics, prebiotics and colorectal cancer prevention. Best.Pract.Res.Clin.Gastroenterol. 2016; 30(1):119-131.

ABSTRACT: Colorectal cancer (CRC), the third major cause of mortality among various cancer types in United States, has been increasing in developing countries due to varying diet and dietary habits and occupational hazards. Recent evidences showed that composition of gut microbiota could be associated with the development of CRC and other gut dysbiosis. Modulation of gut microbiota by probiotics and prebiotics, either alone or in combination could positively influence the cross-talk between immune system and microbiota, would be beneficial in preventing inflammation and CRC. In this review, role of probiotics and prebiotics in the prevention of CRC has been discussed. Various

epidemiological and experimental studies, specifically gut microbiome research has effectively improved the understanding about the role of probiotics and microbial treatment as anticarcinogenic agents. A few human studies support the beneficial effect of probiotics and prebiotics; hence, comprehensive understanding is urgent to realize the clinical applications of probiotics and prebiotics in CRC prevention.

Ambas, I., Suriawan, A., and Fotedar, R. Corrigendum to "Immunological responses of customised probiotics-fed marron, Cherax tenuimanus, (Smith 1912) when challenged with Vibrio mimicus" [Fish Shellfish Immunol. 35 (2) (2013) 262-270]. Fish.Shellfish.Immunol. 2016; 55:747.

No abstract currently available.

Amdekar, S. and Singh, V. Lactobacillus acidophilus maintained oxidative stress from reproductive organs in collagen-induced arthritic rats. J.Hum.Reprod.Sci. 2016; 9(1):41-46.

ABSTRACT: CONTEXTS: Nonsteroidal anti-inflammatory drugs (NSAIDs) induced organ damage is a well-known fact. Previous studies suggest that Lactobacillus scavenge the free radicals from liver and kidney and also protect animals from arthritis. AIMS: Comparing protective properties of Lactobacillus acidophilus in reducing oxidative stress from reproductive organs developed during collagen-induced arthritis in animal model. METHODS: Arthritis was induced in Wistar rats. Oral administration of L. acidophilus, indomethacin, and distilled water were all started on the same day. Arthritis scores were calculated for each group. Oxidative stress parameters were estimated in testis and ovary homogenates. Histopathology of ovary and testis was also performed. RESULTS AND CONCLUSION: L. acidophilus decreased arthritis score ($P < 0.001$) as well as maintained normal histology of reproductive organs. L. acidophilus maintained oxidative stress parameters from ovaries and testis ($P < 0.001$). These results provide strong evidence that NSAIDs increase oxidative stress in reproductive organs while L. acidophilus not only scavenges free radicals from reproductive organs but also protects rats from arthritis symptoms.

Amir, L. H., Griffin, L., Cullinane, M., and Garland, S. M. Probiotics and mastitis: evidence-based marketing? Int.Breastfeed.J. 2016; 11:19

ABSTRACT: Probiotics are defined as live micro-organisms, which when administered in adequate amounts, confer health benefits on the host. Scientists have isolated various strains of Lactobacilli from human milk (such as Lactobacillus fermentum and Lactobacillus salivarius), and the presence of these organisms is thought to be protective against breast infections, or mastitis. Trials of probiotics for treating mastitis in dairy cows have had mixed results: some successful and others unsuccessful. To date, only one trial of probiotics to treat mastitis in women and one trial to prevent mastitis have been published. Although trials of probiotics to prevent mastitis in breastfeeding women are still in progress, health professionals in Australia are receiving marketing of these products. High quality randomised controlled trials are needed to assess the effectiveness of probiotics for the prevention and/or treatment of mastitis.

Amund, O. D. Exploring the relationship between exposure to technological and gastrointestinal stress and probiotic functional properties of lactobacilli and bifidobacteria. Can.J.Microbiol. 6-14-2016; 1-11.

ABSTRACT: Strains of Lactobacillus and Bifidobacterium are considered probiotic because of their associated potential health benefits. Probiotics are commonly administered orally via incorporation into food products. Microorganisms for use as probiotics encounter stress conditions, which include acid, bile, osmotic, oxidative, heat and cold stresses. These can occur during processing and storage and during passage through the gastrointestinal tract, and can affect viability. Probiotic bacteria have to remain viable to confer any health benefits. Therefore, the ability to withstand technological and gastrointestinal stresses is crucial probiotic selection criteria. While the stress tolerance mechanisms of lactobacilli and bifidobacteria are largely understood, the impact of exposure to stressful conditions on the functional properties of surviving probiotic microorganisms is not clear. This review explores the potentially positive and negative relationships between exposure to stress conditions and probiotic functional properties, such as resistance to gastric acid and bile, adhesion and colonization potential, and tolerance to antibiotics. Protective strategies can be employed to combat negative effects of stress on functional properties. However, further research is needed to ascertain synergistic relationships between exposure to stress and probiotic properties.

Anand, S., Mandal, S., Patil, P., and Tomar, S. K. Pathogen-induced secretory diarrhea and its prevention. Eur.J.Clin.Microbiol.Infect.Dis. 7-29-2016;

ABSTRACT: Secretory diarrhea is a historically known serious health implication around the world which primarily originates through pathogenic microorganisms rather than immunological or genetical disorders. This review highlights infective mechanisms of non-inflammatory secretory diarrhea causing pathogens, known therapeutics and their efficacy against them. These non-inflammatory diarrheal pathogens breach cell barriers, induce inflammation, disrupt fluid secretion across the epithelium by alteration in ion transport by faulting cystic fibrosis transmembrane conductance regulator (CFTR), calcium activated chloride channels and ion exchanger functions. Currently, a variety of prevention strategies have been used to treat these symptoms like use of antibacterial drugs, vaccines, fluid and nutritional therapy, probiotics and prebiotics as adjuncts. In progression of the need for a therapy having quick physiological effects, withdrawing the symptoms with a wide and safe therapeutic index, newer antisecretory agents like potent inhibitors, agonists and herbal remedies are some of the interventions which have come into light through greater understanding of the mechanisms and molecular targets involved in intestinal fluid secretion. Although these therapies have their own pros and cons inside the host, the quest for new antisecretory agents has been a successful elucidation to reduce burden of diarrheal disease.

Anderson, S. Barriers to Knowledge Translation Regarding the Use of Probiotics as a Risk-Reduction Strategy for Necrotizing Enterocolitis. Adv.Neonatal Care. 2016; 16(4):E3-E14.

ABSTRACT: BACKGROUND: Increasingly, evidence supports enteral probiotics are an important risk-reduction strategy for necrotizing enterocolitis (NEC) among very low birth-weight and extremely low birth-weight preterm infants. Yet, the majority of providers remain reluctant to implement practice changes. PURPOSE: The aim of this study was to

better understand the discrepancy between the available evidence and clinical practice regarding the use of probiotics and other NEC prevention strategies in New Jersey. METHODS: Using an exploratory descriptive design, a multimodal interprofessional survey was developed and executed to elicit intensive care nursery provider knowledge, views, and current practice. RESULTS: Although the sample size was small (N = 29), approximately one-half of respondents familiar with the literature rated the quality of the evidence regarding probiotics as "above average" to "excellent." These respondents were "very likely" to "extremely likely" to recommend probiotics as an NEC prevention strategy; however, none actually prescribed this intervention. The most important reason respondents did not prescribe probiotics was the focus on providing exclusive maternal and donor breast milk feedings. Other confounding factors included provision of oral colostrum care, standardized feeding protocols, and withholding feedings during blood transfusion. IMPLICATIONS FOR PRACTICE: Study results suggested that some providers (primarily nurses) were not familiar with probiotic literature, which may contribute to deficits in knowledge translation to practice. IMPLICATIONS FOR RESEARCH: Areas for future study include identifying improved mechanisms for knowledge dissemination, recognizing and addressing barriers and facilitators to knowledge translation, and understanding how probiotics fit and/or contrast with other NEC risk-reduction strategies in the research and clinical settings.

Andrabi, S. T., Bhat, B., Gupta, M., and Bajaj, B. K. Phytase-Producing Potential and Other Functional Attributes of Lactic Acid Bacteria Isolates for Prospective Probiotic Applications. Probiotics.Antimicrob.Proteins. 2016; 8(3):121-129.

ABSTRACT: Wide variations among multifaceted-health benefitting attributes of probiotics fueled investigations on targeting efficacious probiotics. In the current study, lactic acid bacteria (LAB) isolated from poultry gut, feces of rat, chicken, human infants, and fermented foods were characterized for desired probiotic functional properties including the phytase-producing ability which is one of the wanted characteristics for probiotics for potential applications for upgrading animal nutrition, enhancing feed conversion, and minimizing anti-nutritional properties. Among 62 LAB isolates Weissella kimchii R-3 an isolate from poultry gut exhibited substantial phytase-producing ability (1.77 U/ml) in addition to other functional probiotic characteristics viz. hydrophobicity, autoaggregation, coaggregation with bacterial pathogens, and antimicrobial activity against pathogens. Survival of W. kimchii R-3 cells (in free and calcium alginate encapsulated state) was examined sequentially in simulated gastric and intestinal juices. Encapsulated cells exhibited better survival under simulated gut conditions indicating that encapsulation conferred considerable protection against adverse gut conditions. Furthermore, simulated gastric and intestinal juices with pepsin and pancreatin showed higher survival of cells than the juices without pepsin and pancreatin. W. kimchii R-3 due to its significant functional probiotic attributes may have prospective for commercial applications in human/animal nutrition.

Ang, L. Y., Too, H. K., Tan, E. L., Chow, T. K., Shek, P. C., Tham, E., and Alonso, S. Antiviral activity of Lactobacillus reuteri Protectis against Coxsackievirus A and Enterovirus 71 infection in human skeletal muscle and colon cell lines. Virol.J. 2016; 13:111

ABSTRACT: BACKGROUND: Recurrence of hand, foot and mouth disease (HFMD) pandemics continues to threaten public health. Despite increasing awareness and efforts, effective vaccine and drug treatment have yet to be available. Probiotics have

gained recognition in the field of healthcare worldwide, and have been extensively prescribed to babies and young children to relieve gastrointestinal (GI) disturbances and diseases, associated or not with microbial infections. Since the faecal-oral axis represents the major route of HFMD transmission, transient persistence of probiotic bacteria in the GI tract may confer some protection against HFMD and limit transmission among children. METHODS: In this work, the antiviral activity of two commercially available probiotics, namely Lactobacillus reuteri Protectis (L. reuteri Protectis) and Lactobacillus casei Shirota (L. casei Shirota), was assayed against Coxsackieviruses and Enterovirus 71 (EV71), the main agents responsible for HFMD. In vitro infection set-ups using human skeletal muscle and colon cell lines were designed to assess the antiviral effect of the probiotic bacteria during entry and post-entry steps of the infection cycle. RESULTS: Our findings indicate that L. reuteri Protectis displays a significant dose-dependent antiviral activity against Coxsackievirus type A (CA) strain 6 (CA6), CA16 and EV71, but not against Coxsackievirus type B strain 2. Our data support that the antiviral effect is likely achieved through direct physical interaction between bacteria and virus particles, which impairs virus entry into its mammalian host cell. In contrast, no significant antiviral effect was observed with L. casei Shirota. CONCLUSIONS: Should the antiviral activity of L. reuteri Protectis observed in vitro be translated in vivo, such probiotics-based therapeutic approach may have the potential to address the urgent need for a safe and effective means to protect against HFMD and limit its transmission among children.

Anwar, H. and Rahman, Z. U. Dynamics of anterior pituitary immunoreactive gonadotrophs in moulted hens supplemented with protein, symbiotic and probiotics. J.Anim Physiol Anim Nutr.(Berl). 2016; 100(3):448-455.

ABSTRACT: The present work delineates redistribution patterns of the hormone-producing cells of the anterior pituitary, after the phase of moulting. Two hundred single comb White Leghorn hens at the end of their first production cycle (Age = 70 week) were purchased from the commercial poultry farm and were induced to moult by high-dietary zinc (3 g/kg feed/day) after 1 week of acclimatization, at the experimental research station, Department of Physiology and Pharmacology, University of Agriculture, Faisalabad. The moulted birds were equally (n = 50) and randomly allocated to their respective groups as G1 (control; CP (Crude protein) 16%, no supplement), G2 (CP18%, no other supplement), G3 (CP16%, symbiotic at does rate of 85 mg/l in drinking water daily) and G4 (CP16%, probiotic at dose rate of 85 mg/l in drinking water daily). Ten birds were slaughtered in each group at 5% and at peak of post-moult production stage to collect their pituitary glands. An earlier post-moult production recovery, sustained and lengthier production span was seen in the G2 as compared to all other groups. The lowest production and an earlier production decline were seen in G1. The cell diameter and area of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) gonadotroph increased (p </= 0.01) in G2 and G3 as compared to G1. The FSH gonadotroph nucleus diameter and area did increase (p </= 0.01) in G2 and G3, while LH gonadotroph nucleus diameter and area decreased (p </= 0.01) in G2 and G3 as compared to G1. The increased FSH and LH gonadotroph diameter in protein and symbiotic supplemented birds is accountable for the increased egg production in these groups.

Aoki-Yoshida, A., Saito, S., Fukiya, S., Aoki, R., Takayama, Y., Suzuki, C., and Sonoyama, K. Lactobacillus rhamnosus GG increases Toll-like receptor 3 gene expression in murine small intestine ex vivo and in vivo. Benef.Microbes. 2016; 7(3):421-429.

ABSTRACT: Administration of Lactobacillus rhamnosus GG (LGG) has been reported to be therapeutically effective against acute secretory diarrhoea resulting from the structural and functional intestinal mucosal lesions induced by rotavirus infection; however, the underlying mechanisms remain to be completely elucidated. Because Toll-like receptor 3 (TLR3) plays a key role in the innate immune responses following the recognition of rotavirus, the present study examined whether LGG influences TLR3 gene expression in murine small intestine ex vivo and in vivo. We employed cultured intestinal organoids derived from small intestinal crypts as an ex vivo tissue model. LGG supplementation increased TLR3 mRNA levels in the intestinal organoids, as estimated by quantitative real-time polymerase chain reaction. Likewise, single and 7-day consecutive daily administrations of LGG increased TLR3 mRNA levels in the small intestine of C57BL/6N mice. The mRNA levels of other TLRs were not substantially altered both ex vivo and in vivo. In addition, LGG supplementation increased the mRNA levels of an antiviral type 1 interferon, interferon-alpha (IFN-alpha), and a neutrophil chemokine, CXCL1, upon stimulation with a synthetic TLR3 ligand, poly(I:C) in the intestinal organoids. LGG administration did not alter IFN-alpha and CXCL1 mRNA levels in the small intestine in vivo. Supplementation of other bacterial strains, Bifidobacterium bifidum and Lactobacillus paracasei, failed to increase TLR3 and poly(I:C)-stimulated CXCL1 mRNA levels ex vivo. We propose that upregulation of TLR3 gene expression may play a pivotal role in the therapeutic efficacy of LGG against rotavirus-associated diarrhoea. In addition, we demonstrated that intestinal organoids may be a promising ex vivo tissue model for investigating host-pathogen interactions and the antiviral action of probiotics in the intestinal epithelium.

Arase, S., Watanabe, Y., Setoyama, H., Nagaoka, N., Kawai, M., and Matsumoto, S. Disturbance in the Mucosa-Associated Commensal Bacteria Is Associated with the Exacerbation of Chronic Colitis by Repeated Psychological Stress; Is That the New Target of Probiotics? PLoS.One. 2016; 11(8):e0160736

ABSTRACT: Psychological stress can exacerbate inflammatory bowel disease. However, the mechanisms underlying how psychological stress affects gut inflammation remain unclear. Here, we focused on the relationship between changes in the microbial community of mucosa-associated commensal bacteria (MACB) and mucosal immune responses induced by chronic psychological stress in a murine model of ulcerative colitis. Furthermore, we examined the effect of probiotic treatment on exacerbated colitis and MACB composition changes induced by chronic psychological stress. Repeated water avoidance stress (rWAS) in B6-Tcra-/- mice severely exacerbated colitis, which was evaluated by both colorectal tissue weight and histological score of colitis. rWAS treatment increased mRNA expression of UCN2 and IFN-gamma in large intestinal lamina propria mononuclear cells (LI-LPMC). Interestingly, exacerbated colitis was associated with changes in the microbial community of MACB, specifically loss of bacterial species diversity and an increase in the component ratio of Clostridium, revealed by 16S rRNA gene amplicon analysis. Finally, the oral administration of a probiotic Lactobacillus strain was protective against the exacerbation of colitis and was associated with a change in the bacterial community of MACB in rWAS-exposed Tcra-/- mice. Taken together, these results suggested that loss of species diversity in MACB might play a key role in exacerbated colitis induced by chronic psychological stress. In addition, probiotic treatment may be used as a tool to preserve the diversity of bacterial species in MACB and alleviate gut inflammation induced by psychological stress.

Araujo, C., Munoz-Atienza, E., Poeta, P., Igrejas, G., Hernandez, P. E., Herranz, C., and Cintas, L. M. Characterization of Pediococcus acidilactici strains isolated from rainbow trout (Oncorhynchus mykiss) feed and larvae: safety, DNA fingerprinting, and bacteriocinogenicity. Dis.Aquat.Organ. 5-3-2016; 119(2):129-143.

ABSTRACT: The use of lactic acid bacteria (LAB) as probiotics constitutes an alternative or complementary strategy to chemotherapy and vaccination for disease control in aquaculture. The objectives of this work were (1) the in vitro safety assessment of 8 Pediococcus acidilactici strains isolated from rainbow trout (Oncorhynchus mykiss, Walbaum) feed and larvae; (2) the evaluation of their genetic relatedness; (3) the study of their antimicrobial/bacteriocin activity against fish pathogens; and (4) the biochemical and genetic characterization of the bacteriocin produced by the strain displaying the greatest antimicrobial activity. Concerning the safety assessment, none of the pediococci showed antibiotic resistance nor produced hemolysin or gelatinase, degraded gastric mucin, or deconjugated bile salts. Four strains (50%) produced tyramine or putrescine, but the corresponding genes were not amplified by PCR. Enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR) fingerprinting allowed clustering of the pediococci into 2 well-defined groups (68% similarity). From the 8 pediococci displaying direct antimicrobial activity against at least 3 out of 9 fish pathogens, 6 strains (75%) were identified as bacteriocin producers. The bacteriocin produced by P. acidilactici L-14 was purified, and mass spectrometry and DNA sequencing revealed its identity to pediocin PA-1 (PedPA-1). Altogether, our results allowed the identification of 4 (50%) putatively safe pediococci, including 2 bacteriocinogenic strains. ERIC-PCR fingerprinting was a valuable tool for genetic profiling of P. acidilactici strains. This work reports for the first time the characterization of a PedPA-1-producing P. acidilactici strain isolated from an aquatic environment (rainbow trout larvae), which shows interesting properties related to its potential use as a probiotic in aquaculture.

Armanian, A. M., Barekatain, B., Hoseinzadeh, M., and Salehimehr, N. Prebiotics for the management of hyperbilirubinemia in preterm neonates. J.Matern.Fetal Neonatal Med. 2016; 29(18):3009-3013.

ABSTRACT: OBJECTIVE: We evaluated if prebiotics have benefits for the management of hyperbilirubinemia in preterm neonates. METHODS: Preterm neonates were entered into the study when enteral feeding volume met 30 mL/kg/day. They randomly received a mixture of short-chain galacto-oligosacarids/long-chain fructo-oligosacarids or distilled water (placebo) for 1 week. Total serum bilirubin level was measured by transcutaneous bilirubinometry. Stool frequency and meeting full enteral feeding during the study period were considered as secondary outcomes. RESULTS: Twenty-five neonates in each group completed the trial. Bilirubin level was decreased with the prebiotic (-1.3 +/- 1.8 mg/dL, p = 0.004), but not placebo (-0.1 +/- 3.3 mg/dL, p = 0.416). Peak bilirubin level was lower with the prebiotic than placebo (8.3 +/- 1.7 versus 10.1 +/- 2.2 mg/dL, p = 0.003). Stool frequency was increased with the prebiotic (0.7 +/- 1.9 defecation/day, p = 0.014), but not with placebo (0.6 +/- 1.5 defecation/day, p = 0.133). Average stool frequency (2.4 +/- 0.4 versus 1.9 +/- 0.5 defecation/day, p = 0.003) and frequently of meeting full enteral feeding (60% versus 16%, p = 0.002) were higher with the prebiotic than placebo. CONCLUSIONS: Prebiotic oligosaccharides increase stool frequency, improve feeding tolerance and reduce bilirubin level in preterm neonates and therefore can be efficacious for the management of neonatal hyperbilirubinemia.

Arumugam, S., Lau, C. S., and Chamberlain, R. S. Probiotics and Synbiotics Decrease Postoperative Sepsis in Elective Gastrointestinal Surgical Patients: a Meta-Analysis. J.Gastrointest.Surg. 2016; 20(6):1123-1131.

ABSTRACT: BACKGROUND: The health benefits of probiotics and synbiotics are well established in healthy adults, but their role in preventing postoperative sepsis remains controversial. This meta-analysis assesses the impact of probiotics and synbiotics on the incidence of postoperative sepsis in gastrointestinal (GI) surgical patients. METHODS: A comprehensive literature search of all published randomized control trials (RCTs) was conducted using PubMed, Cochrane Central Registry of Controlled Trials, and Google Scholar (1966-2015). Inclusion criteria included RCTs comparing the use of any strain or dose of a specified probiotic/synbiotic with placebo or a "no treatment" control group. The incidence of postoperative sepsis (within 1 month of surgery) and postoperative mortality were analyzed. RESULTS: Fifteen RCTs involving 1201 patients (192 receiving probiotics, 413 receiving synbiotics, and 596 receiving placebo) were analyzed. Overall, probiotic and synbiotic uses significantly reduced the risk of developing postoperative sepsis by 38 % (relative risk (RR) = 0.62, 95 % confidence interval (CI) 0.52-0.74, $p < 0.001$). CONCLUSIONS: The use of probiotic/synbiotic supplementation is associated with a significant reduction in the risk of developing postoperative sepsis in patients undergoing elective GI surgery. Probiotic/synbiotic supplementation is a valuable adjunct in the care of patients undergoing GI surgery. Additional studies are required to determine the optimal dose and strain of probiotic/synbiotic.

Aryantini, N. P., Yamasaki, E., Kurazono, H., Sujaya, I. N., Urashima, T., and Fukuda, K. In vitro safety assessments and antimicrobial activities of Lactobacillus rhamnosus strains isolated from a fermented mare's milk. Anim Sci.J. 8-1-2016;

ABSTRACT: Safety and probiotic characteristics such as antimicrobial activities of three Lactobacillus rhamnosus strains, FSMM15, FSMM22 and FSMM26, previously isolated as potential probiotics from fermented mare's milk were investigated. The three FSMM strains were susceptible to ampicillin, gentamycin, kanamycin, streptomycin, tetracycline and chloramphenicol, whereas they were resistant to erythromycin (minimal inhibitory concentration (MIC) = 4-8 microg/mL) and clindamycin (MIC = 4 microg/mL); bioconversion of bile salts, hemolytic activity and mucin degradation activity were negative; enzymatic activities of alpha-chymotrypsin and beta-glucosidase were detected, but those of alpha-galactosidase, beta-glucuronidase and N-acetyl-beta-glucosaminidase, were undetectable. Among the strains, strain FSMM15 was chosen as a safer probiotic candidate due mainly to the lack of plasminogen binding ability. Despite lower acid production of strain FSMM15 than others, its cell-free culture supernatant inhibited growths of Salmonella Typhimurium LT-2, Shigella sonnei, Listeria monocytogenes, and Escherichia coli O157 with comparable levels of ampicillin, suggesting a favorable aspect of strain FSMM15 as a probiotic strain.

Asahara, T., Takahashi, A., Yuki, N., Kaji, R., Takahashi, T., and Nomoto, K. Protective Effect of a Synbiotic against Multidrug-Resistant Acinetobacter baumannii in a Murine Infection Model. Antimicrob.Agents Chemother. 2016; 60(5):3041-3050.

ABSTRACT: This study investigated the ability of the probiotic Bifidobacterium breve strain Yakult (BbY) to protect against infection, as well as the potentiation of BbY activity by the

synbiotic combination of BbY and prebiotic galactooligosaccharides (GOS). The study employed a mouse model of lethal intestinal multidrug-resistant Acinetobacter baumannii (MDRAb) infection. The endogenous intestinal microbiota was disrupted by the administration of multiple antibiotics, causing the loss of endogenous Bifidobacterium Oral infection of these mice with MDRAb resulted in marked growth of this organism. Additional treatment of the infected mice with a sublethal dose of 5-fluorouracil (5-FU) induced systemic invasion by MDRAb and subsequent animal death. The continuous oral administration of BbY increased the survival rate and inhibited the intestinal growth and invasion by MDRAb in the infection model. Disruptions of the intestinal environment and barrier function in the infected mice were attenuated by BbY. Protection against the MDRAb infection was markedly potentiated by a synbiotic combination of BbY and GOS, although GOS by itself did not provide protection. Negative correlations were observed between intestinal MDRAb and BbY counts or acetic acid levels; positive correlations were observed between acetic acid levels and intestinal epithelium expression of tight-junction-related genes. These results demonstrated that the probiotic and synbiotic markedly potentiated protection against fatal intestinal infection caused by a multidrug-resistant bacterium. Probiotics and synbiotics are presumed to provide protection by compensation for the disrupted indigenous populations, thereby maintaining the intestinal environments and barrier functions otherwise targeted during opportunistic infection by MDRAb.

Asgari, F., Madjd, Z., Falak, R., Bahar, M. A., Nasrabadi, M. H., Raiani, M., and Shekarabi, M. Probiotic feeding affects T cell populations in blood and lymphoid organs in chickens. Benef.Microbes. 6-28-2016; 1-8.

ABSTRACT: This study was performed to evaluate the effects of Lactobacillus acidophilus bacteria as a probiotic on chicken T cell subset populations in peripheral blood and lymphoid tissues. Thirty chickens were divided into three groups and fed sterilised cow milk, a mixture of milk and L. acidophilus (probiotic), or neither, as the control group. Chickens were euthanised after 14 and 21 days, and whole blood and ileal, bursal, and caecal tonsillar tissues were collected. The populations of T cell subsets, including CD4+, CD8+, and TCR1+ cells, were evaluated by immunohistochemistry and flow cytometry. After 21 days of treatment the percentage of blood CD4+, CD8+, and TCR1+ cells was significantly higher in the probiotic-fed group than in the control group. After 14 days of treatment, a significantly greater number of CD4+ T cells were found in the ileum of probiotic-fed chickens than in chickens from the other two groups. This difference was even greater after 21 days. In addition, after 21 days, a significantly greater number of TCR1+ cells were found in the caecal tonsils of milk-fed chickens than in chickens from the control group. The findings indicate that probiotics may alter the distribution of T cells in the blood and lymphoid tissues in young chickens; however, transient changes in lymphoid tissues indicate that probiotics likely do not permanently affect mucosal immunity.

Athalye-Jape, G., Rao, S., and Patole, S. Lactobacillus reuteri DSM 17938 as a Probiotic for Preterm Neonates: A Strain-Specific Systematic Review. JPEN J.Parenter.Enteral Nutr. 2016; 40(6):783-794.

ABSTRACT: INTRODUCTION: Prevention of necrotizing enterocolitis (NEC) while optimizing enteral nutrition (EN) is a priority in preterm neonates. Lactobacillus reuteri DSM 17938 (L reuteri) is known to improve gut motility. Previous systematic reviews have not adequately assessed

the effects of L reuteri in improving feed tolerance in preterm neonates. OBJECTIVE: To assess the effects of L reuteri in preterm neonates. DESIGN: A systematic review of randomized controlled trials (RCTs) and non-RCTs of L reuteri was conducted. We searched the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and CINAHL databases and proceedings of Pediatric Academic Society meetings in December 2014. RESULTS: Six RCTs (n = 1778) and 2 non-RCTs (n = 665) were included. Meta-analysis of RCTs estimated that the time to full feeds (mean difference [MD], -1.34 days; 95% confidence interval [CI], -1.81 to -0.86; 2 RCTs), duration of hospitalization (-10.77 days; 95% CI, -13.67 to -7.86; 3 RCTs), and late-onset sepsis (LOS) (relative risk [RR], 0.66; 95% CI, 0.52 to 0.83; 4 RCTs) were reduced in the L reuteri group. Mortality (RR, 0.79; 95% CI, 0.57-1.09; 3 RCTs) and >/= stage II NEC (RR, 0.69; 95% CI, 0.47-1.01; 3 RCTs) were reduced but statistically not significant. There were no adverse effects of supplementation. Both non-RCT studies showed significant improvement in the incidence of NEC with L reuteri supplementation. CONCLUSIONS: Evidence from a limited number of studies suggests that L reuteri supplementation has the potential to reduce the risk of NEC and LOS while facilitating EN in preterm infants. Larger definitive RCTs are needed to confirm these findings.

Awasthi, S., Wilken, R., Patel, F., German, J. B., Mills, D. A., Lebrilla, C. B., Kim, K., Freeman, S. L., Smilowitz, J. T., Armstrong, A. W., and Maverakis, E. Dietary supplementation with Bifidobacterium longum subsp. infantis (B. infantis) in healthy breastfed infants: study protocol for a randomised controlled trial. Trials. 2016; 17(1):340

ABSTRACT: BACKGROUND: The development of probiotics as therapies to cure or prevent disease lags far behind that of other investigational medications. Rigorously designed phase I clinical trials are nearly non-existent in the field of probiotic research, which is a contributing factor to this disparity. As a consequence, how to appropriately dose probiotics to study their efficacy is unknown. Herein we propose a novel phase I ascending dose trial of Bifidobacterium longum subsp. infantis (B. infantis) to identify the dose required to produce predominant gut colonisation in healthy breastfed infants at 6 weeks of age. METHODS/DESIGN: This is a parallel-group, placebo-controlled, randomised, double-blind ascending dose phase I clinical trial of dietary supplementation with B. infantis in healthy breastfed infants. The objective is to determine the pharmacologically effective dose (ED) of B. infantis required to produce predominant (>50 %) gut colonisation in breastfed infants at 6 weeks of age. Successively enrolled infant groups will be randomised to receive two doses of either B. infantis or placebo on days 7 and 14 of life. Stool samples will be used to characterise the gut microbiota at increasing doses of B. infantis. DISCUSSION: Probiotic supplementation has shown promising results for the treatment of a variety of ailments, but evidence-based dosing regimes are currently lacking. The ultimate goal of this trial is to establish a recommended starting dose of B. infantis for further efficacy-testing phase II trials designed to evaluate B. infantis for the prevention of atopic dermatitis and food allergies in at-risk children. TRIAL REGISTRATION: Clinicaltrials.gov # NCT02286999 , date of trial registration 23 October 2014.

Azimirad, M., Meshkini, S., Ahmadifard, N., and Hoseinifar, S. H. The effects of feeding with synbiotic (Pediococcus acidilactici and fructooligosaccharide) enriched adult Artemia on skin mucus immune responses, stress resistance, intestinal microbiota and performance of angelfish (Pterophyllum scalare). Fish.Shellfish.Immunol. 2016; 54:516-522.

ABSTRACT: The aim of this study was to evaluate the effects of feeding on synbiotic (Pediococcus acidilactici and fructooligosaccharide) enriched adult Artemia franciscana on skin mucus immune responses, stress resistance, intestinal microbiota and growth performance of angelfish (Pterophyllum scalare). Three hundred and sixty fish with initial weight 3.2 +/- 0.13 g were randomly divided into twelve aquaria (50 L) assigned to four groups in triplicates. Fish were fed for 7 weeks with dietary treatments, including treatment 1: feeding adult Artemia without enrichment (control group), treatment 2: feeding adult Artemia enriched with lyophilised probiotic P. acidilactici (700 mg L(-1)), 3: feeding adult Artemia enriched with prebiotic fructooligosaccharide (FOS) (100 mg L(-1)), group 4: feeding adult Artemia enriched with synbiotic (P. acidilactici (700 mg L(-1)) + FOS (100 mg L(-1))). Skin mucus immune responses (lysozyme activity, total Immunoglobulin and protease), stress resistance against environmental stress (acute decrease of temperature and increase salinity), intestinal microbiota as well as growth indices were measured at the end of feeding trial. Artemia enriched with synbiotic significantly improved growth performance compared to other treatments ($P < 0.05$). The highest weight gain and specific growth rate (SGR) was observed in synbiotic fed fish ($P < 0.05$). Compared to the other treatments, the population of lactic acid bacteria was significantly higher in the intestinal microbiota of fish fed synbiotic supplemented diet ($P < 0.05$). In the environmental stress challenge test, the maximum resistance to abrupt decrease of temperature (17 degrees C) or elevation of salinity (12 g per liter) was observed in the synbiotic treatment. Also, the total immunoglobulin and lysozyme activity level of skin mucus was significantly elevated in fish fed Artemia enriched with synbiotic ($P < 0.05$). These results revealed that feeding angelfish with synbiotic enriched Artemia was more effective than singular enrichment with probiotics or prebiotics.

Babot, J. D., rganaraz-Martinez, E., Lorenzo-Pisarello, M. J., Apella, M. C., and Perez, Chaia A. Cytotoxic damage of soybean agglutinin on intestinal epithelial cells of broiler chicks: in vitro protection by Bifidobacterium infantis CRL1395. FEMS Microbiol.Lett. 2016; 363(12)

ABSTRACT: Plant lectins, which are proteins/glycoproteins present in a wide range of vegetables, fruits, cereals and beans, are resistant to digestive enzymes and food cooking temperatures. They bind reversibly to specific glycosidic residues expressed on the membrane of intestinal epithelial cells (IEC) and cause anti-nutritional effects in humans and animals. Soybean lectin (SBA) has been detected in poultry diets, and its ability to bind to the intestinal epithelium has been reported. The development of new methods for removing SBA from feeds or to prevent interaction with the intestinal mucosa is of interest. In this study, the in vitro cytotoxicity of SBA on IEC of chicks was demonstrated for the first time. The LD50, assessed after 2 h exposure of IEC to SBA, was 6.13 mug mL(-1) The ability of Bifidobacterium infantis CRL1395 to bind SBA on the bacterial envelope was confirmed, and prevention of IEC cytotoxicity by lectin removal was demonstrated. Safety of B. infantis CRL1395, resistance to gastrointestinal stress and adhesion were also determined. It was concluded that the early administration of B. infantis CRL1395 to chicks would effectively reduce the toxicity of SBA. Besides, it would favour the colonization of the gut with a beneficial microbiota.

Bansal, S., Mangal, M., Sharma, S. K., and Gupta, R. K. Non-dairy Based Probiotics: A Healthy Treat for Intestine. Crit Rev.Food Sci.Nutr. 8-17-2016; 56(11):1856-1867.

ABSTRACT: Dairy-based fermented products and yoghurts have been utilized as potential probiotic products since ancient times. However, recent upsurge in interest of consumers

towards dairy alternatives has opened up new vistas for non-dairy probiotic research and development. Various matrices and substrates such as cereals, fruit juices, or mixture thereof are being utilized for delivering these beneficial microorganisms. Each matrix offers some advantages over the other. Vast knowledge available on a number of conventional fermented foods can also be utilized for future research in this area. The present review provides an insight on the recent research/developments in the field of non-dairy probiotic foods with particular reference to the foods consumed conventionally, in addition to their commercial availability and a way forward.

Barengolts, E. GUT MICROBIOTA, PREBIOTICS, PROBIOTICS, AND SYNBIOTICS IN MANAGEMENT OF OBESITY AND PREDIABETES: REVIEW OF RANDOMIZED CONTROLLED TRIALS. Endocr.Pract. 7-13-2016.

No abstract currently available.

Barrangou, R. and Dudley, E. G. CRISPR-Based Typing and Next-Generation Tracking Technologies. Annu.Rev.Food Sci.Technol. 2016; 7:395-411.

ABSTRACT: Bacteria occur ubiquitously in nature and are broadly relevant throughout the food supply chain, with diverse and variable tolerance levels depending on their origin, biological role, and impact on the quality and safety of the product as well as on the health of the consumer. With increasing knowledge of and accessibility to the microbial composition of our environments, food supply, and host-associated microbiota, our understanding of and appreciation for the ratio of beneficial to undesirable bacteria are rapidly evolving. Therefore, there is a need for tools and technologies that allow definite, accurate, and high-resolution identification and typing of various groups of bacteria that include beneficial microbes such as starter cultures and probiotics, innocuous commensals, and undesirable pathogens and spoilage organisms. During the transition from the current molecular biology-based PFGE (pulsed-field gel electrophoresis) gold standard to the increasingly accessible omics-level whole-genome sequencing (WGS) N-gen standard, high-resolution technologies such as CRISPR-based genotyping constitute practical and powerful alternatives that provide valuable insights into genome microevolution and evolutionary trajectories. Indeed, several studies have shown potential for CRISPR-based typing of industrial starter cultures, health-promoting probiotic strains, animal commensal species, and problematic pathogens. Emerging CRISPR-based typing methods open new avenues for high-resolution typing of a broad range of bacteria and constitute a practical means for rapid tracking of a diversity of food-associated microbes.

Barszcz, M., Taciak, M., and Skomial, J. The effects of inulin, dried Jerusalem artichoke tuber and a multispecies probiotic preparation on microbiota ecology and immune status of the large intestine in young pigs. Arch.Anim Nutr. 2016; 70(4):278-292.

ABSTRACT: The study aimed at determining the effect of two types of prebiotics and a multispecies probiotic on microbiota activity and composition, as well as mucosal immunity in the large intestine of young pigs. In total 48 piglets were divided into 6 groups (n = 8), which received from day 10 of life probiotic-unsupplemented (PU) or probiotic-supplemented (PS) diets. Probiotics were added at 0.5 g/kg diet and contained: Lactococcus lactis, Carnobacterium divergens, Lactobacillus casei, Lactobacillus plantarum and Saccharomyces cerevisiae. The PU and PS diets were formulated without

prebiotic addition (control) or with addition of 2% of inulin from chicory root (IN) or 4% of dried Jerusalem artichoke tubers (DJA). After 40 days of feeding, digesta and tissue samples were taken from the caecum and three sections of the colon for analyses of microbiota activity and composition, secretory immunoglobulin A (sIgA) and intraepithelial lymphocytes (IEL). IN diets decreased the caecal digesta pH and beta-glucosidase activity but increased propionic, valeric and total short chain fatty acid (SCFA) concentrations compared to control diets. Feeding DJA diets increased caecal valeric acid level, decreased the concentration of isoacids in the colon, reduced beta-glucosidase and beta-glucuronidase activity in the middle colon and increased Bifidobacterium spp. populations in the proximal and distal colon. PS diets increased the caecal acetic acid and total SCFA level, and Clostridium spp. populations in the distal colon. Neither probiotic nor prebiotics affected sIgA level or IEL number in the large intestine. In conclusion, DJA modified the microbiota ecology in the large intestine of young pigs to a greater extent than IN and the applied probiotic did not enhance effects of prebiotics.

Barthow, C., Wickens, K., Stanley, T., Mitchell, E. A., Maude, R., Abels, P., Purdie, G., Murphy, R., Stone, P., Kang, J., Hood, F., Rowden, J., Barnes, P., Fitzharris, P., Craig, J., Slykerman, R. F., and Crane, J. The Probiotics in Pregnancy Study (PiP Study): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy. BMC.Pregnancy.Childbirth. 2016; 16(1):133

ABSTRACT: BACKGROUND: Worldwide there is increasing interest in the manipulation of human gut microbiota by the use of probiotic supplements to modify or prevent a range of communicable and non-communicable diseases. Probiotic interventions administered during pregnancy and breastfeeding offer a unique opportunity to influence a range of important maternal and infant outcomes. The aim of the Probiotics in Pregnancy Study (PiP Study) is to assess if supplementation by the probiotic Lactobacillus rhamnosus HN001 administered to women from early pregnancy and while breastfeeding can reduce the rates of infant eczema and atopic sensitisation at 1 year, and maternal gestational diabetes mellitus, bacterial vaginosis and Group B Streptococcal vaginal colonisation before birth, and depression and anxiety postpartum. METHODS/DESIGN: The PiP Study is a two-centre, randomised, double-blind placebo-controlled trial in Wellington and Auckland, New Zealand. Four hundred pregnant women expecting infants at high risk of allergic disease will be enrolled in the study at 14-16 weeks gestation and randomised to receive either Lactobacillus rhamnosus HN001 (6 x 10(9) colony-forming units per day (cfu/day)) or placebo until delivery and then continuing until 6 months post-partum, if breastfeeding. Primary infant outcomes are the development and severity of eczema and atopic sensitisation in the first year of life. Secondary outcomes are diagnosis of maternal gestational diabetes mellitus, presence of bacterial vaginosis and vaginal carriage of Group B Streptococcus (at 35-37 weeks gestation). Other outcome measures include maternal weight gain, maternal postpartum depression and anxiety, infant birth weight, preterm birth, and rate of caesarean sections. A range of samples including maternal and infant faecal samples, maternal blood samples, cord blood and infant cord tissue samples, breast milk, infant skin swabs and infant buccal swabs will be collected for the investigation of the mechanisms of probiotic action. DISCUSSION: The study will investigate if mother-only supplementation with Lactobacillus rhamnosus HN001 in pregnancy and while breastfeeding can reduce rates of eczema and atopic sensitisation in infants by 1 year, and reduce maternal rates of gestational diabetes mellitus, bacterial vaginosis, vaginal carriage of Group B Streptococcus before birth and

maternal depression and anxiety postpartum. TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registration: ACTRN12612000196842. Date Registered: 15/02/12.

Basholli-Salihu, M., Schuster, R., Mulla, D., Praznik, W., Viernstein, H., and Mueller, M. Bioconversion of piceid to resveratrol by selected probiotic cell extracts. Bioprocess.Biosyst.Eng. 8-6-2016;

ABSTRACT: Resveratrol exerts several pharmacological activities, including anti-cancer, anti-inflammatory, cardioprotective, or antioxidant effects. However, due to its occurrence in plants more in glycosidic form as piceid, the bioavailability and bioactivity are limited. The enzymatic potential of probiotics for the transformation of piceid to resveratrol was elucidated. Cell extract from Bifidobacteria (B.) infantis, B. bifidum, Lactobacillus (L.) casei, L. plantarum, and L. acidophilus was evaluated for their effect in this bioconversion using high-performance liquid chromatography (HPLC) as analytical tool. Cell extract of B. infantis showed the highest effect on the deglycosylation of piceid to resveratrol, already after 30 min. Cell extracts of all other tested strains showed a significant biotransformation with no further metabolization of resveratrol. The conversion of piceid to resveratrol is of importance to increase bioavailability and bioactivity as shown for anti-inflammation in this study. Cell extracts from probiotics, especially from B. infantis, may be added to piceid containing products, for achieving higher biological effects caused by the bioactivity of resveratrol or by health promoting of the probiotics. These findings open a new perspective of novel combination of cell extracts from probiotics and piceid, in health-promoting pharmaceutical and food products.

Bastos, R. W., Pedroso, S. H., Vieira, A. T., Moreira, L. M., Franca, C. S., Cartelle, C. T., Arantes, R. M., Generoso, S. V., Cardoso, V. N., Neves, M. J., Nicoli, J. R., and Martins, F. S. Saccharomyces cerevisiae UFMG A-905 treatment reduces intestinal damage in a murine model of irinotecan-induced mucositis. Benef.Microbes. 5-2-2016; 1-10.

ABSTRACT: Indigenous microbiota plays a crucial role in the development of several intestinal diseases, including mucositis. Gastrointestinal mucositis is a major and serious side effect of cancer therapy, and there is no effective therapy for this clinical condition. However, some probiotics have been shown to attenuate such conditions. To evaluate the effects of Saccharomyces cerevisiae UFMG A-905 (Sc-905), a potential probiotic yeast, we investigated whether pre- or post-treatment with viable or inactivated Sc-905 could prevent weight loss and intestinal lesions, and maintain integrity of the mucosal barrier in a mucositis model induced by irinotecan in mice. Only post-treatment with viable Sc-905 was able to protect mice against the damage caused by chemotherapy, reducing the weight loss, increase of intestinal permeability and jejunal lesions (villous shortening). Besides, this treatment reduced oxidative stress, prevented the decrease of goblet cells and stimulated the replication of cells in the intestinal crypts of mice with experimental mucositis. In conclusion, Sc-905 protects animals against irinotecan-induced mucositis when administered as a post-treatment with viable cells, and this effect seems to be related with the reduction of oxidative stress and preservation of intestinal mucosa.

Batista, S., Medina, A., Pires, M. A., Morinigo, M. A., Sansuwan, K., Fernandes, J. M., Valente, L. M., and Ozorio, R. O. Innate immune response, intestinal morphology and microbiota

changes in Senegalese sole fed plant protein diets with probiotics or autolysed yeast. Appl.Microbiol.Biotechnol. 2016; 100(16):7223-7238.

ABSTRACT: The effects of using plant ingredients in Senegalese sole (Solea senegalensis) diet on immune competence and intestine morphology and microbial ecology are still controversial. Probiotics or immunostimulants can potentially alter the intestinal microbiota in a way that protects fish against pathogens. The current study aimed to examine the intestine histology and microbiota and humoral innate immune response in juvenile sole fed diets with low (35 %) or high (72 %) content of plant protein (PP) ingredients supplemented with a multispecies probiotic bacteria or autolysed yeast. Fish fed the probiotic diet had lower growth performance. Lysozyme and complement activities were significantly higher in fish fed PP72 diets than in their counterparts fed PP35 diets after 17 and 38 days of feeding. At 2 days of feeding, fish fed unsupplemented PP72 showed larger intestine section area and longer villus than fish fed unsupplemented PP35. At 17 days of feeding, fish fed unsupplemented PP72 showed more goblet cells than the other dietary groups, except the group fed yeast supplemented PP35 diet. High dietary PP level, acutely stimulate fish innate immune defence of the fish after 2 and 17 days of feeding. However, this effect does not occur after 73 days of feeding, suggesting a habituation to dietary treatments and/or immunosuppression, with a reduction in the number of the goblet cells. Fish fed for 38 days with diets supplemented with autolysed yeast showed longer intestinal villus. The predominant bacteria found in sole intestine were Vibrio sp. and dietary probiotic supplementation caused a reduction in Vibrio content, regardless of the PP level.

Bauer, H. W. and Bessler, W. G. [Non-Antibiotic Strategies to Prevent the Recurrence of Uncomplicated Urinary Tract Infections in Women]. Aktuelle Urol. 2016; 47(3):214-219.

ABSTRACT: The aim of all medical treatment is "primum nihil nocere" ("First, do no harm").Restoring the integrity of intestinal microbiota and optimising the immune response in recurrent infections, especially in the urinary tract, are treatment alternatives which are closer to this target than the usual focus on antibiotic prevention of recurrence.In the future, antibiotics will continue to be recommended for the prevention of urinary tract infections on a case-by-case basis. However, the problems of an excessive use of antibiotics, e. g. resistance and long-term interference with intestinal microbiota, are forcing us to search for alternatives. The use of probiotics alone or in combination with immunotherapeutics, or the sole use of immunotherapeutics, are important treatment options, which are already routinely available in clinical practice. These therapies are focused on the pathomechanism of an infection and tackle the root cause of the problem. Phytotherapeutics or small molecules like mannose, which restricts the adherence of bacteria to the urothelium, are complementary approaches.The EAU guidelines recommend the following treatments for the long-term prevention of urinary tract infections:Oral and parenteral immunostimulants (StroVac((R))), local estrogen replacement and administration of Lactobacillus rhamnosus and Lactobacillus reuteri.

Beck, B. R., Song, J. H., Park, B. S., Kim, D., Kwak, J. H., Do, H. K., Kim, A. R., Kim, W. J., and Song, S. K. Distinct immune tones are established by Lactococcus lactis BFE920 and Lactobacillus plantarum FGL0001 in the gut of olive flounder (Paralichthys olivaceus). Fish.Shellfish.Immunol. 2016; 55:434-443.

ABSTRACT: The immune tone is defined as an immunological state during which the readiness for immune response is potentiated. The establishment of immune tone in the gut of olive flounder (Paralichthys olivaceus) was investigated by feeding Lactococcus lactis BFE920 (LL) or Lactobacillus plantarum FGL0001 (LP). LL-fed flounder showed significantly increased levels of regulatory genes (FOXP3, IL-10, and TGF-beta1), CD18, and CD83 in the gut. In contrast, LP feeding drastically increased proinflammatory genes (T-bet, IL-1beta, and IFN-gamma) and CD18. This indicates that LL and LP establish different types of local immune tones in the gut through differential activation of innate immune cells: LL activates both macrophages and dendritic cells while LP activates macrophages only. Both of the immune tones required at least a total of 6 probiotic feeds during 72 h for a stable establishment. Once established, the type of immune tone remained steady even up to 30 days (a total of 60 feeds) probiotics feeding. The LL-induced regulatory immune tone enhanced the level of occludin, a tight junction molecule, significantly more than that observed with the proinflammatory immune tone established by LP feeding. Consequently, LL-fed fish showed considerably lower gut permeability than that of the LP-fed group. Furthermore, when orally challenged by Edwardsiella tarda, LL-fed flounder survived at a significantly higher rate than LP-fed fish. The data clearly demonstrate that individual probiotics establish distinct types of immune tone in the fish gut, which in turn influences the immunological status as well as the physiology of the gut. Selection of proper probiotics may be essential for optimal effects in aquaculture farming.

Belamarich, P. F., Bochner, R. E., and Racine, A. D. A Critical Review of the Marketing Claims of Infant Formula Products in the United States. Clin.Pediatr.(Phila). 2016; 55(5):437-442.

ABSTRACT: A highly competitive infant formula market has resulted in direct-to-consumer marketing intended to promote the sale of modified formulas that claim to ameliorate common infant feeding problems. The claims associated with these marketing campaigns are not evaluated with reference to clinical evidence by the Food and Drug Administration. We aimed to describe the language of claims made on formula labels and compare it with the evidence in systematic reviews. Of the 22 product labels we identified, 13 product labels included claims about colic and gastrointestinal symptoms. There is insufficient evidence to support the claims that removing or reducing lactose, using hydrolyzed or soy protein or adding pre-/probiotics to formula benefits infants with fussiness, gas, or colic yet claims like "soy for fussiness and gas" encourage parents who perceive their infants to be fussy to purchase modified formula. Increased regulation of infant formula claims is warranted.

Bellary, A. N. and Rastogi, N. K. Ways and Means for the Infusion of Bioactive Constituents in Solid Foods. Crit Rev.Food Sci.Nutr. 5-18-2016; 56(7):1126-1145.

ABSTRACT: The development and consumption of functional food, or foods that promote health not merely basic nutrition, is on rise. In recent years, industrial and consumer interests have focused on developing foods supplemented with bioactive constituents that provide greater physiological benefits. The direct addition of these components to liquid or fabricated solid foods has led to a wide range of new products appearing on the market. Osmotic dehydration, an operation in which food stuff is soaked in solution of low water activity, has been reported as a suitable technology for formulating new products because of the twofold effect that it has on food where it partially removes water and impregnates the food pieces (solid food matrix) with solutes from the osmotic

solution. The article focuses on the impregnation of bioactive constituents having added advantage to human health such as antioxidants, minerals, vitamins, and probiotics. The infusion of enzymes and aroma also has been discussed. Application of ultrasound, vacuum, high pressure, and/or atmospheric impregnation techniques appears to be the feasible technologies for impregnation of solid food matrix for the incorporation of bioactive ingredients.

Ben, Taheur F., Kouidhi, B., Fdhila, K., Elabed, H., Ben, Slama R., Mahdouani, K., Bakhrouf, A., and Chaieb, K. Anti-bacterial and anti-biofilm activity of probiotic bacteria against oral pathogens. Microb.Pathog. 2016; 97:213-220.

ABSTRACT: In this study, three lactic acid bacteria (LAB), isolated from barley, traditional dried meat and fermented olive were characterized and tested for their anti-bacterial and anti-biofilm activities against oral bacteria. Our results revealed that the tested LAB were gamma-hemolytic and were susceptible to four antibiotics. All the strains were resistant to low pH, bile salt, pepsin and pancreatin. Furthermore, FB2 displayed a high aut-oaggregative phenotype (99.54%) while FF2 exhibited the best co-aggregation rate. Concerning the microbial adhesion to solvent, FB2 was the most hydrophobic strain (data obtained with chloroform and n-hexadecane). In addition Pediococcus pentosaceus FB2 and Lactobacillus brevis FF2 displayed a significant inhibitory effect against Streptococcus salivarius B468 (MIC = 10%). Moreover the selected strains were able to inhibit biofilm formation of Bacillus cereus ATCC14579 (MBIC50 = 28.16%) and S. salivarius B468 (MBIC50 = 42.28%). The selected LAB could be considered as candidate probiotics for further application in functional food and mainly in the prevention of oral diseases.

Benitez-Paez, A., Moreno, F. J., Sanz, M. L., and Sanz, Y. Genome Structure of the Symbiont Bifidobacterium pseudocatenulatum CECT 7765 and Gene Expression Profiling in Response to Lactulose-Derived Oligosaccharides. Front Microbiol. 2016; 7:624

ABSTRACT: Bifidobacterium pseudocatenulatum CECT 7765 was isolated from stools of a breast-fed infant. Although, this strain is generally considered an adult-type bifidobacterial species, it has also been shown to have pre-clinical efficacy in obesity models. In order to understand the molecular basis of its adaptation to complex carbohydrates and improve its potential functionality, we have analyzed its genome and transcriptome, as well as its metabolic output when growing in galacto-oligosaccharides derived from lactulose (GOS-Lu) as carbon source. B. pseudocatenulatum CECT 7765 shows strain-specific genome regions, including a great diversity of sugar metabolic-related genes. A preliminary and exploratory transcriptome analysis suggests candidate over-expression of several genes coding for sugar transporters and permeases; furthermore, five out of seven beta-galactosidases identified in the genome could be activated in response to GOS-Lu exposure. Here, we also propose that a specific gene cluster is involved in controlling the import and hydrolysis of certain di- and tri-saccharides, which seemed to be those primarily taken-up by the bifidobacterial strain. This was discerned from mass spectrometry-based quantification of different saccharide fractions of culture supernatants. Our results confirm that the expression of genes involved in sugar transport and metabolism and in the synthesis of leucine, an amino acid with a key role in glucose and energy homeostasis, was up-regulated by GOS-Lu. This was done using qPCR in addition to the exploratory information derived from the

single-replicated RNAseq approach, together with the functional annotation of genes predicted to be encoded in the B. pseudocatenulatum CETC 7765 genome.

Bengtsson, J., Adlerberth, I., Ostblom, A., Saksena, P., Oresland, T., and Borjesson, L. Effect of probiotics (Lactobacillus plantarum 299 plus Bifidobacterium Cure21) in patients with poor ileal pouch function: a randomised controlled trial. Scand.J.Gastroenterol. 2016; 51(9):1087-1092.

ABSTRACT: OBJECTIVE: Poor pouch function after restorative proctocolectomy for ulcerative colitis is a considerable problem. Pouchitis and functional disorders are the most common reasons. Probiotics seem to have a beneficial effect in pouchitis but have not been assessed in functional pouch disorders. The aim was to analyse the effects of probiotics in patients with poor pouch function. METHODS: Thirty-three patients were randomized to probiotics (Lactobacillus plantarum 299 and Bifidobacterium infantis Cure 21) or placebo in a double blinded, 1:1 fashion. The treatment effect was assessed by the pouch functional score (PFS; 0-15, 15 worst), pouchitis disease activity index (PDAI; 0-18, 18 worst), and levels of four faecal biomarkers of inflammation (calprotectin, lactoferrin, myeloperoxidase [MPO] and eosinophilic cationic protein [ECP]). RESULTS: Thirty-two patients were included (probiotics = 17, placebo = 16). There was no difference in change in the PFS from before to after treatment between the groups (median difference: -1.00, 95% C.I. -3.00 to 0.00, p = 0.119). Furthermore, probiotics had no effect on PDAI (median difference: 0.00, 95% C.I. 0.00-1.00, p = 0.786), or on faecal biomarkers. Significant correlations were observed between PDAI and each of the faecal biomarkers at study start. There were no correlations between PFS or PDAI symptom subscore and the biomarkers. PDAI endoscopic and histologic subscores correlated significantly to each of the biomarkers. CONCLUSION: The hypothesis that probiotics improves pouch-related dysfunction was not confirmed. Faecal biomarkers could play a future role in the management of pouch patients.

Bentzon-Tilia, M., Sonnenschein, E. C., and Gram, L. Monitoring and managing microbes in aquaculture - Towards a sustainable industry. Microb.Biotechnol. 7-24-2016;

ABSTRACT: Microorganisms are of great importance to aquaculture where they occur naturally, and can be added artificially, fulfilling different roles. They recycle nutrients, degrade organic matter and, occasionally, they infect and kill the fish, their larvae or the live feed. Also, some microorganisms may protect fish and larvae against disease. Hence, monitoring and manipulating the microbial communities in aquaculture environments hold great potential; both in terms of assessing and improving water quality, but also in terms of controlling the development of microbial infections. Using microbial communities to monitor water quality and to efficiently carry out ecosystem services within the aquaculture systems may only be a few years away. Initially, however, we need to thoroughly understand the microbiomes of both healthy and diseased aquaculture systems, and we need to determine how to successfully manipulate and engineer these microbiomes. Similarly, we can reduce the need to apply antibiotics in aquaculture through manipulation of the microbiome, i.e. by the use of probiotic bacteria. Recent studies have demonstrated that fish pathogenic bacteria in live feed can be controlled by probiotics and that mortality of infected fish larvae can be reduced significantly by probiotic bacteria. However, the successful management of the aquaculture microbiota is currently hampered by our lack of knowledge of relevant microbial interactions and the overall ecology of these systems.

Bernini, L. J., Simao, A. N., Alfieri, D. F., Lozovoy, M. A., Mari, N. L., de Souza, C. H., Dichi, I., and Costa, G. N. Beneficial effects of Bifidobacterium lactis on lipid profile and cytokines in patients with metabolic syndrome: A randomized trial. Effects of probiotics on metabolic syndrome. Nutrition. 2016; 32(6):716-719.

ABSTRACT: OBJECTIVE: Human studies have shown the beneficial effects of probiotic microorganisms on the parameters of metabolic syndrome (MetS) and other cardiovascular risks, but to our knowledge the effect of Bifidobacterium lactis has not yet been reported. The aim of this study was to evaluate the effect of consumption of milk containing the probiotic B. lactis HN019 on the classical parameters of MetS and other related cardiovascular risk factors. METHODS: Fifty-one patients with MetS were selected and divided into a control group (n = 25) and a probiotic group (n = 26). The probiotic group consumed fermented milk with probiotics over the course of 45 d. The effects of B. lactis on lipid profile, glucose metabolism, and proinflammatory cytokines (tumor necrosis factor-alpha and interleukin-6) were assessed in blood samples of the individuals at the baseline and after 45 d. RESULTS: Daily ingestion of 80 mL fermented milk with 2.72 x 10(10) colony-forming units of B. lactis HN019 showed significant reduction in body mass index (P = 0.017), total cholesterol (P = 0.009), and low-density lipoprotein (P = 0.008) compared with baseline and control group values. Furthermore, a significant decrease in tumor necrosis factor-alpha (P = 0.033) and interleukin-6 (P = 0.044) proinflammatory cytokines was observed. CONCLUSION: These data showed potential effects of B. lactis HN019 in reducing obesity, blood lipids, and some inflammatory markers, which may reduce cardiovascular risk in patients with MetS.

Berstad, A., Raa, J., Midtvedt, T., and Valeur, J. Probiotic lactic acid bacteria - the fledgling cuckoos of the gut? Microb.Ecol.Health Dis. 2016; 27:31557

ABSTRACT: It is tempting to look at bacteria from our human egocentric point of view and label them as either 'good' or 'bad'. However, a microbial society has its own system of government - 'microcracy' - and its own rules of play. Lactic acid bacteria are often referred to as representatives of the good ones, and there is little doubt that those belonging to the normal intestinal flora are beneficial for human health. But we should stop thinking of lactic acid bacteria as always being 'friendly' - they may instead behave like fledgling cuckoos.

Bertelsen, R. J., Jensen, E. T., and Ringel-Kulka, T. Use of probiotics and prebiotics in infant feeding. Best.Pract.Res.Clin.Gastroenterol. 2016; 30(1):39-48.

ABSTRACT: Gut colonization by beneficial bacteria in early life is necessary for establishing the gut mucosal barrier, maturation of the immune system and preventing infections with enteric pathogens. Mode of delivery, prematurity, breastfeeding, and use of antibiotics are some of many factors that have been described to influence early life colonization. Dysbiosis, the absence of normal colonization, is associated with many disease conditions. Pre- and probiotics are commonly used as supplementation in infant formula, such as prebiotic oligosaccharides for stimulation of Bifidobacterium growth aiming to mimic the high levels of these commensal bacteria in the gut of breastfed infants. Studies suggest that probiotic supplementation may be beneficial in prevention and management of disease (e.g., reducing the risk of necrotizing enterocolitis in

preterm infants and treatment of acute gastroenteritis in children). Although these studies show promising beneficial effects, the long-term risks or health benefits of pre- and probiotic supplementation are not clear.

Bilkova, A., Bilka, F., and Kinova, Sepova H. [Potential immunomodulatory and antiinflammatory mechanisms of probiotics]. Ceska.Slov.Farm. 2016; 65(2):43-51.

ABSTRACT: The number of preclinical and clinical studies showing efficacy of probiotics in the treatment and prophylaxis of certain diseases, e.g. diarrhoea of various origin, irritable bowel syndrome, inflammatory bowel disease, allergies, hypercholesterolemia, bacterial vaginosis, and colorectal cancer, is increasing. These health benefits are often species and strain specific. This article provides an overview of available knowledge about the supposed mechanisms of probiotic microorganisms action focusing in particular on the interaction between probiotic and host cells. One of the results of this interaction is induction of pro- or anti-inflammatory immune response in the macroorganism. Detailed knowledge of the signalling pathways involved in the communication between bacterial and human cells can find application in the selection of optimal probiotics for the targeted treatment of selected diseases. Additional possibilities for their use in clinical practice are provided by genetic manipulation of probiotic microorganisms. KEY WORDS: probiotics inflammation signalling pathways immunomodulation genetic manipulation.

Blandino, G., Inturri, R., Lazzara, F., Di, Rosa M., and Malaguarnera, L. Impact of gut microbiota on diabetes mellitus. Diabetes Metab. 5-11-2016;

ABSTRACT: Various functions of the gut are regulated by sophisticated interactions among its functional elements, including the gut microbiota. These microorganisms play a crucial role in gastrointestinal mucosa permeability. They control the fermentation and absorption of dietary polysaccharides to produce short-chain fatty acids, which may explain their importance in the regulation of fat accumulation and the subsequent development of obesity-related diseases, suggesting that they are a crucial mediator of obesity and its consequences. In addition, gut bacteria play a crucial role in the host immune system, modulation of inflammatory processes, extraction of energy from the host diet and alterations of human gene expression. Dietary modulation of the human colonic microbiota has been shown to confer a number of health benefits to the host. Simple therapeutic strategies targeted at attenuating the progression of chronic low-grade inflammation and insulin resistance are urgently required to prevent or slow the development of diabetes in susceptible individuals. The main objective of this review is to address the pathogenic association between gut microbiota and diabetes, and to explore any novel related therapeutic targets. New insights into the role of the gut microbiota in diabetes could lead to the development of integrated strategies using probiotics to prevent and treat these metabolic disorders.

Blattner, C. M., Crosby, M. S., Goedken, M., and Murase, J. E. Update: Do probiotics prevent or treat pediatric atopic dermatitis? Pediatr.Allergy Immunol. 2016; 27(4):425-428.

No abstract currently available.

Blot, S., Torres, A., and Francois, B. Evidence in the eye of the beholder: about probiotics and VAP prevention. Intensive Care Med. 2016; 42(7):1182-1184.

No abstract currently available.

Boltin, D. Probiotics in Helicobacter pylori-induced peptic ulcer disease. Best.Pract.Res.Clin.Gastroenterol. 2016; 30(1):99-109.

ABSTRACT: The ideal treatment regimen for the eradication Helicobacter pylori infection has yet to be identified. Probiotics, particularly Lactobacillus, Bifidobacterium and Saccharomyces, have been suggested as adjuncts to antibiotics for the treatment of H. pylori. There is in vitro evidence that probiotics dampen the Th1 response triggered by H. pylori, attenuate H. pylori associated hypochlorhydria and secrete bacteriocidal metabolites. Probiotics interact with the innate host immune system through adherence to the gastric epithelium and secretion of bacterial adhesins. In prospective human studies, probiotic monotherapy effectively decrease H. pylori density (expired (13)CO2) by 2.0%-64.0%. Probiotic monotherapy has also been shown to eradicate H. pylori in up to 32.5%, although subsequent recrudescence is likely. Eleven meta-analyses have evaluated the efficacy of probiotics as adjuvants to antibiotics for the eradication of H. pylori. The addition of a probiotic increased treatment efficacy, OR 1.12-2.07. This benefit is probably strain-specific and may only be significant with relatively ineffective antibiotic regimens. The pooled prevalence of adverse effects was 12.9%-31.5% among subjects receiving adjuvant probiotics, compared with 24.3%-45.9% among controls. Diarrhea in particular was significantly reduced in subjects receiving adjuvant probiotics, compared with controls (OR 0.16-0.47). A reduction in adverse events other than diarrhea is variable. Despite the apparent benefit on efficacy and side effects conferred by probiotics, the optimal probiotic species, dose and treatment duration has yet to be determined. Further studies are needed to identify the probiotic, antibiotic and patient factors which might predict benefit from probiotic supplementation.

Boursier, J. and Diehl, A. M. Nonalcoholic Fatty Liver Disease and the Gut Microbiome. Clin.Liver Dis. 2016; 20(2):263-275.

ABSTRACT: Recent progress has allowed a more comprehensive study of the gut microbiota. Gut microbiota helps in health maintenance and gut dysbiosis associates with chronic metabolic diseases. Modulation of short-chain fatty acids and choline bioavailability, lipoprotein lipase induction, alteration of bile acid profile, endogenous alcohol production, or liver inflammation secondary to endotoxemia result from gut dysbiosis. Modulation of the gut microbiota by pre/probiotics gives promising results in animal, but needs to be evaluated in human before use in clinical practice. Gut microbiota adds complexity to the pathophysiology of nonalcoholic fatty liver disease but represents an opportunity to discover new therapeutic targets.

Braff, D., Shis, D., and Collins, J. J. Synthetic biology platform technologies for antimicrobial applications. Adv.Drug Deliv.Rev. 4-18-2016;

ABSTRACT: The growing prevalence of antibiotic resistance calls for new approaches in the development of antimicrobial therapeutics. Likewise, improved diagnostic measures are essential in guiding the application of targeted therapies and preventing the

evolution of therapeutic resistance. Discovery platforms are also needed to form new treatment strategies and identify novel antimicrobial agents. By applying engineering principles to molecular biology, synthetic biologists have developed platforms that improve upon, supplement, and will perhaps supplant traditional broad-spectrum antibiotics. Efforts in engineering bacteriophages and synthetic probiotics demonstrate targeted antimicrobial approaches that can be fine-tuned using synthetic biology-derived principles. Further, the development of paper-based, cell-free expression systems holds promise in promoting the clinical translation of molecular biology tools for diagnostic purposes. In this review, we highlight emerging synthetic biology platform technologies that are geared toward the generation of new antimicrobial therapies, diagnostics, and discovery channels.

Briskey, D., Heritage, M., Jaskowski, L. A., Peake, J., Gobe, G., Subramaniam, V. N., Crawford, D., Campbell, C., and Vitetta, L. Probiotics modify tight-junction proteins in an animal model of nonalcoholic fatty liver disease. Therap.Adv.Gastroenterol. 2016; 9(4):463-472.

ABSTRACT: BACKGROUND: We have investigated the effects of a multispecies probiotic preparation containing a combination of probiotic bacterial genera that included Bifidobacteria, Lactobacilli and a Streptococcus in a mouse model of high-fat diet or obesity-induced liver steatosis. METHODS: Three groups of C57B1/6J mice were fed either a standard chow or a high-fat diet for 20 weeks, while a third group was fed a high-fat diet for 10 weeks and then concomitantly administered probiotics for a further 10 weeks. Serum, liver and large bowel samples were collected for analysis. RESULTS: The expression of the tight-junction proteins ZO-1 and ZO-2 was reduced ($p < 0.05$) in high-fat diet-fed mice compared to chow-fed mice. Probiotic supplementation helped to maintain tight ZO-1 and ZO-2 expression compared with the high-fat diet group ($p < 0.05$), but did not restore ZO-1 or ZO-2 expression compared with chow-fed mice. Mice fed a high-fat diet +/- probiotics had significant steatosis development compared with chow-fed mice ($p < 0.05$); steatosis was less severe in the probiotics group compared with the high-fat diet group. Hepatic triglyceride concentration was higher in mice fed a high-fat diet +/- probiotics compared with the chow group ($p < 0.05$), and was lower in the probiotics group compared with the high-fat diet group ($p < 0.05$). Compared with chow-fed mice, serum glucose, cholesterol concentration and the activity of alanine transaminase were higher ($p < 0.05$), whereas serum triglyceride concentration was lower ($p < 0.05$) in mice fed a high-fat diet +/- probiotics. CONCLUSIONS: Supplementation with a multispecies probiotic formulation helped to maintain tight-junction proteins ZO-1 and ZO-2, and reduced hepatic triglyceride concentration compared with a high-fat diet alone.

Broecker, F., Klumpp, J., and Moelling, K. Long-term microbiota and virome in a Zurich patient after fecal transplantation against Clostridium difficile infection. Ann.N.Y.Acad.Sci. 2016; 1372(1):29-41.

ABSTRACT: Fecal microbiota transplantation (FMT) is an emerging therapeutic option for Clostridium difficile infections that are refractory to conventional treatment. FMT introduces fecal microbes into the patient's intestine that prevent the recurrence of C. difficile, leading to rapid expansion of bacteria characteristic of healthy microbiota. However, the long-term effects of FMT remain largely unknown. The C. difficile patient described in this paper revealed protracted microbiota adaptation processes from 6 to 42 months post-FMT. Ultimately, bacterial communities were donor similar, suggesting sustainable stool engraftment. Since little is known about the consequences of

transmitted viruses during C. difficile infection, we also interrogated virome changes. Our approach allowed identification of about 10 phage types per sample that represented larger viral communities, and phages were found to be equally abundant in the cured patient and donor. The healthy microbiota appears to be characterized by low phage abundance. Although viruses were likely transferred, the patient established a virome distinct from the donor. Surprisingly, the patient had sequences of algal giant viruses (chloroviruses) that have not previously been reported for the human gut. Chloroviruses have not been associated with intestinal disease, but their presence in the oropharynx may influence cognitive abilities. The findings suggest that the virome is an important indicator of health or disease. A better understanding of the role of viruses in the gut ecosystem may uncover novel microbiota-modulating therapeutic strategies.

Broeckx, G., Vandenheuvel, D., Claes, I. J., Lebeer, S., and Kiekens, F. Drying techniques of probiotic bacteria as an important step towards the development of novel pharmabiotics. Int.J.Pharm. 5-30-2016; 505(1-2):303-318.

ABSTRACT: The increasing knowledge about the human microbiome leads to the awareness of how important probiotics can be for our health. Although further substantiation is required, it appears that several pathologies could be treated or prevented by the administration of pharmaceutical formulations containing such live health-beneficial bacteria. These pharmabiotics need to provide their effects until the end of shelf life, which can be optimally achieved by drying them before further formulation. However, drying processes, including spray-, freeze-, vacuum- and fluidized bed drying, induce stress on probiotics, thus decreasing their viability. Several protection strategies can be envisaged to enhance their viability, including addition of protective agents, controlling the process parameters and prestressing the probiotics prior to drying. Moreover, probiotic viability needs to be maintained during long-term storage. Overall, lower storage temperature and low moisture content result in good survival rates. Attention should also be given to the rehydration conditions of the dried probiotics, as this can exert an important effect on their revival. By describing not only the characteristics, but also the viability results obtained by the most relevant drying techniques in the probiotic industry, we hope to facilitate the deliberate choice of drying process and protection strategy for specific probiotic and pharmabiotic applications.

Brussow, H. Biome engineering-2020. Microb.Biotechnol. 7-29-2016;

ABSTRACT: The gut microbiome research is going from a descriptive into an intervention phase. To optimize beneficial microbe-host interaction, we need to understand how to steer the system by modulating the nutrient input with which the system is literally fed (e.g. diets, fibres, prebiotics, human milk oligosaccharides), and we must learn how to modulate the composition of the gut microbiota by adding beneficial microbes (e.g. probiotics, faecal transplants) and by eliminating disturbing microbial members using, for example, bacteriophages in this highly complex ecosystem. The current status of the field is reviewed together with an outlook what might be expected until 2020, highlighting obstacles to progress and possible solutions to these problems.

Bruzzese, E., Fedele, M. C., Bruzzese, D., Viscovo, S., Giannattasio, A., Mandato, C., Siani, P., and Guarino, A. Randomised clinical trial: a Lactobacillus GG and micronutrient-containing

mixture is effective in reducing nosocomial infections in children, vs. placebo. Aliment.Pharmacol.Ther. 7-28-2016;

ABSTRACT: BACKGROUND: Nosocomial infections are a major public health issue and preventative strategies using probiotics and micronutrients are being evaluated. AIM: To investigate the efficacy of a mixture of Lactobacillus GG and micronutrients in preventing nosocomial infections in children. METHODS: A randomised, double-blind, placebo-controlled trial was conducted in hospitalised children. Children (6 months to 5 years of age) received Lactobacillus GG (6 x 109 CFU/day) together with vitamins B and C and zinc or placebo, for 15 days, starting on the first day of hospitalisation. The incidence of gastrointestinal and respiratory nosocomial infections after discharge was determined by follow-up telephone call at 7 days. After 3 months, another telephone call estimated the incidence of further infections during follow-up. RESULTS: Ninety children completed the follow-up. Of 19/90 children with a nosocomial infection (20%), 4/45 children (9%) were in the treatment group and 15/45 (33%) in the placebo group (P = 0.016). Specifically, 2/45 (4%) children in the treatment group vs. 11/45 (24%) children in the placebo group (P = 0.007) presented with diarrhoea. The duration of hospitalisation was significantly shorter in the treatment group (3.9 days +/- 1.7 vs. 4.9 +/- 1.2; P = 0.003). At the follow-up, a total of 11/45 (24.4%) children in the treatment group had at least one episode of infection compared to 22/45 (48.9%) in the placebo group (P = 0.016). CONCLUSION: A mixture containing Lactobacillus GG and micronutrients may reduce the incidence of nosocomial infections, supporting the hypothesis that this may represent a valid strategy to prevent nosocomial infections.

Cabello, F. C., Godfrey, H. P., Buschmann, A. H., and Dolz, H. J. Aquaculture as yet another environmental gateway to the development and globalisation of antimicrobial resistance. Lancet Infect.Dis. 2016; 16(7):e127-e133.

ABSTRACT: Aquaculture uses hundreds of tonnes of antimicrobials annually to prevent and treat bacterial infection. The passage of these antimicrobials into the aquatic environment selects for resistant bacteria and resistance genes and stimulates bacterial mutation, recombination, and horizontal gene transfer. The potential bridging of aquatic and human pathogen resistomes leads to emergence of new antimicrobial-resistant bacteria and global dissemination of them and their antimicrobial resistance genes into animal and human populations. Efforts to prevent antimicrobial overuse in aquaculture must include education of all stakeholders about its detrimental effects on the health of fish, human beings, and the aquatic ecosystem (the notion of One Health), and encouragement of environmentally friendly measures of disease prevention, including vaccines, probiotics, and bacteriophages. Adoption of these measures is a crucial supplement to efforts dealing with antimicrobial resistance by developing new therapeutic agents, if headway is to be made against the increasing problem of antimicrobial resistance in human and veterinary medicine.

Cabezas, Cruz A., Valdes, J. J., and de la, Fuente J. Control of vector-borne infectious diseases by human immunity against alpha-Gal. Expert.Rev.Vaccines. 2016; 15(8):953-955.

No abstract currently available.

Cai, M., Zeng, L., Li, L. J., Mo, L. H., Xie, R. D., Feng, B. S., Zheng, P. Y., Liu, Z. G., Liu, Z. J., and Yang, P. C. Specific immunotherapy ameliorates ulcerative colitis. Allergy Asthma Clin.Immunol. 2016; 12:37

ABSTRACT: BACKGROUND: Hypersensitivity reaction to certain allergens plays a role in the pathogenesis of inflammatory bowel disease (IBD). This study aims to observe the effect of specific immunotherapy in a group of IBD patients. METHODS: Patients with both ulcerative colitis (UC) and food allergy were recruited into this study. Food allergy was diagnosed by skin prick test and serum specific IgE. The patients were treated with specific immunotherapy (SIT) and Clostridium butyricum (CB) capsules. RESULTS: After treating with SIT and CB, the clinical symptoms of UC were markedly suppressed as shown by reduced truncated Mayo scores and medication scores. The serum levels of specific IgE, interleukin (IL)-4 and tumor necrosis factor (TNF)-alpha were also suppressed. Treating with SIT alone or CB alone did not show appreciable improvement of the clinical symptoms of UC. CONCLUSIONS: UC with food allergy can be ameliorated by administration with SIT and butyrate-production probiotics.

Campbell, A. W. Nanoparticles, the Microbiome, and Probiotics. Altern.Ther.Health Med. 2016; 22(S1):6-7.

ABSTRACT: No Abstract Available.

Capurso, L. [Probiotics]. Recenti Prog.Med. 2016; 107(6):267-277.

ABSTRACT: On the basis of the currently available literature, which includes well-designed clinical trials, systematic reviews and meta-analyses, certain effects can be ascribed to probiotics as a general class. It is accepted that sufficient evidence has accumulated to support the concept of benefits of certain probiotics; it is reasonable to expect that evidence gained from a defined class of live microbes might be appropriate for certain, but not all, health outcomes. Moreover there is a need for clear communication to consumers and health-care providers of the activity of differentiate probiotic products.

Carbone, D. and Faggio, C. Importance of prebiotics in aquaculture as immunostimulants. Effects on immune system of Sparus aurata and Dicentrarchus labrax. Fish.Shellfish.Immunol. 2016; 54:172-178.

ABSTRACT: Infectious diseases in fish represent a major problem for the aquaculture field as they produce extensive damages and loss. Over the last few years, with increased development of the aquaculture industry, different methods have been used to contrast these pathologies. Common interest has led to the use of components (as additives in diets) that could contrast diseases without causing any negative impact on the environment. These components are represented by prebiotics, probiotics, and plant extracts. In this review, the effects of prebiotics are described. Prebiotics are indigestible fibres fermented by gut enzymes and commensal bacteria, whose beneficial effects are due to the by-products generated from fermentation. The influence of pre-biotics on the immune system of fish is called immunosaccharides. Mannanoligosaccharides (MOS), Fructooligosaccharides (FOS) and Inulin act at different levels in the innate immune response. For example, through phagocytosis, lysozyme activity, and the complement system activity, an increase in fish growth and an amelioration of their health status is

brought about. In this review, the use of prebiotics in aquaculture, such as immunostimulants, has been highlighted: particularly in two teleost fish species, Sparus aurata and Dicentrarchus labrax. The results demonstrate that the road is still long and further studies are required, but the use of prebiotics, individually or coupled together, can open the doors to pioneering a new model of alternative components to antimicrobial agents.

Cardoso Umbelino, Cavallini D., Jovenasso Manzoni, M. S., Bedani, R., Roselino, M. N., Celiberto, L. S., Vendramini, R. C., de Valdez, G. F., Saes Parra, Abdalla D., Aparecida, Pinto R., Rosetto, D., Roberto, Valentini S., and Antonio, Rossi E. Probiotic Soy Product Supplemented with Isoflavones Improves the Lipid Profile of Moderately Hypercholesterolemic Men: A Randomized Controlled Trial. Nutrients. 2016; 8(1)

ABSTRACT: BACKGROUND: Cardiovascular disease is the leading cause of worldwide morbidity and mortality. Several studies have demonstrated that specific probiotics affect the host's metabolism and may influence the cardiovascular disease risk. OBJECTIVES: The aim of this study was to investigate the influence of an isoflavone-supplemented soy product fermented with Enterococcus faecium CRL 183 and Lactobacillus helveticus 416 on cardiovascular risk markers in moderately hypercholesterolemic subjects. DESIGN: Randomized placebo-controlled double-blind trial Setting: Sao Paulo State University in Araraquara, SP, Brazil. PARTICIPANTS: 49 male healthy men with total cholesterol (TC) >5.17 mmol/L and <6.21 mmol/L Intervention: The volunteers have consumed 200 mL of the probiotic soy product (group SP-10(10) CFU/day), isoflavone-supplemented probiotic soy product (group ISP-probiotic plus 50 mg of total isoflavones/100 g) or unfermented soy product (group USP-placebo) for 42 days in a randomized, double-blind study. MAIN OUTCOME MEASURES: Lipid profile and additional cardiovascular biomarkers were analyzed on days 0, 30 and 42. Urine samples (24 h) were collected at baseline and at the end of the experiment so as to determine the isoflavones profile. RESULTS: After 42 days, the ISP consumption led to improved total cholesterol, non-HDL-C (LDL + IDL + VLDL cholesterol fractions) and electronegative LDL concentrations (reduction of 13.8%, 14.7% and 24.2%, respectively, $p < 0.05$). The ISP and SP have prevented the reduction of HDL-C level after 42 days. The C-reactive protein and fibrinogen levels were not improved. The equol production by the ISP group subjects was inversely correlated with electronegative LDL concentration. CONCLUSIONS: The results suggest that a regular consumption of this probiotic soy product, supplemented with isoflavones, could contribute to reducing the risk of cardiovascular diseases in moderately hypercholesterolemic men, through the an improvement in lipid profile and antioxidant properties.

Caselli, E., Antonioli, P., and Mazzacane, S. Safety of probiotics used for hospital environmental sanitation. J.Hosp.Infect. 7-5-2016.

No abstract currently available.

Cavaillon, J. M. and Legout, S. Centenary of the death of Elie Metchnikoff: a visionary and an outstanding team leader. Microbes.Infect. 6-7-2016;

ABSTRACT: Elie Metchnikoff passed away on July 15th, 1916. He is considered to be the father of phagocytes, cellular innate immunity, probiotics, and gerontology. In all of

these fields, he was a visionary. To achieve such a notability and produce so many masterpieces, Metchnikoff used more than 30 animal species to support his findings, and his pasteurian laboratory published more than 200 papers in the Annales de l'Institut Pasteur. As a wonderful team leader and a great mentor, during his 28 years at Institut Pasteur, he welcomed and supervised more than 100 young trainees. Trained as an embryologist, he contributed to the birth of immunology and to the understanding of physiology and pathology. Indeed, Metchnikoff and his team investigated inflammation in guinea pigs, rats, frogs; studied infectious diseases in monkeys, caimans, geese; investigated aging in parrots, dogs, humans; proposed hypotheses to understand age-associated senility using rabbits and humans; developed germ free tadpoles, flies, chicks; studied the gut flora in bats, horses, birds, humans; and popularized the use of probiotics as a tool to delay the deleterious effects of toxic compounds derived from putrefactive gut bacteria. He was also a philosopher and penned essays on human disharmony and on pessimism and optimism.

Cavallini, D. C., Manzoni, M. S., Bedani, R., Roselino, M. N., Celiberto, L. S., Vendramini, R. C., de, Valdez G., Abdalla, D. S., Pinto, R. A., Rosetto, D., Valentini, S. R., and Rossi, E. A. Probiotic Soy Product Supplemented with Isoflavones Improves the Lipid Profile of Moderately Hypercholesterolemic Men: A Randomized Controlled Trial. Nutrients. 2016; 8(1)

ABSTRACT: BACKGROUND: Cardiovascular disease is the leading cause of worldwide morbidity and mortality. Several studies have demonstrated that specific probiotics affect the host's metabolism and may influence the cardiovascular disease risk. OBJECTIVES: The aim of this study was to investigate the influence of an isoflavone-supplemented soy product fermented with Enterococcus faecium CRL 183 and Lactobacillus helveticus 416 on cardiovascular risk markers in moderately hypercholesterolemic subjects. DESIGN: Randomized placebo-controlled double-blind trial Setting: Sao Paulo State University in Araraquara, SP, Brazil. PARTICIPANTS: 49 male healthy men with total cholesterol (TC) >5.17 mmol/L and <6.21 mmol/L Intervention: The volunteers have consumed 200 mL of the probiotic soy product (group SP-10(10) CFU/day), isoflavone-supplemented probiotic soy product (group ISP-probiotic plus 50 mg of total isoflavones/100 g) or unfermented soy product (group USP-placebo) for 42 days in a randomized, double-blind study. MAIN OUTCOME MEASURES: Lipid profile and additional cardiovascular biomarkers were analyzed on days 0, 30 and 42. Urine samples (24 h) were collected at baseline and at the end of the experiment so as to determine the isoflavones profile. RESULTS: After 42 days, the ISP consumption led to improved total cholesterol, non-HDL-C (LDL + IDL + VLDL cholesterol fractions) and electronegative LDL concentrations (reduction of 13.8%, 14.7% and 24.2%, respectively, $p < 0.05$). The ISP and SP have prevented the reduction of HDL-C level after 42 days. The C-reactive protein and fibrinogen levels were not improved. The equol production by the ISP group subjects was inversely correlated with electronegative LDL concentration. CONCLUSIONS: The results suggest that a regular consumption of this probiotic soy product, supplemented with isoflavones, could contribute to reducing the risk of cardiovascular diseases in moderately hypercholesterolemic men, through the an improvement in lipid profile and antioxidant properties.

Charnchai, P., Jantama, S. S., Prasitpuriprecha, C., Kanchanatawee, S., and Jantama, K. Effects of the Food Manufacturing Chain on the Viability and Functionality of Bifidobacterium animalis through Simulated Gastrointestinal Conditions. PLoS.One. 2016; 11(6):e0157958

ABSTRACT: The viability and functionality of probiotics may be influenced by industrial production processes resulting in a decrease in probiotic efficiency that benefit the health of humans. This study aimed to investigate the probiotic characteristics of Bifidobacterium strains isolated from fecal samples of healthy Thai infants. In the present work, three local strains (BF014, BF052, and BH053) belonging to Bifidobacterium animalis showed a great resistance against conditions simulating the gastrointestinal tract. Among these, B. animalis BF052 possessed considerable probiotic properties, including high acid and bile tolerance, strong adhesion capability to Caco-2 cells, and inhibitory activity against pathogens including Salmonella typhimurium and Vibrio cholerae. This strain also exhibited a high survival rate compared to commercial strains during storage in a wide variety of products, including pasteurized milk, soy milk, drinking yogurt, and orange juice. The impact of food processing processes as well as the freeze-drying process, storage of freeze-dried powders, and incorporation of freeze-dried cells in food matrix on probiotic properties was also determined. The stability of the probiotic properties of the BF052 strain was not affected by food processing chain, especially its resistance in the simulated gastrointestinal conditions and its adherence ability to Caco-2 cells. It indicates that it satisfies the criteria as a potential probiotic and may be used as an effective probiotic starter in food applications.

Chen, M. F., Weng, K. F., Huang, S. Y., Liu, Y. C., Tseng, S. N., Ojcius, D. M., and Shih, S. R. Pretreatment with a heat-killed probiotic modulates monocyte chemoattractant protein-1 and reduces the pathogenicity of influenza and enterovirus 71 infections. Mucosal.Immunol. 4-13-2016;

ABSTRACT: It has been proposed that inactivated probiotics may modulate the host immune system and contribute to mitigation of viral infections. This study demonstrated that administration of heat-killed Enterococcus faecalis, a widely used probiotic, can protect host animals against viral infections. The influenza-mediated morbidity and lung inflammation in E. faecalis-treated mice decreased significantly compared with those of the control mice. Furthermore, we found that the protection is associated with production of monocyte chemoattractant protein-1 (MCP-1). The intratracheal injection of a recombinant mouse MCP-1 protein abrogated the antiviral effects elicited by pretreatment with E. faecalis. CC chemokine receptor 2 (CCR2) is a receptor for MCP-1, and the intraperitoneal administration of a CCR2 antagonist effectively inhibited viral pathogenicity. The reduced pathogenicity was also observed in CCR2-deficient mice. Finally, E. faecalis significantly attenuated neuropathogenicity induced by another RNA virus, enterovirus 71. This study demonstrates that killed probiotics can reduce viral disease severity and identify that the MCP-1 pathway might act as a key mediator in the improved antiviral immune response. Our findings suggest that MCP-1 and its related signaling pathway can serve as critical therapeutic targets for development of new antiviral strategies.Mucosal Immunology advance online publication 13 April 2016; doi:10.1038/mi.2016.31.

Chen, S., Sanderson, M. W., Lee, C., Cernicchiaro, N., Renter, D. G., and Lanzas, C. Basic reproduction number and transmission dynamics of common serogroups of enterohemorrhagic Escherichia coli. Appl.Environ.Microbiol. 7-8-2016;

ABSTRACT: Understanding pathogens' transmission dynamics are essential to determine the epidemiology, ecology and ways of controlling enterohemorrhagic Escherichia coli (EHEC) in the animals and their environment. Our objective was to estimate the

epidemiological fitness of common EHEC strains in cattle populations. For that purpose, we developed a Markov chain model to characterize the dynamics of 7 serogroups of enterohemorrhagic Escherichia coli (O26, O45, O103, O111, O121, O145, and O157) in cattle production environments based on a set of cross-sectional data on infection prevalence in two years at two states. The basic reproduction number (R0) was estimated using a Bayesian framework for each serogroup based on two criteria (using serogroup alone: the O-group data; and using O serogroup, Shiga toxin gene(s), and intimin (eae) gene together: the EHEC data). In addition, correlations between external covariates (e.g., location, ambient temperature, dietary, and probiotics usage) and prevalence/R0 were quantified. R0 estimates varied substantially among different EHEC serogroups, with EHEC O157 having R0 >1 (approximately 1.5) and all other six EHEC serogroups less than 1. Using the O-group data substantially increased R0 estimates for O26, O45, and O103 serogroups (R0 >1), but not for others. Different covariates had distinct influences on different serogroups: the coefficients for each covariate were different among serogroups. Our modeling and analysis of this system can be readily expanded to other pathogen systems in order to estimate the pathogen and external factors that influence spread of infectious agents. IMPORTANCE AND HIGHLIGHTS: In this paper we describe a Bayesian modeling framework to estimate basic reproduction numbers of multiple serotypes of Shiga toxin-producing Escherichia coli respectively according to a cross-sectional study.We then couple compartmental model to reconstruct infection dynamics of these serotypes and quantify their risk in the population.We incorporate different sensitivity levels of detecting different serotypes and evaluate their potential influence on the estimation of basic reproduction numbers.

Chen, Y. M., Wei, L., Chiu, Y. S., Hsu, Y. J., Tsai, T. Y., Wang, M. F., and Huang, C. C. Lactobacillus plantarum TWK10 Supplementation Improves Exercise Performance and Increases Muscle Mass in Mice. Nutrients. 2016; 8(4):205

ABSTRACT: Lactobacillus plantarum (L. plantarum) is a well-known probiotic among the ingested-microorganism probiotics (i.e., ingested microorganisms associated with beneficial effects for the host). However, few studies have examined the effects of L. plantarum TWK10 (LP10) supplementation on exercise performance, physical fatigue, and gut microbial profile. Male Institute of Cancer Research (ICR) strain mice were divided into three groups (n = 8 per group) for oral administration of LP10 for six weeks at 0, 2.05 x 10(8), or 1.03 x 10(9) colony-forming units/kg/day, designated the vehicle, LP10-1X and LP10-5X groups, respectively. LP10 significantly decreased final body weight and increased relative muscle weight (%). LP10 supplementation dose-dependently increased grip strength ($p < 0.0001$) and endurance swimming time ($p < 0.001$) and decreased levels of serum lactate ($p < 0.0001$), ammonia ($p < 0.0001$), creatine kinase ($p = 0.0118$), and glucose ($p = 0.0151$) after acute exercise challenge. The number of type I fibers (slow muscle) in gastrocnemius muscle significantly increased with LP10 treatment. In addition, serum levels of albumin, blood urea nitrogen, creatinine, and triacylglycerol significantly decreased with LP10 treatment. Long-term supplementation with LP10 may increase muscle mass, enhance energy harvesting, and have health-promotion, performance-improvement, and anti-fatigue effects.

Cheng, J. R., Liu, X. M., Chen, Z. Y., Zhang, Y. S., and Zhang, Y. H. Mulberry anthocyanin biotransformation by intestinal probiotics. Food Chem. 12-15-2016; 213:721-727.

ABSTRACT: This study was designed to evaluate mulberry anthocyanins bioconversion traits for intestinal probiotics. Five intestinal beneficial bacteria were incubated with mulberry anthocyanins under anaerobic conditions at 37 degrees C, and bacterial beta-glucosidase activity and anthocyanin level were determined. Results demonstrated that all strains could convert mulberry anthocyanins to some extent. With high beta-glucosidase production capacity, Streptococcus thermophiles GIM 1.321 and Lactobacillus plantarum GIM 1.35 degraded mulberry anthocyanins by 46.17% and 43.62%, respectively. Mulberry anthocyanins were mainly biotransformed to chlorogenic acid, crypto-chlorogenic acid, caffeic acid, and ferulic acid during the anaerobic process. Non-enzymatic deglycosylation of anthocyanins also occurred and approximately 19.42% of the anthocyanins were degraded within 48h by this method.

Chenoll, E., Casinos, B., Bataller, E., Buesa, J., Ramon, D., Genoves, S., Fabrega, J., Rivero, Urgell M., and Moreno Munoz, J. A. Identification of a Peptide Produced by Bifidobacterium longum CECT 7210 with Antirotaviral Activity. Front Microbiol. 2016; 7:655

ABSTRACT: Rotavirus is one of the main causes of acute diarrhea and enteritis in infants. Currently, studies are underway to assess the use of probiotics to improve rotavirus vaccine protection. A previous work demonstrated that the probiotic strain Bifidobacterium longum subsp. infantis CECT 7210 is able to hinder rotavirus replication both in vitro and in vivo. The present study takes a systematic approach in order to identify the molecule directly involved in rotavirus inhibition. Supernatant protease digestions revealed both the proteinaceous nature of the active substance and the fact that the molecule responsible for inhibiting rotavirus replication is released to the supernatant. Following purification by cationic exchange chromatography, active fractions were obtained and the functional compound was identified as an 11-amino acid peptide (MHQPHQPLPPT, named 11-mer peptide) with a molecular mass of 1.282 KDa. The functionality of 11-mer was verified using the synthesized peptide in Wa, Ito, and VA70 rotavirus infections of both HT-29 and MA-104 cell lines. Finally, protease activity was detected in B. longum subsp. infantis CECT 7210 supernatant, which releases 11-mer peptide. A preliminary identification of the protease is also included in the study.

Choi, W. J., Konkit, M., Kim, Y., Kim, M. K., and Kim, W. Oral administration of Lactococcus chungangensis inhibits 2,4-dinitrochlorobenzene-induced atopic-like dermatitis in Nc/Nga mice. J.Dairy Sci. 6-8-2016;

ABSTRACT: Interest is increasing in the potentially beneficial role of probiotics in the prevention and treatment of atopic diseases. In this study, we investigated the protective effects of Lactococcus chungangensis CAU 28T against atopic dermatitis using murine macrophage RAW 264.7 cells, human keratinocyte HaCaT cells, human mast cell line HMC-1 cells, and a 2,4-dinitrochlorobenzene-induced atopic dermatitis model (Nc/Nga mice). The results showed that L. chungangensis CAU 28T exhibited potent antiinflammatory activity by inhibiting the production of the proinflammatory mediators nitric oxide and prostaglandin E2 in lipopolysaccharide-stimulated RAW 264.7 cells. Treatment with L. chungangensis CAU 28T reduced the release of beta-hexosaminidase and histamine in HMC-1 cells stimulated with mast cell activator compound 48/80. In addition, the back skin and ears of Nc/Nga mice exhibited reduced histological manifestations of atopic skin lesions such as erosion, hyperplasia of the epidermis and dermis, and inflammatory cell infiltration. Oral administration of L. chungangensis CAU 28T suppressed the production of IL-4, IL-5, IL-12, IFN-gamma, tumor necrosis factor-alpha,

and thymus- and activation-regulated chemokine (TARC) in skin lesions, indicating that it strongly drives the local immune system with efficacy comparable to that of tacrolimus, a topical immunomodulatory drug used for the treatment of atopic dermatitis. The findings indicate that L. chungangensis CAU 28T could be a novel probiotic candidate for controlling the symptoms of atopic dermatitis.

Ciernikova, S., Mego, M., Semanova, M., Wachsmannova, L., Adamcikova, Z., Stevurkova, V., Drgona, L., and Zajac, V. Probiotic Survey in Cancer Patients Treated in the Outpatient Department in a Comprehensive Cancer Center. Integr.Cancer Ther. 5-5-2016;

ABSTRACT: PURPOSE: Availability without prescription restriction, low cost, and simple oral administration allow cancer patients to use probiotics without knowledge of potential risks. We present a survey of probiotic use and the association with patient tumor characteristics in cancer patients treated at the outpatient department of the National Cancer Institute in Slovakia. PATIENTS AND METHODS: Between March and December 2014, 499 patients were asked to evaluate their overall experience with probiotics by questionnaire form, including the length and method of use relative to anticancer therapy, expectations, side-effect experiences, understanding of the possible risks, dietary supplement use, and others. The relevant data were statistically evaluated. RESULTS: The cohort consisted of 323 women (64.7%) and 176 men (35.3%); 91.6% were undergoing chemotherapy (2.6% together with radiotherapy) and 8.4% had no anticancer therapy. The prevalence of probiotic use was 28.5% and only 12 patients using probiotics (8.5%) described negative side effects. Most patients declared consideration of probiotic use based on recommendation from a physician (37.3%) or a pharmacist (14.8%). Nevertheless, up to 86.6% of patients declared no knowledge of possible risks. Statistically significant correlation was found between probiotic use and age of patients ($P < .008$), gender ($P < .023$), and taking other dietary supplements ($P < .000002$). CONCLUSIONS: In this prospective study, we present for the first time the prevalence, side-effect experience, and aspects that most likely influence probiotic use in cancer patients. Minimal knowledge of risks underlines the importance of an active approach by oncologists to inform patients about probiotic safety.

Coghetto, C. C., Brinques, G. B., and Ayub, M. A. Probiotics production and alternative encapsulation methodologies to improve their viabilities under adverse environmental conditions. Int.J.Food Sci.Nutr. 7-26-2016; 1-15.

ABSTRACT: Probiotic products are dietary supplements containing live microorganisms producing beneficial health effects on the host by improving intestinal balance and nutrient absorption. Among probiotic microorganisms, those classified as lactic acid bacteria are of major importance to the food and feed industries. Probiotic cells can be produced using alternative carbon and nitrogen sources, such as agroindustrial residues, at the same time contributing to reduce process costs. On the other hand, the survival of probiotic cells in formulated food products, as well as in the host gut, is an essential nutritional aspect concerning health benefits. Therefore, several cell microencapsulation techniques have been investigated as a way to improve cell viability and survival under adverse environmental conditions, such as the gastrointestinal milieu of hosts. In this review, different aspects of probiotic cells and technologies of their related products are discussed, including formulation of culture media, and aspects of cell microencapsulation techniques required to improve their survival in the host.

Cohen, S. A., Woodfield, M. C., Boyle, N., Stednick, Z., Boeckh, M., and Pergam, S. A. Incidence and outcomes of bloodstream infections among hematopoietic cell transplant recipients from species commonly reported to be in over-the-counter probiotic formulations. Transpl.Infect.Dis. 8-8-2016;

ABSTRACT: BACKGROUND: Probiotic supplementation has been promoted for numerous health conditions, however safety in immunosuppressed patients is unknown. We evaluated bloodstream infections (BSIs) caused by common probiotic organisms in hematopoietic cell transplant recipients. METHODS: All blood culture (BC) results from a cohort of hematopoietic cell transplant recipients transplanted at Fred Hutchinson Cancer Research Center in Seattle, Washington, between 2002 and 2011 were reviewed. Patients with at least 1 positive BC for common probiotic organisms (Lactobacillus species, Bifidobacterium species, Streptococcus thermophiles, and Saccharomyces species) within 1 year post hematopoietic cell transplantation (HCT) were considered cases. Data were collected from center databases, which contain archived laboratory data, patient demographics, and clinical summaries. RESULTS: A total of 19/3796 (0.5%) patients developed a BSI from 1of these organisms within 1 year post HCT; no Bifidobacterium species or S. thermophilus were identified. Cases had a median age of 49 years (interquartile range [IQR]: 39-53), and the majority were allogeneic hematopoietic cell transplant recipients (14/19, 74%). Most positive BCs were Lactobacillus species (18/19) and occurred at a median of 84 days (IQR: 34-127) post transplant. The incidence rate of Lactobacillus bacteremia was 1.62 cases per 100,000 patient-days; the highest rate occurred within 100 days post transplant (3.3 per 100,000 patient-days). Eight patients (44%) were diagnosed with acute graft-versus-host disease of the gut prior to the development of bacteremia. No mortality was attributable to any of these infections. CONCLUSION: Organisms frequently incorporated in available over-the-counter probiotics are infrequent causes of bacteremia after HCT. Studies evaluating the use of probiotics among high-risk patients are needed. This article is protected by copyright. All rights reserved.

Colombo, J., Codazzi, D., and Langer, M. Ventilation-associated pneumonia and probiotics: many clues do not make evidence. Intensive Care Med. 7-28-2016.

No abstract currently available.

Comerford, K. B. and Pasin, G. Emerging Evidence for the Importance of Dietary Protein Source on Glucoregulatory Markers and Type 2 Diabetes: Different Effects of Dairy, Meat, Fish, Egg, and Plant Protein Foods. Nutrients. 2016; 8(8)

ABSTRACT: Observational studies provide evidence that a higher intake of protein from plant-based foods and certain animal-based foods is associated with a lower risk for type 2 diabetes. However, there are few distinguishable differences between the glucoregulatory qualities of the proteins in plant-based foods, and it is likely their numerous non-protein components (e.g., fibers and phytochemicals) that drive the relationship with type 2 diabetes risk reduction. Conversely, the glucoregulatory qualities of the proteins in animal-based foods are extremely divergent, with a higher intake of certain animal-based protein foods showing negative effects, and others showing neutral or positive effects on type 2 diabetes risk. Among the various types of animal-based protein foods, a higher intake of dairy products (such as milk, yogurt, cheese and

whey protein) consistently shows a beneficial relationship with glucose regulation and/or type 2 diabetes risk reduction. Intervention studies provide evidence that dairy proteins have more potent effects on insulin and incretin secretion compared to other commonly consumed animal proteins. In addition to their protein components, such as insulinogenic amino acids and bioactive peptides, dairy products also contain a food matrix rich in calcium, magnesium, potassium, trans-palmitoleic fatty acids, and low-glycemic index sugars-all of which have been shown to have beneficial effects on aspects of glucose control, insulin secretion, insulin sensitivity and/or type 2 diabetes risk. Furthermore, fermentation and fortification of dairy products with probiotics and vitamin D may improve a dairy product's glucoregulatory effects.

Cook, D. J., Johnstone, J., Marshall, J. C., Lauzier, F., Thabane, L., Mehta, S., Dodek, P. M., McIntyre, L., Pagliarello, J., Henderson, W., Taylor, R. W., Cartin-Ceba, R., Golan, E., Herridge, M., Wood, G., Ovakim, D., Karachi, T., Surette, M. G., Bowdish, D. M., Lamarche, D., Verschoor, C. P., Duan, E. H., Heels-Ansdell, D., Arabi, Y., and Meade, M. Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial-PROSPECT: a pilot trial. Trials. 2016; 17:377

ABSTRACT: BACKGROUND: Probiotics are live microorganisms that may confer health benefits when ingested. Randomized trials suggest that probiotics significantly decrease the incidence of ventilator-associated pneumonia (VAP) and the overall incidence of infection in critically ill patients. However, these studies are small, largely single-center, and at risk of bias. The aim of the PROSPECT pilot trial was to determine the feasibility of conducting a larger trial of probiotics to prevent VAP in mechanically ventilated patients in the intensive care unit (ICU). METHODS: In a randomized blinded trial, patients expected to be mechanically ventilated for >/=72 hours were allocated to receive either 1 x 10(10) colony-forming units of Lactobacillus rhamnosus GG or placebo, twice daily. Patients were excluded if they were at increased risk of L. rhamnosus GG infection or had contraindications to enteral medication. Feasibility objectives were: (1) timely recruitment; (2) maximal protocol adherence; (3) minimal contamination; and (4) estimated VAP rate >/=10 %. We also measured other infections, diarrhea, ICU and hospital length of stay, and mortality. RESULTS: Overall, in 14 centers in Canada and the USA, all feasibility goals were met: (1) 150 patients were randomized in 1 year; (2) protocol adherence was 97 %; (3) no patients received open-label probiotics; and (4) the VAP rate was 19 %. Other infections included: bloodstream infection (19.3 %), urinary tract infections (12.7 %), and skin and soft tissue infections (4.0 %). Diarrhea, defined as Bristol type 6 or 7 stools, occurred in 133 (88.7 %) of patients, the median length of stay in ICU was 12 days (quartile 1 to quartile 3, 7-18 days), and in hospital was 26 days (quartile 1 to quartile 3, 14-44 days); 23 patients (15.3 %) died in the ICU. CONCLUSIONS: The PROSPECT pilot trial supports the feasibility of a larger trial to investigate the effect of L. rhamnosus GG on VAP and other nosocomial infections in critically ill patients. TRIAL REGISTRATION: Clinicaltrials.gov NCT01782755 . Registered on 29 January 2013.

Correa-Fiz, F., Fraile, L., and Aragon, V. Piglet nasal microbiota at weaning may influence the development of Glasser's disease during the rearing period. BMC.Genomics. 2016; 17:404

ABSTRACT: BACKGROUND: The microbiota, the ensemble of microorganisms on a particular body site, has been extensively studied during the last few years, and demonstrated to influence the development of many diseases. However, these studies focused mainly on the human digestive system, while the populations in the respiratory

tract have been poorly assessed, especially in pigs. The nasal mucosa of piglets is colonized by an array of bacteria, many of which are unknown. Among the early colonizers, Haemophilus parasuis also has clinical importance, since it is also the etiological agent of Glasser's disease. This disease produces economical losses in all the countries with pig production, and the factors influencing its development are not totally understood. Hence, the purpose of this work was to characterize the nasal microbiota composition of piglets, and its possible role in Glasser's disease development. RESULTS: Seven farms from Spain (4 with Glasser's disease and 3 control farms without any respiratory disease) and three farms from UK (all control farms) were studied. Ten piglets from each farm were sampled at 3-4 weeks of age before weaning. The total DNA extracted from nasal swabs was used to amplify the 16S RNA gene for sequencing in Illumina MiSeq. Sequencing data was quality filtered and analyzed using QIIME software. The diversity of the nasal microbiota was low in comparison with other body sites, showing a maximum number of operational taxonomic units (OTUs) per pig of 1,603, clustered in five phyla. Significant differences were found at various taxonomical levels, when the microbiota was compared regarding the farm health status. Healthy status was associated to higher species richness and diversity, and UK farms demonstrated the highest diversity. CONCLUSIONS: The composition of the nasal microbiota of healthy piglets was uncovered and different phylotypes were shown to be significantly altered in animals depending on the clinical status of the farm of origin. Several OTUs at genus level were identified over-represented in piglets from control farms, indicating their potential as probiotics. Although we provide relevant data, fully metagenomic approaches could give light on the genes and metabolic pathways involved in the roles of the nasal microbiota to prevent respiratory diseases.

Coverdale, J. A. HORSE SPECIES SYMPOSIUM: Can the microbiome of the horse be altered to improve digestion? J.Anim Sci. 2016; 94(6):2275-2281.

ABSTRACT: Intensive management practices in the horse industry present a unique challenge to the microbiome of the large intestine. Common management practices such as high-concentrate diets, low forage quality, meal feeding, and confinement housing have an impact on intestinal function, specifically large intestinal fermentation. The microbiome of the equine large intestine is a complex and diverse ecosystem, and disruption of microbiota and their environment can lead to increased incidence of gastrointestinal disorder. Digestion in the horse can be improved through a variety of approaches such as feedstuff selection, forage quality, feeding management, and inclusion of digestive aids. These digestive aids, such as prebiotics and probiotics, have been used to improve digestibility of equine diets and stabilize the microbiome of the large intestine. Probiotics, or direct-fed microbials, have been widely used in horses for treatment and prevention of gastrointestinal disease. The introduction of these live, beneficial microorganisms orally into the intestinal tract has yielded variable results. However, it is difficult to compare data due to variations in choice of organism, dosage, and basal diet. Although there are still many unanswered questions about the mode of action of successful probiotics, evidence indicates competitive inhibition and enhanced immunity. Lactic acid bacteria such as , and and yeast have all successfully been used in the horse. Use of these products has resulted in improved fiber digestibility in horses offered both high-starch and high-fiber diets. When high-concentrate diets were fed, probiotic supplementation helped maintain cecal pH, decreased lactic acid concentrations, and enhanced populations of cellulolytic bacteria. Similarly, use of prebiotic preparations containing fructooligosaccharide (FOS) or mannanoligosaccharides have improved DM, CP, and NDF digestibility when added to

high-fiber diets. Furthermore, use of FOS in horses reduced disruptions in colonic microbial populations after an abrupt change in diet and altered fecal VFA concentrations toward propionate and butyrate. Potential use of prebiotics and probiotics to create greater stability in the equine microbiome impacts not only the digestibility of feed but also the health of the horse.

Cowan, C. S., Callaghan, B. L., and Richardson, R. The effects of a probiotic formulation (Lactobacillus rhamnosus and L. helveticus) on developmental trajectories of emotional learning in stressed infant rats. Transl.Psychiatry. 2016; 6(5):e823

ABSTRACT: Recently, scientific interest in the brain-gut axis has grown dramatically, particularly with respect to the link between gastrointestinal and psychiatric dysfunction. However, the role of gut function in early emotional dysregulation is yet to be examined, despite the prevalence and treatment resistance of early-onset psychiatric disorders. The present studies utilized a developmental rodent model of early-life stress (ELS) to explore this gap. Rats were exposed to maternal separation (MS) on postnatal days 2-14. Throughout MS, dams received either vehicle or a probiotic formulation (previously shown to reduce gastrointestinal dysfunction) in their drinking water. Replicating past research, untreated MS infants exhibited an adult-like profile of long-lasting fear memories and fear relapse following extinction. In contrast, probiotic-exposed MS infants exhibited age-appropriate infantile amnesia and resistance to relapse. These effects were not mediated by changes in pups' or dams' anxiety at the time of training, nor by maternal responsiveness. Overall, probiotics acted as an effective and non-invasive treatment to restore normal developmental trajectories of emotion-related behaviors in infant rats exposed to ELS. These results provide promising initial evidence for this novel approach to reduce the risk of mental health problems in vulnerable individuals. Future studies are needed to test this treatment in humans exposed to ELS and to elucidate mechanisms for the observed behavioral changes.

Damodharan, K., Palaniyandi, S. A., Yang, S. H., and Suh, J. W. Functional probiotic characterization and in vivo cholesterol-lowering activity of Lactobacillus helveticus isolated from fermented cow milk. J.Microbiol.Biotechnol. 7-19-2016;

ABSTRACT: We characterized the probiotic properties of Lactobacillus helveticus strains KII13 and KHI1 isolated from fermented cow milk by in vitro and in vivo studies. The strains exhibited tolerance to simulated oro-gastrointestinal (OGT) condition, adherence to Caco-2 cells, and antimicrobial activity. Both the L. helveticus strains produced bioactive tripeptides isoleucyl-prolyl-proline (IPP) and valyl-prolyl-proline (VPP) during fermentation of milk. KII13 showed higher in vitro cholesterol-lowering activity (47%) compared to KHI1 (28%) and L. helveticus ATCC 15009 (22%), hence, it was selected for in vivo study of cholesterol-lowering activity in atherogenic diet-fed hypercholesterolemic mice. For the study, mice were divided into 4 groups viz., normal diet-control group (NCD), atherogenic diet-control group (HCD), KII13-atherogenic diet (HCD-KII13), and Lactobacillus acidophilus ATCC 43121-atherogenic diet (HCD-L.ac) as positive control. Serum total cholesterol (T-CHO) level was significantly decreased by 8.6% and 7.78% in the HCD-KII13 and HCD-L.ac group ($P<0.05$), respectively, compared with HCD group. Low density lipoprotein (LDL) cholesterol levels in both HCD-KII13 and HCD-L.ac groups were decreased by 13% and 11%, respectively, compared to HCD group (both, $P<0.05$). Analysis of cholesterol metabolism related gene expression in mice liver showed increased expression of LDLR and SREBF2 genes in mice fed with KII13. By comparing all

the results, we conclude that L. helveticus KII13 could be used as potential probiotic strain to produce anti-hypertensive peptides and reduce serum cholesterol.

Das, S., Gupta, P. K., and Das, R. R. Efficacy and Safety of Saccharomyces boulardii in Acute Rotavirus Diarrhea: Double Blind Randomized Controlled Trial from a Developing Country. J.Trop.Pediatr. 6-9-2016;

ABSTRACT: OBJECTIVE: To study the efficacy and safety of Saccharomyces boulardii (SB) in acute childhood rotavirus diarrhea. METHODS: Children (3 months to 5 years) with WHO-defined acute watery diarrhea and stool rotavirus positive (n = 60) were randomized into intervention (n = 30) and control (n = 30) groups. The intervention group received SB (500 mg/day) for 5 days. RESULTS: The median duration (hours) of diarrhea was significantly shorter in the intervention group (60 vs. 89; 95% CI: -41.2 to - 16.8). A significantly shorter duration of hospitalization (74 vs. 91; 95% CI: -33.46 to - 0.54) was also seen in the intervention group, but no significant difference was seen for fever and vomiting. There was also no difference between the two groups in the proportion of children requiring parenteral rehydration and persistence of diarrhea lasting beyond day 7. There was no report of any adverse events. CONCLUSIONS: The present trial showed that SB is effective and safe in acute rotavirus diarrhea.

Davar, R., Nokhostin, F., Eftekhar, M., Sekhavat, L., Bashiri, Zadeh M., and Shamsi, F. Comparing the Recurrence of Vulvovaginal Candidiasis in Patients Undergoing Prophylactic Treatment with Probiotic and Placebo During the 6 Months. Probiotics.Antimicrob.Proteins. 2016; 8(3):130-133.

ABSTRACT: This is a randomized, double-blind, clinical/comparative trial study, involving the recurrence of vaginal candidiasis (VVC) after initial treatment with oral fluconazole in patients undergoing prophylactic management with a probiotic and placebo for 6 months. Fifty-nine VVC patients who were diagnosed based on their history, physical examination, and culture of vaginal discharge were initially treated by a single dose of 150 mg fluconazole. According to the table of random numbers, the sample was divided into two groups. The patients from one group took probiotics, while those from the other group took a placebo, with all of them being continuously monitored for 6 months. The patients complaining of vaginal candidiasis symptoms, such as burning, pruritus, and a vaginal (curd-like) discharge, were examined and the discharge was cultured for candida. The positive cultures were considered to be recurring for the patients in each group. Thirty-one cases from the placebo group and 28 cases from the probiotic group were carefully observed. In total, the 6-month recurrence in the control group was eleven (35.5 %) and in the research group was two (7.2 %). The results from Fisher's exact test for the value p = 0.01 and OR 0.14 95 % CI (0.028-0.7) showed significant recurrence in the placebo group. The findings demonstrated that taking probiotics withazole antifungal drugs could be highly effective in treating VVC, resulting in a lower recurrence rate as well.

de Moreno de, LeBlanc A., Del, Carmen S., Chatel, J. M., Azevedo, V., Bermudez-Humaran, L., Langella, P., and LeBlanc, J. G. Evaluation of the biosafety of recombinant lactic acid bacteria designed to prevent and to treat colitis. J.Med.Microbiol. 7-26-2016;

ABSTRACT: Inflammatory Bowel Diseases or IBD affect the gastrointestinal tract and are characterized by recurrent inflammation that requires lifelong therapies. Probiotics such as lactic acid bacteria (LAB) have been proposed to complement current treatment

protocols for these patients; however, their characteristics are strain dependent. In this regard certain novel characteristics are only possible through the genetic modification of these beneficial microorganisms. Different delivery systems, such as protein delivery of anti-oxidant enzymes and the anti-inflammatory cytokines such as IL-10 and DNA delivery have been shown to be effective for preventing and treating IBD in animal models. In this study, the safety of the recombinant LAB (recLAB) Streptococcus thermophilus (S.) CRL807:CAT, S. thermophilus CRL807: SOD, Lactococcus (L.) lactis NCDO2118 pXILCYT:IL-10, L. lactis MG1363 pValac:IL-10 and L. lactis MG1363 pGroESL:IL-10 with proven beneficial effects were compared to their progenitor strains S. thermophilus CRL807, L. lactis NCDO2118 or L. lactis MG1363. The prolonged administration of genetically modified strains evaluated in the present work showed that they were just as safe as the administration of the native strains from which they derive as demonstrated by normal animal growth and relative organ weights, absence of microbial translocation, altered blood parameters and modifications of intestinal histology. The results show the potential use of these recLAB in future therapeutic formulations; however, the use of modern bio-containment systems is required for the future acceptance of these recLAB by the medical community and patients suffering IBD.

De, T., Kondekar, S., and Rathi, S. Hospital Based Prospective Observational Study to Audit the Prescription Practices and Outcomes of Paediatric Patients (6 months to 5 years age group) Presenting with Acute Diarrhea. J.Clin.Diagn.Res. 2016; 10(5):SC01-SC05.

ABSTRACT: INTRODUCTION: Diarrhea is a leading killer of children, accounting for 9% of all deaths among under-five children worldwide. WHO protocol deviation in management of diarrheas in children is likely due to various reasons. AIM: To study the prescription practices, regarding adherence to WHO protocol and deviations, in the management of acute diarrhea in children presenting at a tertiary care hospital and its impact on the outcome. MATERIALS AND METHODS: This was a prospective observational hospital based study at a tertiary care carried out over a 12-month period including all cases of acute diarrhea (defined as 3 or more loose stools in last 24 hours) in children belonging to the age group of 6 months to 5 years. Patients were followed up on day 3,7,14 and 28 from the day of presentation. Software SPSS Version 17.0 was used for analysis. Correlation regression analysis was used to study predictiveness of different variables affecting outcome. RESULTS: In this study, 447 children aged between 6 months and 5 years were enrolled, of which 45 cases were lost in follow-up and excluded. The median age was 14 months. Some deviation from WHO protocol was noted in 78.4% of the cases. Most common deviations from WHO protocol were addition of probiotics (78.1% of cases) and addition of race cadotril (15.9% of cases). Inadvertent use of antibiotics in diarrhea was noted in 12.2% of cases. Presence of fever was strong predictor for use of antibiotics. Cases of early recovery within 3 days of presentation were higher in WHO protocol deviation group. Use of probiotics had statistically significant association with early recovery. CONCLUSION: In diarrhea management, WHO protocol deviation is common. Probiotics are likely to help in early recovery.

de, Waard M., Brands, B., Kouwenhoven, S. M., Lerma, J. C., Crespo-Escobar, P., Koletzko, B., Zalewski, B. M., and van Goudoever, J. B. Optimal Nutrition In Lactating Women And Its Effect On Later Health Of Offspring: A Systematic Review Of Current Evidence And Recommendations (Early Nutrition Project). Crit Rev.Food Sci.Nutr. 4-29-2016; 0

ABSTRACT: Background EarlyNutrition (www.project-earlynutrition.eu) is an international research consortium investigating the effects of early nutrition on metabolic

programming. Objective To summarize current evidence and standards, recommendations, guidelines, and regulations on nutrition or supplements in lactating women with emphasis placed on long-term health effects in offspring, including cardiovascular disease, hypertension, overweight/obesity, metabolic syndrome, diabetes, or glucose intolerance. Methods Medline, Embase, selected databases and websites were searched for documents published between 2010 and 2015. Results Thirteen documents met the inclusion criteria. Effects of maternal long-chain polyunsaturated fatty acid (LC-PUFA) supplementation on overweight/obesity or hypertension in offspring were assessed in 10 studies. One study described the effect of maternal vitamin D supplementation on overweight/obesity, and the remaining 2 studies assessed the effects of maternal probiotic/synbiotic supplementation during lactation on overweight/obesity or metabolic syndrome in their infants. Forty-one documents contained dietary recommendations on various macro- and micronutrients for lactating women, but without consideration of our long-term health outcomes in infants. Conclusion Literature on nutrition of lactating women and its effect on their infants/ later health with respect to metabolic programming outcomes appeared to be scarce, and focused mostly on supplementation of LC-PUFA's. No recent guidelines or recommendations were available, highlighting the significant research gaps regarding this topic.

Deans, E. Microbiome and mental health in the modern environment. J.Physiol Anthropol. 2016; 36(1):1

ABSTRACT: A revolution in the understanding of the pathophysiology of mental illness combined with new knowledge about host/microbiome interactions and psychoneuroimmunology has opened an entirely new field of study, the "psychobiotics". The modern microbiome is quite changed compared to our ancestral one due to diet, antibiotic exposure, and other environmental factors, and these differences may well impact our brain health. The sheer complexity and scope of how diet, probiotics, prebiotics, and intertwined environmental variables could influence mental health are profound obstacles to an organized and useful study of the microbiome and psychiatric disease. However, the potential for positive anti-inflammatory effects and symptom amelioration with perhaps few side effects makes the goal of clarifying the role of the microbiota in mental health a vital one.

Deepak, V., Ram Kumar, Pandian S., Sivasubramaniam, S. D., Nellaiah, H., and Sundar, K. Optimization of anticancer exopolysaccharide production from probiotic Lactobacillus acidophilus by response surface methodology. Prep.Biochem.Biotechnol. 4-2-2016; 46(3):288-297.

ABSTRACT: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the Western world. Recently, much attention has been focused on decreasing the risk of CRC by consuming probiotics. In the present study, exopolysaccharide (EPS) extracted from Lactobacillus acidophilus was found to inhibit the growth of CaCo2 colon cancer cell line in a dose-dependent manner. The experiment was performed in both normoxic and hypoxic conditions, and EPS was found to reduce the survival of CaCo2 cell line in both the conditions. Quantitative polymerase chain reaction (qPCR) studies demonstrated that EPS treatment upregulated the expression of peroxisome proliferator activator receptor-gamma (PPAR-gamma) in both normoxia and hypoxia conditions, whereas it upregulated the expression of erythropoietin (EPO) in the normoxic condition,

but there was no significant expression under hypoxic conditions. Hence, the EPS production was optimized by Plackett-Burman design followed by central composite rotatory design. The optimized production of EPS at 24 hr was found to be 400 mg/L. During batch cultivation the production peaked at 21 hr, resulting in an EPS concentration of 597 mg/L.

Del, Coco, V, Sparo, M. D., Sidoti, A., Santin, M., Basualdo, J. A., and Cordoba, M. A. Effects of Enterococcus faecalis CECT 7121 on Cryptosporidium parvum infection in mice. Parasitol.Res. 2016; 115(8):3239-3244.

ABSTRACT: Cryptosporidium is an opportunistic protozoan parasite of humans and animals worldwide and causes diarrheal disease that is typically self-limiting in immunocompetent hosts but often life threatening to immunocompromised individuals. However, there is a lack of completely efficient therapy available. Probiotics have attracted the attention as potential antiparasite compounds against protozoa involved in intestinal infections. This study investigated the effects of administration of probiotic Enterococcus faecalis CECT 7121 on Cryptosporidium parvum infection in immunosuppressed mice. Effects on C. parvum infection at the intestinal mucosa were studied and scored at each portion of the gut. It was demonstrated that Ef CECT 7121 interfered with C. parvum infection when both probiotic and parasite were present in the same intestinal location suggesting that Ef CECT 7121 supplementation can alleviate the negative effects of C. parvum infection.

Demirci, H., Ozturk, K., and Kurt, O. Effects of daily telephone-based re-education before taking medicine on Helicobacter pylori eradication. World J.Gastroenterol. 4-21-2016; 22(15):4071-4072.

ABSTRACT: We read the article "Effects of daily telephone-based re-education before taking medicine on Helicobacter pylori (H. pylori) eradication: A prospective single-center study from China" written by Wang et al with great interest. It is reported in American and European guidelines that there is no sufficient test for the diagnosis of H. pylori except culture and that using at least two different tests for diagnosis of H. pylori is recommended. Patients who used antibiotics or bismuth salts in the previous 2 wk were excluded from study. But patients who used probiotics and antioxidant vitamins such as vitamins C and E were not excluded.

Demont, A., Hacini-Rachinel, F., Doucet-Ladeveze, R., Ngom-Bru, C., Mercenier, A., Prioult, G., and Blanchard, C. Live and heat-treated probiotics differently modulate IL10 mRNA stabilization and microRNA expression. J.Allergy Clin.Immunol. 2016; 137(4):1264-1267.

No abstract currently available.

Deng, Q., Odhiambo, J. F., Farooq, U., Lam, T., Dunn, S. M., and Ametaj, B. N. Intravaginal probiotics modulated metabolic status and improved milk production and composition of transition dairy cows. J.Anim Sci. 2016; 94(2):760-770.

ABSTRACT: The objective of this investigation was to evaluate whether intravaginal infusion of probiotics (a lactic acid bacteria cocktail) around parturition would influence

metabolic status and increase milk production of transition dairy cows. One hundred pregnant Holstein dairy cows were assigned to 1 of the 3 experimental groups receiving intravaginal infusion of probiotics or carrier (i.e., sterile skim milk) once a week at wk -2, -1, and +1 relative to calving as follows: 2 consecutive probiotics before parturition and 1 carrier dose after parturition (TRT1), 3 consecutive probiotics doses around parturition (TRT2), and 3 consecutive carrier doses around parturition (CTR). The probiotics were a lyophilized culture mixture composed of FUA3089 and FUA3138 and FUA3140 with a cell count of 10 to 10 cfu/dose. Blood was sampled from wk -2 to +3 and milk was sampled on the third day in milk (DIM) and from wk +1 to +5 on a weekly basis. Feed intake and milk production was monitored until wk +8. Results showed that the TRT2 group (366.12 +/- 49.77 mumol/L) had a lower (= 0.01) concentration of NEFA in the serum than the CTR group (550.85 +/- 47.16 mumol/L). The concentrations of IgG in the milk were 32.71 +/- 3.00 mg/mL in the TRT1 group, 17.47 +/- 4.54 mg/mL in the TRT2 group, and 6.73 +/- 3.43 mg/mL in the CTR group at 3 DIM (< 0.01). Meanwhile, both the TRT1 and the TRT2 group had lower haptoglobin in the milk compared with the CTR group at 3 DIM (< 0.01). The TRT1 group had greater milk protein content than the CTR group (2.99 +/- 0.04 vs. 2.82 +/- 0.04%; = 0.02), whereas the TRT2 group tended to have greater lactose content compared with the CTR group (4.53 +/- 0.03 vs. 4.44 +/- 0.03%; = 0.05). The effect of treatment interacted with parity with regards to milk production and feed efficiency. Multiparous cows in the TRT1 and TRT2 groups had greater milk production and feed efficiency than those in the CTR group (< 0.01 and = 0.02, respectively). Among primiparous cows, those in the TRT2 group had greater milk production (= 0.04) whereas those in the TRT1 group had lower feed intake (< 0.01) than those in the CTR group. Both the TRT1 and the TRT2 groups had enhanced feed efficiency compared with the CTR group (< 0.01). In conclusion, intravaginal infusion of lactic acid bacteria modulated concentrations of selected serum metabolites and milk components and increased milk efficiency of transition dairy cows.

Denkel, L. A., Schwab, F., Garten, L., Geffers, C., Gastmeier, P., and Piening, B. Protective Effect of Dual-Strain Probiotics in Preterm Infants: A Multi-Center Time Series Analysis. PLoS.One. 2016; 11(6):e0158136

ABSTRACT: OBJECTIVE: To determine the effect of dual-strain probiotics on the development of necrotizing enterocolitis (NEC), mortality and nosocomial bloodstream infections (BSI) in preterm infants in German neonatal intensive care units (NICUs). DESIGN: A multi-center interrupted time series analysis. SETTING: 44 German NICUs with routine use of dual-strain probiotics on neonatal ward level. PATIENTS: Preterm infants documented by NEO-KISS, the German surveillance system for nosocomial infections in preterm infants with birth weights below 1,500 g, between 2004 and 2014. INTERVENTION: Routine use of dual-strain probiotics containing Lactobacillus acidophilus and Bifidobacterium spp. (Infloran) on the neonatal ward level. MAIN OUTCOME MEASURES: Incidences of NEC, overall mortality, mortality following NEC and nosocomial BSI. RESULTS: Data from 10,890 preterm infants in 44 neonatal wards was included in this study. Incidences of NEC and BSI were 2.5% (n = 274) and 15.0%, (n = 1631), respectively. Mortality rate was 6.1% (n = 665). The use of dual-strain probiotics significantly reduced the risk of NEC (HR = 0.48; 95% CI = 0.38-0.62), overall mortality (HR = 0.60, 95% CI = 0.44-0.83), mortality after NEC (HR = 0.51, 95% CI = 0.26-0.999) and nosocomial BSI (HR = 0.89, 95% CI = 0.81-0.98). These effects were even more pronounced in the subgroup analysis of preterm infants with birth weights below 1,000 g. CONCLUSION: In order to reduce NEC and mortality in preterm infants, it is advisable to add routine prophylaxis with dual-strain probiotics to clinical practice in neonatal wards.

Derikx, L. A., Dieleman, L. A., and Hoentjen, F. Probiotics and prebiotics in ulcerative colitis. Best.Pract.Res.Clin.Gastroenterol. 2016; 30(1):55-71.

ABSTRACT: The intestinal microbiota is one of the key players in the etiology of ulcerative colitis. Manipulation of this microflora with probiotics and prebiotics is an attractive strategy in the management of ulcerative colitis. Several intervention studies for both the induction and maintenance of remission in ulcerative colitis patients have been performed. Most of these studies evaluated VSL#3 or E. Coli Nissle 1917 and in general there is evidence for efficacy of these agents for induction and maintenance of remission. However, studies are frequently underpowered, lack a control group, and are very heterogeneous investigating different probiotic strains in different study populations. The absence of well-powered robust randomized placebo-controlled trials impedes the widespread use of probiotics and prebiotics in ulcerative colitis. However, given the promising results that are currently available, probiotics and prebiotics may find their way to the treatment algorithm for ulcerative colitis in the near future.

Dianawati, D., Mishra, V., and Shah, N. P. Viability, Acid and Bile Tolerance of Spray Dried Probiotic Bacteria and Some Commercial Probiotic Supplement Products Kept at Room Temperature. J.Food Sci. 2016; 81(6):M1472-M1479.

ABSTRACT: Production of probiotic food supplements that are shelf-stable at room temperature has been developed for consumer's convenience, but information on the stability in acid and bile environment is still scarce. Viability and acid and bile tolerance of microencapsulated Bifidobacterium spp. and Lactobacillus acidophilus and 4 commercial probiotic supplements were evaluated. Bifidobacterium and L. acidophilus were encapsulated with casein-based emulsion using spray drying. Water activity (aw) of the microspheres containing Bifidobacterium or L. acidophilus (SD GM product) was adjusted to 0.07 followed by storage at 25 degrees C for 10 wk. Encapsulated Bifidobacterium spp. and Lactobacillus acidophilus and 4 commercial probiotic supplement products (AL, GH, RE, and BM) were tested. Since commercial probiotic products contained mixed bacteria, selective media MRS-LP (containing L-cysteine and Na-propionate) and MRS-clindamycin agar were used to grow Bifidobacterium spp. or L. acidophilus, respectively, and to inhibit the growth of other strains. The results showed that aw had a strong negative correlation with the viability of dehydrated probiotics of the 6 products. Viable counts of Bifidobacterium spp. and L. acidophilus of SD GM, AL, and GH were between 8.3 and 9.2 log CFU/g, whereas that of BM and RE were between 6.7 and 7.3 log CFU/g. Bifidobacterium in SD GM, in AL, and in GH products and L. acidophilus in SD GM, in AL, and in BM products demonstrated high tolerance to acid. Most of dehydrated probiotic bacteria were able to survive in bile environment except L. acidophilus in RE product. Exposure to gastric juice influenced bacterial survivability in subsequent bile environment.

Dinan, T. G. and Cryan, J. F. Microbes, Immunity, and Behavior: Psychoneuroimmunology Meets the Microbiome. Neuropsychopharmacology. 7-13-2016;

ABSTRACT: There is now a large volume of evidence to support the view that the immune system is a key communication pathway between the gut and brain, which plays an important role in stress-related psychopathologies and thus provides a potentially fruitful

target for psychotropic intervention. The gut microbiota is a complex ecosystem with a diverse range of organisms and a sophisticated genomic structure. Bacteria within the gut are estimated to weigh in excess of 1 kg in the adult human and the microbes within not only produce antimicrobial peptides, short chain fatty acids, and vitamins, but also most of the common neurotransmitters found in the human brain. That the microbial content of the gut plays a key role in immune development is now beyond doubt. Early disruption of the host-microbe interplay can have lifelong consequences, not just in terms of intestinal function but in distal organs including the brain. It is clear that the immune system and nervous system are in continuous communication in order to maintain a state of homeostasis. Significant gaps in knowledge remain about the effect of the gut microbiota in coordinating the immune-nervous systems dialogue. However, studies using germ-free animals, infective models, prebiotics, probiotics, and antibiotics have increased our understanding of the interplay. Early life stress can have a lifelong impact on the microbial content of the intestine and permanently alter immune functioning. That early life stress can also impact adult psychopathology has long been appreciated in psychiatry. The challenge now is to fully decipher the molecular mechanisms that link the gut microbiota, immune, and central nervous systems in a network of communication that impacts behavior patterns and psychopathology, to eventually translate these findings to the human situation both in health and disease. Even at this juncture, there is evidence to pinpoint key sites of communication where gut microbial interventions either with drugs or diet or perhaps fecal microbiota transplantation may positively impact mental health.Neuropsychopharmacology advance online publication, 13 July 2016; doi:10.1038/npp.2016.103.

Dos Santos, K. M., de, Oliveira, I, Lopes, M. A., Cruz, A. P., Buriti, F. C., and Cabral, L. M. Addition of grape pomace extract to probiotic fermented goat milk: the effect on phenolic content, probiotic viability and sensory acceptability. J.Sci.Food Agric. 6-10-2016;

ABSTRACT: BACKGROUND: Grape pomace is a source of phenolic compounds, which are associated with health benefits in humans. Additionally, fermented dairy foods with probiotics can be good vehicles to deliver these bioactive compounds. The effects of the addition of grape pomace extract (GPE) on the total phenolic (TP) content, physico-chemical characteristics and viability of Lactobacillus acidophilus LA-5 or Lactobacillus rhamnosus HN001 in fermented goat milks prepared with grape juice were investigated. RESULTS: The TP concentration increased significantly in fermented milks with the addition of GPE. A protective effect of GPE on the viability of L. acidophilus was observed. However, after 14 days of storage, the populations of L. acidophilus were significantly lower when compared with those of L. rhamnosus, and only the last probiotic maintained its viability above 7 log CFU mL-1 throughout the period investigated. The sensory scores of flavor, color and overall acceptability of the fermented milk containing L. rhamnosus HN001 were significantly increased when GPE was added. CONCLUSION: The use of GPE might increase the functionality of probiotic fermented goat milk processed with L. rhamnosus HN001 and grape juice because grape polyphenols are known for their antioxidant properties and positive effect on the modulation of gut microbiota. (c) 2016 Society of Chemical Industry.

Dvoroznakova, E., Buckova, B., Hurnikova, Z., Revajova, V., and Laukova, A. Effect of probiotic bacteria on phagocytosis and respiratory burst activity of blood polymorphonuclear leukocytes (PMNL) in mice infected with Trichinella spiralis. Vet.Parasitol. 7-7-2016;

ABSTRACT: This study focusses on the effect of probiotic (bacteriocinogenic) strains on parasite infection and innate immunity - phagocytosis and oxidative burst of blood monocytes and polymorphonuclear leukocytes (PMNL) in mice infected with Trichinella spiralis. Bacteriocinogenic and probiotic strains of different origin (Enterococcus faecium AL41=CCM8558, Enterococcus durans ED26E/7, Lactobacillus fermentum AD1=CCM7421, Lactobacillus plantarum 17L/1) were administered daily in dose of 109CFU/ml in 100mul and mice were infected with 400 larvae of T. spiralis on 7th day of treatment. Phagocytic activity of blood leukocytes was inhibited at week 3 and 4 post infection (p.i.), i.e. in the time of massive muscle invasion with larvae T. spiralis. Administration of bacterial strains to mice prior to T. spiralis infection elevated and prolonged phagocytic activity of blood leukocytes and their ingestion capability from week 1 to 3 of the infection and the phagocytosis was inhibited only at week 4 p.i. The highest stimulative effect on phagocytosis was induced by strains E. durans ED26E/7, L. fermentum AD1=CCM7421, and L. plantarum 17L/1. The percentage of cells with respiratory burst and their enzymatic activity was increased after T. spiralis infection with the exception of week 3 p.i. In contrast, in all mice treated with bacterial strains the enzymatic stimulation was observed after the infection, with the highest intensity caused by strains E. durans ED26E/7, L. fermentum AD1=CCM7421 and L. plantarum 17L/1. The administration of probiotic strains stimulated phagocytosis and respiratory burst of blood PMNL that could contribute to a decreased larval migration and a destruction of muscle larvae and then reduced parasite burden in the host. The protective effect against T. spiralis infection was induced by all strains, but the highest reduction was recorded by E. faecium AL41=CCM8558.

Ejtahed, H. S., Soroush, A. R., Angoorani, P., Larijani, B., and Hasani-Ranjbar, S. Gut Microbiota as a Target in the Pathogenesis of Metabolic Disorders: A New Approach to Novel Therapeutic Agents. Horm.Metab Res. 2016; 48(6):349-358.

ABSTRACT: As the prevalence of metabolic disorders increases dramatically, the importance of identifying environmental factors affecting metabolism control becomes greater accordingly. Gut microbiota, a complex ecosystem inhabiting the human gastrointestinal tract, is one of these potential factors. Recently, the evidence has shown the associations between alteration in gut microbiota composition and obesity, diabetes, and osteoporosis. However, the causality of gut microbiota on metabolic health has yet to be explored in intervention studies and the underlying mechanisms need to be investigated more in depth. Gut microbiota plays critical roles in the control of immunity, food intake, lipid accumulation, production of short chain fatty acids, insulin signaling, and regulation of bone mass. The gut microbiota represents a novel potential therapeutic strategy for the treatment of metabolic disorders. In this review, we provide insights into the role of the gut microbiota in metabolic disorders and its modulating interventions such as prebiotics, probiotics, and fecal microbiota transplantation.

Emge, J. R., Huynh, K., Miller, E. N., Kaur, M., Reardon, C., Barrett, K. E., and Gareau, M. G. Modulation of the microbiota-gut-brain axis by probiotics in a murine model of inflammatory bowel disease. Am.J.Physiol Gastrointest.Liver Physiol. 6-1-2016; 310(11):G989-G998.

ABSTRACT: Anxiety, depression, and altered memory are associated with intestinal diseases, including inflammatory bowel disease (IBD). Understanding the link between these behavioral changes and IBD is important clinically since concomitant mood

disorders often increase a patient's risk of requiring surgery and developing secondary functional gastrointestinal diseases. Anxiety-like behavior (light/dark box test) and recognition memory (novel object recognition task) were determined at the peak and during resolution of inflammation in the dextran sodium sulfate (DSS) mouse model of acute colitis. DSS (5 days) was administered via drinking water followed by 3 or 9 days of normal drinking water to assess behavior during active or resolving inflammation, respectively. Disease (weight, colon length, and histology) was assessed and the composition of the gut microbiota was characterized by using qPCR on fecal pellet DNA. In a subset of mice, pretreatment with probiotics was started 1 wk prior to commencing DSS. During active inflammation (8 days), mice demonstrated impaired recognition memory and exhibited anxiety-like behavior vs. CONTROLS: These behavioral defects were normalized by 14 days post-DSS. Shifts in the composition of the gut microbiota were evident during active inflammation, notably as decreases in lactobacilli and segmented filamentous bacteria, which were also reversed once the disease had resolved. Administration of probiotics could prevent the behavioral defects seen in acute DSS. Taken together, our findings indicate that changes in mood and behavior are present during acute inflammation in murine IBD and associated with dysbiosis and that these outcomes can be prevented by the administration of probiotics.

Escalante, A., Lopez Soto, D. R., Velazquez Gutierrez, J. E., Giles-Gomez, M., Bolivar, F., and Lopez-Munguia, A. Pulque, a Traditional Mexican Alcoholic Fermented Beverage: Historical, Microbiological, and Technical Aspects. Front Microbiol. 2016; 7:1026

ABSTRACT: Pulque is a traditional Mexican alcoholic beverage produced from the fermentation of the fresh sap known as aguamiel (mead) extracted from several species of Agave (maguey) plants that grow in the Central Mexico plateau. Currently, pulque is produced, sold and consumed in popular districts of Mexico City and rural areas. The fermented product is a milky white, viscous, and slightly acidic liquid beverage with an alcohol content between 4 and 7 degrees GL and history of consumption that dates back to pre-Hispanic times. In this contribution, we review the traditional pulque production process, including the microbiota involved in the biochemical changes that take place during aguamiel fermentation. We discuss the historical relevance and the benefits of pulque consumption, its chemical and nutritional properties, including the health benefits associated with diverse lactic acid bacteria with probiotic potential isolated from the beverage. Finally, we describe the actual status of pulque production as well as the social, scientific and technological challenges faced to preserve and improve the production of this ancestral beverage and Mexican cultural heritage.

Etyemez, M. and Balcazar, J. L. Isolation and characterization of bacteria with antibacterial properties from Nile tilapia (Oreochromis niloticus). Res.Vet.Sci. 2016; 105:62-64.

ABSTRACT: One hundred and twenty bacterial isolates were obtained from the intestinal mucus of Nile tilapia (Oreochromis niloticus) and screened for antagonistic activity and adherence abilities. Based on in vitro antagonism against two pathogens (Streptococcus iniae and Edwardsiella piscicida), five isolates were selected and identified by 16S rRNA gene sequence analysis. All antagonistic isolates were affiliated to the genus Bacillus, which showed inhibitory activity against S. iniae. Only the isolate B191 (closely related to Bacillus mojavensis) inhibited the growth of both pathogens. Moreover, isolate B191 adhered significantly better to fish intestinal mucus than other antagonistic isolates.

According to our results, these bacterial isolates, particularly isolate B191, should be further studied to explore their probiotic effects under in vivo conditions.

Evans, M., Salewski, R. P., Christman, M. C., Girard, S. A., and Tompkins, T. A. Effectiveness of Lactobacillus helveticus and Lactobacillus rhamnosus for the management of antibiotic-associated diarrhoea in healthy adults: a randomised, double-blind, placebo-controlled trial. Br.J.Nutr. 2016; 116(1):94-103.

ABSTRACT: Broad-spectrum antibiotic use can disrupt the gastrointestinal microbiota resulting in diarrhoea. Probiotics may be beneficial in managing this type of diarrhoea. The aim of this 10-week randomised, double-blind, placebo-controlled, parallel study was to investigate the effect of Lactobacillus helveticus R0052 and Lactobacillus rhamnosus R0011 supplementation on antibiotic-associated diarrhoea in healthy adults. Subjects were randomised to receive 1 week of amoxicillin-clavulanic acid (875 mg/125 mg) once per day, plus a daily dose of 8x109 colony-forming units of a multi-strain probiotic (n 80) or placebo (n 80). The probiotic or placebo intervention was maintained for 1 week after completion of the antibiotic. Primary study outcomes of consistency and frequency of bowel movements were not significantly different between the probiotic and placebo groups. The secondary outcomes of diarrhoea-like defecations, Gastrointestinal Symptoms Rating Scale scores, safety parameters and adverse events were not significantly different between the probiotic intervention and the placebo. A post hoc analysis on the duration of diarrhoea-like defecations showed that probiotic intervention reduced the length of these events by 1 full day (probiotic, 2.70 (sem 0.36) d; placebo, 3.71 (sem 0.36) d; P=0.037; effect size=0.52). In conclusion, this study provides novel evidence that L. helveticus R0052 and L. rhamnosus R0011 supplementation significantly reduced the duration of diarrhoea-like defecations in healthy adults receiving antibiotics.

Ewe, J. A. and Loo, S. Y. Effect of cream fermentation on microbiological, physicochemical and rheological properties of L. helveticus-butter. Food Chem. 6-15-2016; 201:29-36.

ABSTRACT: The primary objective of this study was to evaluate the physicochemical and rheological properties of butter produced by Lactobacillus helveticus fermented cream. The incorporation of putative probiotic - the L. helveticus, to ferment cream prior to butter production was anticipated to alter the nutritional composition of butter. Changes in crude macronutrients and the resultant modification relating to textural properties of butter induced upon metabolic activities of L. helveticus in cream were focused in this research. Fermented butter (LH-butter) was produced by churning the cream that was fermented by lactobacilli at 37 degrees C for 24 h. Physicochemical analysis, proximate analysis and rheology properties of LH-butter were compared with butter produced using unfermented cream (control). LH-butter showed a significantly ($P<0.05$) higher fat content and acid value; lower moisture and ash; and was softer than the control. Cream fermentation modified nutritional and textural properties of butter in which LH-butter contained higher health beneficial unsaturated fatty acids than the control and thus rendered the product softer. Its enrichment with probiotics could thus further enhance its functional property.

Fariq, A. and Saeed, A. Production and Biomedical Applications of Probiotic Biosurfactants. Curr.Microbiol. 2016; 72(4):489-495.

ABSTRACT: Biosurfactants have been widely used for environmental and industrial applications. However, their use in medical field is still limited. Probiotic biosurfactants possess an immense antimicrobial, anti-adhesive, antitumor, and antibiofilm potential. Moreover, they have an additional advantage over conventional microbial surfactants because probiotics are an integral part of normal human microflora and their biosurfactants are innocuous to human. So, they can be effectively exploited for medicinal use. Present review is aimed to discourse the production and biomedical applications of probiotic biosurfactants.

Faseleh, Jahromi M., Wesam, Altaher Y., Shokryazdan, P., Ebrahimi, R., Ebrahimi, M., Idrus, Z., Tufarelli, V., and Liang, J. B. Dietary supplementation of a mixture of Lactobacillus strains enhances performance of broiler chickens raised under heat stress conditions. Int.J.Biometeorol. 2016; 60(7):1099-1110.

ABSTRACT: High ambient temperature is a major problem in commercial broiler production in the humid tropics because high producing broiler birds consume more feed, have higher metabolic activity, and thus higher body heat production. To evaluate the effects of two previously isolated potential probiotic strains (Lactobacillus pentosus ITA23 and Lactobacillus acidophilus ITA44) on broilers growing under heat stress condition, a total of 192 chicks were randomly allocated into four treatment groups of 48 chickens each as follows: CL, birds fed with basal diet raised in 24 degrees C; PL, birds fed with basal diet plus 0.1 % probiotic mixture raised in 24 degrees C; CH, birds fed with basal diet raised in 35 degrees C; and PH, birds fed with basal diet plus 0.1 % probiotic mixture raised in 35 degrees C. The effects of probiotic mixture on the performance, expression of nutrient absorption genes of the small intestine, volatile fatty acids (VFA) and microbial population of cecal contents, antioxidant capacity of liver, and fatty acid composition of breast muscle were investigated. Results showed that probiotic positively affected the final body weight under both temperature conditions (PL and PH groups) compared to their respective control groups (CL and CH). Probiotic supplementation numerically improved the average daily gain (ADG) under lower temperature, but significantly improved ADG under the higher temperature ($P < 0.05$) by sustaining high feed intake. Under the lower temperature environment, supplementation of the two Lactobacillus strains significantly increased the expression of the four sugar transporter genes tested (GLUT2, GLUT5, SGLT1, and SGLT4) indicating probiotic enhances the absorption of this nutrient. Similar but less pronounced effect was also observed under higher temperature (35 degrees C) condition. In addition, the probiotic mixture improved bacterial population of the cecal contents, by increasing beneficial bacteria and decreasing Escherichia coli population, which could be because of higher production of VFA in the cecum, especially at heat stress condition. The two Lactobacillus strains also improved the fatty acid profile of meat, including at heat stress. Generally, the two Lactobacillus strains can be considered as good potential probiotics for chickens due to their good probiotic properties and remarkable efficacy on broiler chickens.

Fatima, A. and Sylvester, F. A. The Gut Microbiome and Probiotics. Adolesc.Med.State Art.Rev. 2016; 27(1):140-154.

No abstract currently available.

Federico, A., Dallio, M., Godos, J., Loguercio, C., and Salomone, F. Targeting gut-liver axis for the treatment of nonalcoholic steatohepatitis: translational and clinical evidence. Transl.Res. 2016; 167(1):116-124.

ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) is widely emerging as the most prevalent liver disorder and is associated with increased risk of liver-related and cardiovascular mortality. Recent experimental and clinical studies have revealed the pivotal role played by the alteration of gut-liver axis in the onset of fatty liver and related metabolic disturbances. Gut-liver cross talk is implicated not only in the impairment of lipid and glucose homeostasis leading to steatogenesis, but also in the initiation of inflammation and fibrogenesis, which characterize nonalcoholic steatohepatitis (NASH), the evolving form of NAFLD. The gut microbiota has been recognized as the key player in the gut-liver liaison and because of its complexity can act as a villain or a victim. Gut microbiota not only influences absorption and disposal of nutrients to the liver, but also conditions hepatic inflammation by supplying toll-like receptor ligands, which can stimulate liver cells to produce proinflammatory cytokines. Thus, the modification of intestinal bacterial flora by specific probiotics has been proposed as a therapeutic approach for the treatment of NASH. In this review, we summarized the evidence regarding the role of gut-liver axis in the pathogenesis of NASH and discussed the potential therapeutic role of gut microbiota modulation in the clinical setting.

Feng, J., Wang, L., Zhou, L., Yang, X., and Zhao, X. Using In Vitro Immunomodulatory Properties of Lactic Acid Bacteria for Selection of Probiotics against Salmonella Infection in Broiler Chicks. PLoS.One. 2016; 11(1):e0147630

ABSTRACT: Poultry is known to be a major reservoir of Salmonella. The use of lactic acid bacteria has become one of successful strategies to control Salmonella in poultry. The purpose of this study was to select lactic acid bacteria strains by their in vitro immunomodulatory properties for potential use as probiotics against Salmonella infection in broiler chicks. Among 101 isolated lactic acid bacteria strains, 13 strains effectively survived under acidic (pH 2.5) and bile salt (ranging from 0.1% to 1.0%) conditions, effectively inhibited growth of 6 pathogens, and adhered to Caco-2 cells. However, their in vitro immunomodulatory activities differed significantly. Finally, three strains with higher in vitro immunomodulatory properties (Lactobacillus plantarum PZ01, Lactobacillus salivarius JM32 and Pediococcus acidilactici JH231) and three strains with lower in vitro immunomodulatory activities (Enterococcus faecium JS11, Lactobacillus salivarius JK22 and Lactobacillus salivarius JM2A1) were compared for their inhibitory effects on Salmonella adhesion and invasion to Caco-2 cells in vitro and their antimicrobial effects in vivo. The former three strains inhibited Salmonella adhesion and invasion to Caco-2 cells in vitro, reduced the number of Salmonella in intestinal content, spleen and liver, reduced the levels of lipopolysaccharide-induced TNF-alpha factor (LITAF), IL-1beta, IL-6 and IL-12 in serum and increased the level of IL-10 in serum during a challenge study in vivo more efficiently than the latter three strains. These results suggest that in vitro immunomodulatory activities could be used as additional parameters to select more effective probiotics as feed supplements for poultry.

Fernandez, J., Tandon, P., Mensa, J., and Garcia-Tsao, G. Antibiotic prophylaxis in cirrhosis: Good and bad. Hepatology. 2016; 63(6):2019-2031.

ABSTRACT: Patients with cirrhosis, particularly those with decompensated cirrhosis, are at increased risk of bacterial infections that may further precipitate other liver decompensations including acute-on-chronic liver failure. Infections constitute the main cause of death in patients with advanced cirrhosis, and strategies to prevent them are essential. The main current strategy is the use of prophylactic antibiotics targeted at specific subpopulations at high risk of infection: prior episode of spontaneous bacterial peritonitis, upper gastrointestinal bleeding, and low-protein ascites with associated poor liver function. Antibiotic prophylaxis effectively prevents not only the development of bacterial infections in all these indications but also further decompensation (variceal bleeding, hepatorenal syndrome) and improves survival. However, antibiotic prophylaxis is also associated with a clinically relevant and increasing drawback, the development of infections due to multidrug-resistant organisms. Several strategies have been suggested to balance the risks and benefits of antibiotic prophylaxis. CONCLUSION: Antibiotic stewardship principles such as the restriction of antibiotic prophylaxis to subpopulations at a very high risk for infection, the avoidance of antibiotic overuse, and early deescalation policies are key to achieve this balance; nonantibiotic prophylactic measures such as probiotics, prokinetics, bile acids, statins, and hematopoietic growth factors could also contribute to ameliorate the development and spread of multidrug-resistant bacteria in cirrhosis. (Hepatology 2016;63:2019-2031).

Fernandez, L., Cardenas, N., Arroyo, R., Manzano, S., Jimenez, E., Martin, V., and Rodriguez, J. M. Prevention of Infectious Mastitis by Oral Administration of Lactobacillus salivarius PS2 During Late Pregnancy. Clin.Infect.Dis. 3-1-2016; 62(5):568-573.

ABSTRACT: BACKGROUND: Previous studies have shown that oral administration of lactobacilli can be an efficient approach to treat lactational infectious mastitis. In this trial, we have evaluated the potential of Lactobacillus salivarius PS2 to prevent this condition when orally administered during late pregnancy to women who had experienced infectious mastitis after previous pregnancies. METHODS: In this study, 108 pregnant women were randomly assigned to one of 2 groups. Those in the probiotic group (n = 55) ingested daily 9 log10 colony-forming units of L. salivarius PS2 from approximately week 30 of pregnancy until delivery, whereas those in the placebo group (n = 53) received a placebo. The occurrence of mastitis was evaluated during the first 3 months after delivery. RESULTS: Globally, 44 of 108 women (41%) developed mastitis; however, the percentage of women with mastitis in the probiotic group (25% [n = 14]) was significantly lower than in the control group (57% [n = 30]). When mastitis occurred, the milk bacterial counts in the probiotic group were significantly lower than those obtained in the placebo group. CONCLUSIONS: Oral administration of L. salivarius PS2 during late pregnancy appears to be an efficient method to prevent infectious mastitis in a susceptible population. CLINICAL TRIALS REGISTRATION: NCT01505361.

Ferreira Dos, Santos T., Alves, Melo T., Almeida, M. E., Passos, Rezende R., and Romano, C. C. Immunomodulatory Effects of Lactobacillus plantarum Lp62 on Intestinal Epithelial and Mononuclear Cells. Biomed.Res.Int. 2016; 2016:8404156

ABSTRACT: Probiotic lactic acid bacteria are known for their ability to modulate the immune system. They have been shown to inhibit inflammation in experiments with animal models, cell culture, and clinical trials. The objective of this study was to elucidate the anti-inflammatory potential of Lactobacillus plantarum Lp62, isolated from cocoa fermentation, in a cell culture model. Lp62 inhibited IL-8 production by Salmonella Typhi-

stimulated HT-29 cells and prevented the adhesion of pathogens to these epithelial cells. The probiotic strain was able to modulate TNF-alpha, IL1-beta, and IL-17 secretion by J774 macrophages. J774 activation was reduced by coincubation with Lp62. PBMC culture showed significantly higher levels of CD4(+)CD25(+) T lymphocytes following treatment with Lp62. Probiotics also induced increased IL-10 secretion by mononuclear cells. L. plantarum Lp62 was able to inhibit inflammatory stimulation in epithelial cells and macrophages and activated a tolerogenic profile in mononuclear cells of healthy donors. These results indicate this strain for a possible application in the treatment or prevention of inflammatory diseases.

Feuerstein, J. D. and Falchuk, K. R. Diverticulosis and Diverticulitis. Mayo Clin.Proc. 2016; 91(8):1094-1104.

ABSTRACT: Diverticular disease is a common condition that is associated with variable presentations. For this review article, we performed a review of articles in PubMed through February 1, 2016, by using the following MeSH terms: colon diverticula, colonic diverticulitis, colonic diverticulosis, colonic diverticulum, colonic diverticula, and diverticula. Diverticula are structural alterations within the colonic wall that classically form "pockets" referred to as diverticula. Diverticula form from herniation of the colonic mucosa and submucosa through defects in the circular muscle layers within the colonic wall. Often this is at the sites of penetrating blood vessels in the colon. Diverticular disease is extremely common, which resulted in 2,682,168 outpatient visits and 283,355 hospitalization discharges for diverticulitis or diverticulosis in 2009. Diverticulosis is one of the most common detected conditions found incidentally on colonoscopy. Risk factors for the development of diverticulitis include obesity, smoking, nonsteroidal anti-inflammatory drugs, corticosteroids, and opiates. In contrast, fiber may be protective, but recent studies have questioned the role of fiber in developing diverticular disease. Most patients with diverticulosis will be asymptomatic, but a subset of patients may develop nonspecific abdominal pain (isolated or recurrent), diverticulitis, or segmental colitis associated with diverticulosis. Classically, the treatment of diverticulitis has included antibiotics for all patients. More recent evidence indicates that in mild to even moderate uncomplicated diverticulitis, antibiotics may not be as necessary as initially believed. In more complicated diverticulitis, intravenous antibiotics and surgery may be necessary. Once a patient has had an attack of diverticulitis, increasing fiber may help prevent future attacks. Other modalities such as 5-aminosalicylate products, antibiotics, and probiotics are still of unclear benefit in preventing future episodes of diverticulitis. Similarly, even when patients develop recurrent episodes of diverticulitis, surgery may not be necessary as a prophylactic treatment.

Fibi, S., Klose, V., Mohnl, M., Weber, B., Haslberger, A. G., and Sattler, V. A. Suppression subtractive hybridisation and real-time PCR for strain-specific quantification of the probiotic Bifidobacterium animalis BAN in broiler feed. J.Microbiol.Methods. 2016; 123:94-100.

ABSTRACT: To ensure quality management during the production processes of probiotics and for efficacy testing in vivo, accurate tools are needed for the identification and quantification of probiotic strains. In this study, a strain-specific qPCR assay based on Suppression Subtractive Hybridisation (SSH) for identifying unique sequences, was developed to quantify the strain Bifidobacterium animalis BAN in broiler feed. Seventy potential BAN specific sequences were obtained after SSH of the BAN genome, with a

pool of closely related strain genomes and subsequent differential screening by dot blot hybridisation. Primers were designed for 30 sequences which showed no match with any sequence database entry, using BLAST and FASTA. Primer specificity was assessed by qPCR using 45 non-target strains and species in a stepwise approach. Primer T39_S2 was the only primer pair without any unspecific binding properties and it showed a PCR efficiency of 80% with a Cq value of 17.32 for 20 ng BAN DNA. Optimised feed-matrix dependent calibration curve for the quantification of BAN was generated, ranging from 6.28 x 10(3)cfu g(-1) to 1.61 x 10(6)cfu g(-1). Limit of detection of the qPCR assay was 2 x 10(1)cfu g(-1) BAN. Applicability of the strain-specific qPCR assay was confirmed in a spiking experiment which added BAN to the feed in two concentrations, 2 x 10(6)cfu g(-1) and 2 x 10(4)cfu g(-1). Results showed BAN mean recovery rates in feed of 1.44 x 10(6) +/- 4.39 x 10(5)cfu g(-1) and 1.59 x 10(4) +/- 1.69 x 10(4)cfu g(-1), respectively. The presented BAN-specific qPCR assay can be applied in animal feeding trials, in order to control the correct inclusion rates of the probiotic to the feed, and it could further be adapted, to monitor the uptake of the probiotic into the gastrointestinal tract of broiler chickens.

Fiocchi, A., Pecora, V., and Dahdah, L. Probiotics, Prebiotics & Food allergy Prevention: Clinical Data in Children. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S14-S17.

ABSTRACT: PURPOSE OF REVIEW: there are accruing evidences on the role of the intestinal microbiota in the development of allergic diseases among infants. Elaborating on this theoretical basis, studies did assess the possibilities to prevent allergic diseases in infancy through manipulation of the intestinal microbiota. We review here such studies. RECENT FINDINGS: interventional studies led to conflicting conclusions on the possible role of probiotics and prebiotics in allergy prevention. Two metanalyses published in 2015 did reconcile all data. Guidelines have been predicated on such studies using the GRADE methodology. SUMMARY: the guidelines for allergy prevention suggest for the first time the use of probiotics and prebiotics. The existing evidences stand for a use of such supplementation in particular for the prevention of eczema. As there is no evidence so far of superiority of one probiotic strand over the others, they should be considered as class and not as individual products.

Firouzi, S., Majid, H. A., Ismail, A., Kamaruddin, N. A., and Barakatun-Nisak, M. Y. Effect of multi-strain probiotics (multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: a randomized controlled trial. Eur.J.Nutr. 3-17-2016;

ABSTRACT: AIM: Evidence of a possible connection between gut microbiota and several physiological processes linked to type 2 diabetes is increasing. However, the effect of multi-strain probiotics in people with type 2 diabetes remains unclear. This study investigated the effect of multi-strain microbial cell preparation-also refers to multi-strain probiotics-on glycemic control and other diabetes-related outcomes in people with type 2 diabetes. DESIGN: A randomized, double-blind, parallel-group, controlled clinical trial. SETTING: Diabetes clinic of a teaching hospital in Kuala Lumpur, Malaysia. PARTICIPANTS: A total of 136 participants with type 2 diabetes, aged 30-70 years, were recruited and randomly assigned to receive either probiotics (n = 68) or placebo (n = 68) for 12 weeks. OUTCOMES: Primary outcomes were glycemic control-related parameters, and secondary outcomes were anthropomorphic variables, lipid profile, blood pressure and high-sensitivity C-reactive protein. The Lactobacillus and Bifidobacterium quantities were

measured before and after intervention as an indicator of successful passage of the supplement through gastrointestinal tract. STATISTICAL ANALYSIS: Intention-to-treat (ITT) analysis was performed on all participants, while per-protocol (PP) analysis was performed on those participants who had successfully completed the trial with good compliance rate. RESULTS: With respect to primary outcomes, glycated hemoglobin decreased by 0.14 % in the probiotics and increased by 0.02 % in the placebo group in PP analysis ($p < 0.05$, small effect size of 0.050), while these changes were not significant in ITT analysis. Fasting insulin increased by 1.8 microU/mL in placebo group and decreased by 2.9 microU/mL in probiotics group in PP analysis. These changes were significant between groups at both analyses ($p < 0.05$, medium effect size of 0.062 in PP analysis and small effect size of 0.033 in ITT analysis). Secondary outcomes did not change significantly. Probiotics successfully passed through the gastrointestinal tract. CONCLUSION: Probiotics modestly improved HbA1c and fasting insulin in people with type 2 diabetes.

Florez, I. D., Al-Khalifah, R., Sierra, J. M., Granados, C. M., Yepes-Nunez, J. J., Cuello-Garcia, C., Perez-Gaxiola, G., Zea, A. M., Hernandez, G. N., Veroniki, A. A., Guyatt, G. H., and Thabane, L. The effectiveness and safety of treatments used for acute diarrhea and acute gastroenteritis in children: protocol for a systematic review and network meta-analysis. Syst.Rev. 2016; 5:14

ABSTRACT: BACKGROUND: Acute diarrhea and acute gastroenteritis (AD/AGE) are common among children in low- and middle-income countries (LMIC) and high-income countries (HIC). Supportive therapy including maintaining feeding, prevention of dehydration, and use of oral rehydration solution (ORS), is the mainstay of treatment in all children. Several additional treatments aiming to reduce the episode duration have been compared to placebo, but the differences in effectiveness among them are unknown. METHODS AND ANALYSIS: We will conduct a systematic review of all randomized controlled trials evaluating the use of zinc, vitamin A, probiotics, prebiotics, synbiotics, racecadotril, smectite, and fermented and lactose-free milk/formula for AD/AGE treatment in children. The primary outcomes are diarrhea duration and mortality. Secondary outcomes are diarrhea lasting 3 or 7 days, stool frequency, treatment failure, hospitalizations, and adverse events. We will search MEDLINE, Ovid EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS through Ovid, as well as grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, and assess the risk of bias (ROB) and the confidence in the estimate (with the grading of recommendations, assessment, development, and evaluation [GRADE] approach). Results will be summarized narratively and statistically. Subgroup analysis according to HIC vs. LMIC, age, nutrition status, and ROB is planned. We will perform a Bayesian network meta-analysis to combine the pooled direct and indirect treatment effect estimates for each outcome, if adequate data is available. DISCUSSION: This is the first systematic review and network meta-analysis that aims to determine the relative effectiveness of pharmacological and nutritional treatments for reducing the duration of AD/AGE in children. The results will help to reduce the uncertainty of the effectiveness of the interventions, find knowledge gaps, and/or encourage further research for other therapeutic options. SYSTEMATIC REVIEW REGISTRATION: PROSPERO registration number: CRD42015023778.

Forte, C., Acuti, G., Manuali, E., Casagrande, Proietti P., Pavone, S., Trabalza-Marinucci, M., Moscati, L., Onofri, A., Lorenzetti, C., and Franciosini, M. P. Effects of two different probiotics on microflora, morphology, and morphometry of gut in organic laying hens. Poult.Sci. 5-3-2016;

ABSTRACT: The current study investigated the effects of Lactobacillus acidophilus and Bacillus subtilis, used as probiotics, on the microflora, morphology, and morphometry of the gut in organic laying hens. The birds (180 Hy-Line laying hens) were divided into 3 homogenous groups and received a pre-deposition diet from 16 to 20 wk of age and a deposition diet for the remaining 7 months of the experiment. The control group (CTR:) was fed a corn-soybean cake-based diet, the second group (L:) received the same diet supplemented with 0.1% of L. acidophilus while in the third group (B:) the basal diet was supplemented with 0.05% of B. subtilis At 18 wk of age (T1:) and at 5 (T2:) and 7 months (T3:) from the beginning of deposition, 9 subjects per group were humanely killed for microbiological, morphological and morphometric analyses of the intestinal tract. The 2 probiotic-supplemented diets increased Lactobacillus spp. and Bifidobacterium spp. counts compared with the CTR diet. The lowest viable counts of E. coli, coliforms and staphylococci were observed in the L group ($P < 0.001$). Clostridium spp. decreased ($P < 0.001$) in both L and B subjects. The probiotic supplementation appeared to affect the intestinal microbial population, promoting the presence of beneficial bacteria such as Lactobacillus spp. and Bifidobacterium spp. and reducing potential harmful bacteria such as E. coli, clostridia and staphylococci. Morphological and morphometric analyses did not reveal substantial differences among groups. At T3, the plasma cell infiltrate in the villi of the CTR hens was more severe than that observed in the L and B groups ($P = 0.009$).

Fortuna, M. C., Garelli, V., Pranteda, G., Romaniello, F., Cardone, M., Carlesimo, M., and Rossi, A. A case of Scalp Rosacea treated with low dose doxycycline and probiotic therapy and literature review on therapeutic options. Dermatol.Ther. 2016; 29(4):249-251.

ABSTRACT: Rosacea is a common chronic inflammatory disorder showing a wide range of clinical features such as telangiectasia, erythema, papules, and pustules primarily involving the central part of face (forehead, cheeks and nose) although extra facial manifestation have been described. We describe a case of rosacea with predominant scalp involvement successfully treated with a 8-week-course of doxycycline 40 mg once a day and probiotic therapy twice a day (Bifidobacterium breve BR03, Lactobacillus salivarius LS01 1 x 10(9) UFC/dose).

Foster, J. A., Lyte, M., Meyer, E., and Cryan, J. F. Gut Microbiota and Brain Function: An Evolving Field in Neuroscience. Int.J.Neuropsychopharmacol. 2016; 19(5)

ABSTRACT: There is a growing appreciation of the importance of gut microbiota to health and disease. This has been driven by advances in sequencing technology and recent findings demonstrating the important role of microbiota in common health disorders such as obesity. Moreover, the potential role of gut microbiota in influencing brain function, behavior, and mental health has attracted the attention of neuroscientists and psychiatrists. At the 29(th) International College of Neuropsychopharmacology (CINP) World Congress held in Vancouver, Canada, in June 2014, a group of experts presented the symposium, "Gut microbiota and brain function: Relevance to psychiatric disorders" to review the latest findings in how gut microbiota may play a role in brain function,

behavior, and disease. The symposium covered a broad range of topics, including gut microbiota and neuroendocrine function, the influence of gut microbiota on behavior, probiotics as regulators of brain and behavior, and imaging the gut-brain axis in humans. This report provides an overview of these presentations.

Francavilla, R., Cristofori, F., and Indrio, F. Indications and Recommendations by Societies and Institutions for the Use of Probiotics and Prebiotics in Paediatric Functional Intestinal Disorders. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S36-S37.

ABSTRACT: PURPOSE OF REVIEW: To report the indications and/or recommendations by Societies and Institutions for the use of probiotics and prebiotics in functional intestinal disorders in childhood. RECENT FINDINGS: A position by Societies and Institutions is available only for infant colic, irritable bowel syndrome and constipation. Supplementation with the probiotic L reuteri DSM 17938 in breastfed term infants with colic appears to be effective in reducing crying, while still debated is its role in the prevention of colic. Irritable bowel syndrome is a common disorder in children and at present no specific treatments are available; existing data show that although high-quality studies are still needed, some evidence support the efficacy of LGG and VSL#3 in paediatric IBS. At present there is no evidence for the use of pre- or probiotics in childhood constipation. SUMMARY: Probiotics in a near future may have a definite role is some FGIDs of infants and children. The main limitations for the recommendation by Societies and Institutions are the methodological issues that limit the quality of the evidence and the heterogeneity of treatments (probiotic strain and dose, mode, dose and duration of supplementation, primary outcomes, etc). Some specific strains are promising for infant colic (L. reuteri DSM 17938) and irritable bowel syndrome (LGG) while at present there is no indication for their use in the treatment of childhood constipation.

Freeman, M. P., Sosinsky, A. Z., Moustafa, D., Viguera, A. C., and Cohen, L. S. Supplement use by women during pregnancy: data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. Arch.Womens Ment.Health. 2016; 19(3):437-441.

ABSTRACT: Women of reproductive age commonly use integrative treatments. However, the reproductive safety for most complementary products lacks systematic study. We aimed to study the use of supplements by women in a prospective pregnancy registry. The Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics was established to evaluate the reproductive safety of atypical antipsychotics. Exposed and control participants were systematically queried about the use of vitamins and supplements. Slightly greater than half (53.2 %) of the participants eligible for analysis (N = 534) were using at least one vitamin or supplement at the time of enrollment, not including prenatal vitamins or folic acid. The most common supplements used were omega-3 fatty acids (38.0 %), vitamin D (11.0 %), calcium (8.2 %), and iron (4.7 %). Probiotics and melatonin were used by 2.6 and 0.9 %, respectively. In this prospective pregnancy registry, we found that over half of the participants were taking supplements or vitamins other than prenatal vitamins and folic acid. These findings underscore the need for active query on the part of health care providers about the use of supplements during pregnancy, and the need to obtain rigorous reproductive safety and efficacy data for supplements used by pregnant women and reproductive aged women.

Fuchs-Tarlovsky, V., Marquez-Barba, M. F., and Sriram, K. Probiotics in dermatologic practice. Nutrition. 2016; 32(3):289-295.

ABSTRACT: OBJECTIVE: Probiotics are live microorganisms that beneficially affect the host when administered in adequate amounts. They have an excellent safety profile. Probiotics have been used as immunomodulators in inflammatory skin conditions, such as atopic dermatitis. The aim of this study was to summarize the available evidence concerning the use of different strains of probiotics in dermatology practice. METHODS: We conducted a literature review of English and Spanish publications listed in standard databases (PubMed, Ovid, Google Scholar, Medline, and EBSCO), between 1994 and 2015 using the words "probiotics" and "dermatology." We found approximately 70 studies containing these criteria and selected 42 in which probiotics were used for dermatologic purposes. RESULTS: We found enough evidence to recommend the use of probiotics in specific conditions in dermatology practice, especially in children with atopic dermatitis. CONCLUSIONS: Further well-designed, large population based trials are needed to validate the use of probiotics in dermatology practice, including innovative therapies to rebuild skin barrier defects, protection against microbial colonization, and restoration of immunologic balance.

Gamallat, Y., Meyiah, A., Kuugbee, E. D., Hago, A. M., Chiwala, G., Awadasseid, A., Bamba, D., Zhang, X., Shang, X., Luo, F., and Xin, Y. Lactobacillus rhamnosus induced epithelial cell apoptosis, ameliorates inflammation and prevents colon cancer development in an animal model. Biomed.Pharmacother. 7-19-2016; 83:536-541.

ABSTRACT: BACKGROUND/AIM: Probiotics have been suggested as prophylactic measure in colon carcinogenesis. This study aimed at determining the potential prophylactic activity of Lactobacillus rhamnosus GG CGMCC 1.2134 (LGG) strain on colorectal carcinogenesis via measuring its effect on Nuclear factor kappa B (NFkappaB) inflammatory pathway and apoptosis. MATERIALS AND METHODS: 64 Sprague Dawley rats were grouped into four as follows; Group 1 (Healthy control), Group 2 (LGG), Group 3 (cancer control Dimethyl hydrazine (DMH)) and Group 4 (LGG+DMH). LGG was administered orally to LGG and LGG+DMH groups. Colon carcinogenesis was chemically induced in LGG+DMH and DMH groups by weekly injection of 40mg/kg DMH. Animals were sacrificed after 25 weeks of experiment and tumor characteristics assessed. The change in expression of NFkappaB-p65, COX-2, TNFalpha, Bcl-2, Bax, iNOS, VEGFalpha, beta-catenin, Casp3 and p53 were evaluated by western blotting and qRT-PCR. RESULTS: LGG treatment significantly reduced tumor incidence, multiplicity and volume in LGG+DMH treatment group compared to DMH cancer control group. Also, LGG treatment reduced the expression of beta-catenin and the inflammatory proteins NFkappaB-p65, COX-2 and TNFalpha; the anti-apoptotic protein Bcl-2, but increased the expression of the pro-apoptotic proteins Bax, casp3 and p53 compared with DMH group. CONCLUSION: LGG have a potential protection effect against colon carcinogenesis; inducing apoptosis and ameliorating inflammation, and may hold a promise as bio-therapeutic dietary agent.

Gao, J., Wu, H., and Liu, J. Importance of gut microbiota in health and diseases of new born infants. Exp.Ther.Med. 2016; 12(1):28-32.

ABSTRACT: The multifarious assortment of microorganisms present in gut of humans is termed as gut microbiota. These include 1,000 species accompanied by approximately 2

million genes in an individual adult. The gut microbiota has multifactorial protective roles against allergic reactions, inflammation, cardiac pathological states and even in the state of malignant carcinogenesis existing in humans. By contrast, adverse alterations in the microbiota result in chronic pathological states, including autoimmune diseases, cancer and circulatory system obstructions. Gut bacteria also maintain sensitivity towards nutritional changes as well as antibiotics. The present review article focused on the importance of gut bacteria in newborn infants with special reference to their protective role in various pediatric pathological states linked with gut bacteria. In addition, the importance of probiotics in relation to gut microbiota are to be discussed.

Gao, M., Song, H., Zheng, H., Ren, Y., Li, S., Liu, X., Yu, W., and Ma, X. Culture of low density E. coli cells in alginate-chitosan microcapsules facilitates stress resistance by up-regulating luxS/AI-2 system. Carbohydr.Polym. 5-5-2016; 141:160-165.

ABSTRACT: Entrapped low density cells with culture (ELDCwc) have been proved as a more effective way than direct entrapped high density cells (dEHDC) and free cells to protect probiotics from harsh environment, that is, to improve their stress resistance. The aim of this study was to investigate whether bacterial quorum sensing (QS) facilitated the stress resistance of Escherichia coli in microcapsules by detecting the expression of luxS/AI-2 system. As a result, both the expression of luxS gene and the concentration of autoinducer-2 (AI-2, QS signal molecule) have been discovered higher in ELDCwc than in dEHDC and free cells. Besides that, the luxS mutant E. coli strain was used as a negative control of QS to verify the influence of QS on bacterial stress resistance in microcapsules. The significantly decreased viability of luxS mutant strain in simulated gastric fluid also indicated that the QS played a critical role in protecting microorganisms from severe environment.

Gao, X., Jia, R., Xie, L., Kuang, L., Feng, L., and Wan, C. Comparing three preparation methods of standard substances for intestinal bifidobacteria of childhood obesity. Acta Paediatr. 5-5-2016;

ABSTRACT: Bifidobacteria are normal intestinal flora that play a physiological role in maintaining intestinal microecology balance, biological antagonism, immune regulation and nutrition (1,2). In recent years, bifidobacteria and probiotics have been widely used in medical treatment, healthcare and food (1-3) and have increasingly become the academic focus of microecology. We published a study that showed that childhood obesity was connected with the change in the proportion of intestinal bifidobacteria (4). This article is protected by copyright. All rights reserved.

Gao, X., Zhu, Y., Wen, Y., Liu, G., and Wan, C. Efficacy of probiotics in nonalcoholic fatty liver disease in adult and children: A meta-analysis of randomized controlled trials. Hepatol.Res. 2-11-2016;

ABSTRACT: OBJECTIVE: To evaluate the efficacy of probiotics in the treatment of adult and childhood Nonalcoholic Fatty Liver Disease (NAFLD). METHODS: Randomized controlled trials (RCTs) on the efficacy of probiotics in the treatment of adult and childhood NAFLD published before July 2015 were searched in multiple databases, including Cochrane library, PubMed/MEDLINE, EBSCO, OVID, SCI, CNKI, and VIP. Literature identification and data extraction were performed by 2 reviewers based on

the inclusion and exclusion criteria. RevMan 5.3 software was used for Meta-analysis. RESULTS: A total of 9 RCTs with a total of 535 cases of NAFLD were included. Statistical differences of homeostasis model assessment (HOMA), total cholesterol (T-chol), high density lipoprotein (HDL), Triglyceride (TG), and Tumor necrosis factor-alpha (TNF- alpha) were detected between the probiotics and control groups with variations in different populations. No significant difference of body mass index (BMI), glucose and insulin were detected between the two groups. Statistically differences of low density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate transaminase (AST), and BMI were detected between the two childhood groups (P </= 0.05). CONCLUSION: Probiotics provided improvements in the outcomes of HOMA, Total-chol, HDL, TNF-alpha in any NAFLD patients, TG in Italian and Spanish patients, but no improvement in the outcomes of BMI, glucose, insulin in adult NAFLD patients; The currently available data are not sufficient to compare the the effects of probiotics between adult and childhood NAFLD patients. This article is protected by copyright. All rights reserved.

Garcia, V. G., Knoll, L. R., Longo, M., Novaes, V. C., Assem, N. Z., Ervolino, E., de Toledo, B. E., and Theodoro, L. H. Effect of the probiotic Saccharomyces cerevisiae on ligature-induced periodontitis in rats. J.Periodontal Res. 2016; 51(1):26-37.

ABSTRACT: BACKGROUND AND OBJECTIVE: This study assessed the effects of the local use of Saccharomyces cerevisiae as monotherapy and as an adjuvant to the mechanical treatment of ligature-induced periodontitis in rats. MATERIAL AND METHODS: Periodontitis was induced in 72 rats via the installation of a ligature around the mandibular first molar. After 7 d, the ligature was removed and the rats were placed in one of the following groups: no treatment (C; n = 18); scaling and root planing (SRP; n = 18); local irrigation with probiotics (PRO; n = 18); and SRP followed by local irrigation with probiotics (SRP/PRO; n = 18). Six rats from each group were killed at 7, 15 and 30 d. The histological characteristics, alveolar bone loss (ABL) and immunolabeling of tumor necrosis factor alpha (TNF-alpha), interleukin-1beta (IL-1beta), interleukin-10 (IL-10) and TRAP on the furcation area of the first molar were assessed. RESULTS: The PRO group showed features of acceleration of the tissue-repair process during the entire experiment. On day 15, there was less ABL in the SRP/PRO group compared with the C group. There were fewer TRAP-positive cells in the SRP and SRP/PRO groups at 30 d. There was less immunostaining for TNF-alpha in the PRO and SRP/PRO groups and less immunostaining for IL-1beta in the PRO group. However, there was more immunostaining for IL-10 in the PRO group on day 15. CONCLUSION: Local use of the probiotic did not result in any adverse effects on periodontal tissues. When used as monotherapy or as an adjuvant, the probiotic was effective at controlling periodontitis in rats.

Gargari, G., Taverniti, V., Balzaretti, S., Ferrario, C., Gardana, C., Simonetti, P., and Guglielmetti, S. Four-week consumption of a Bifidobacterium bifidum strain modulates dominant intestinal bacterial taxa and fecal butyrate in healthy adults. Appl.Environ.Microbiol. 7-22-2016;

ABSTRACT: The modulation of the intestinal microbial ecosystem (IME) is a useful target to establish probiotic efficacy in a healthy population. We conducted a randomized, double-blind, crossover, placebo-controlled intervention study to determine the impact of Bifidobacterium bifidum strain Bb on the IME of adult healthy volunteers of both sexes. High-throughput 16S ribosomal RNA gene sequencing was used to characterize the fecal microbiota before and after four weeks of daily probiotic cell consumption. The intake of

approximately one billion live B. bifidum cells affected the relative abundance of dominant taxa in the fecal microbiota and modulated fecal butyrate levels. Specifically, Prevotellaceae (p = 0.041) and Prevotella (p = 0.034) were significantly decreased, whereas Ruminococcaceae (p = 0.039) and Rikenellaceae (p = 0.010) were significantly increased. We also observed that the probiotic intervention modulated the fecal concentrations of butyrate in a manner dependent on the initial levels of short-chain fatty acids (SCFAs). In conclusion, our study demonstrates that a single daily administration of Bifidobacterium bifidum strain Bb can significantly modify the IME in healthy (not diseased) adults. These findings demonstrate the need to reassess the notion that probiotics do not influence the complex and stable IME of a healthy individual. IMPORTANCE: Foods and supplements claimed to contain health-promoting probiotic microorganisms are everywhere these days and mainly destined to the consumption by healthy people. However, it is still debated which actual effect probiotic products may have on the healthy population. In this study, we report the results of an intervention trial aimed at assessing the modifications induced in the intestinal microbial ecosystem of healthy adults by the consumption of a probiotic product. Our results demonstrate that the introduction of a probiotic product in the dietary habit of healthy people may significantly modify dominant taxa of the intestinal microbiota, resulting into the modulation of short-chain fatty acids concentration in the gut. The overall changes witnessed in the probiotic intervention indicate a mechanism of microbiota modulation that could have potential effects on human health.

Gerard, P. Gut microbiota and obesity. Cell Mol.Life Sci. 2016; 73(1):147-162.

ABSTRACT: The human intestine harbors a complex bacterial community called the gut microbiota. This microbiota is specific to each individual despite the existence of several bacterial species shared by the majority of adults. The influence of the gut microbiota in human health and disease has been revealed in the recent years. Particularly, the use of germ-free animals and microbiota transplant showed that the gut microbiota may play a causal role in the development of obesity and associated metabolic disorders, and lead to identification of several mechanisms. In humans, differences in microbiota composition, functional genes and metabolic activities are observed between obese and lean individuals suggesting a contribution of the gut microbiota to these phenotypes. Finally, the evidence linking gut bacteria to host metabolism could allow the development of new therapeutic strategies based on gut microbiota modulation to treat or prevent obesity.

Gerasimov, S. V., Ivantsiv, V. A., Bobryk, L. M., Tsitsura, O. O., Dedyshin, L. P., Guta, N. V., and Yandyo, B. V. Role of short-term use of L. acidophilus DDS-1 and B. lactis UABLA-12 in acute respiratory infections in children: a randomized controlled trial. Eur.J.Clin.Nutr. 2016; 70(4):463-469.

ABSTRACT: BACKGROUND/OBJECTIVES: Evidence suggests that the long-term consumption of probiotics may help in reducing the incidence of or modifying acute respiratory infection (ARI). We assessed the role of the short-term use of probiotics in ARI in children. SUBJECTS/METHODS: This was a randomized, double-blind, controlled study that enrolled 315 children with 90 dropouts. On the first day of appearance of a sick household member, otherwise healthy children of both sexes aged 3-12 years were allocated to receive Lactobacillus acidophilus DDS-1 and Bifidobacterium lactis UABLA-12 (Up4-Junior) in a dose of 5 billion colony-forming units daily with 50 mg of

fructooligosaccharide (the probiotic group) or rice maltodexrin (the control group). Test supplementation and follow-up lasted for 2 weeks or until the end of the secondary ARI in a child. The primary outcome measure was the incidence of ARI. Time to resolution and the severity of ARI served the secondary outcome measures. RESULTS: In all, 64 of 113 children in the probiotic group (57%) and 73 of 112 children in the control group (65%) developed ARI (P=0.261). Time to resolution of the secondary ARI was shorter in the probiotic group (5.0 (interquartile range (IQR): 4.0-6.0) vs 7.0 (IQR: 6.0-8.0) days, P<0.001). The median severity of ARI was 240 (IQR: 163-350) score-days in the probiotic vs 525 (IQR: 364-736) score-days in the control group (P<0.001). CONCLUSIONS: The short-term use of probiotics does not reduce the incidence, but shortens ARI in preschool and elementary school children.

Ghomrassi, H., ben, Braiek O., Choiset, Y., Haertle, T., Hani, K., Chobert, J. M., and Ghrairi, T. Evaluation of marine bacteriocinogenic enterococci strains with inhibitory activity against fish-pathogenic Gram-negative bacteria. Dis.Aquat.Organ. 2-11-2016; 118(1):31-43.

ABSTRACT: Use of lactic acid bacteria (LAB) as probiotics may provide an alternative to the use of antibiotics in aquaculture. LAB strains isolated from wild fish viscera and skin were evaluated for bacteriocin production and safety aspects (lack of antibiotic resistance, production of virulence factors). 16S rRNA gene sequences revealed the presence of Enterococcus faecium (13 isolates) and Lactococcus lactis (3 isolates) from fish samples. Pulsed-field gel electrophoresis analyses of the 13 enterococci isolates showed that they were all clustered, with greater than 95% similarity. However, RAPD analysis revealed significant molecular diversity between enterococci strains. Six enterococci strains were chosen and evaluated for their antibacterial activities. These strains produced a bacteriocin-like substance and exhibited a broad spectrum of inhibition against pathogenic bacteria isolated from diseased fish, including Streptococcus parauberis, Vagococcus spp., and Carnobacterium maltaromaticum, and in particular against the Gram-negative bacteria Flavobacterium frigidarium, Vibrio pectenicida, V. penaeicida, and Photobacterium damselae. The inhibition activity towards bacterial indicator strains was at a maximum when bacteria were grown at 37 degrees C. However, bacteriocin production was observed at 15 degrees C after 12 h of incubation. Only structural genes of enterocins A and B were detected by PCR in the 6 enterococci strains, suggesting the production of these enterocins. In addition, these strains did not harbor any virulence factors or any significant antibiotic resistance, and they tolerated bile. Our results suggest that enterococci are an important part of the bacterial flora of fish and that some strains have the potential to be used as probiotics.

Ghoneim, M. A. and Moselhy, S. S. Antioxidant status and hormonal profile reflected by experimental feeding of probiotics. Toxicol.Ind.Health. 2016; 32(4):741-750.

ABSTRACT: Excessive production of free radicals can result in tissue damage, which mainly involves generation of hydroxyl radical and other oxidants. Such free radical-induced cell damage appears to play a major role in the pathogenesis of many diseases. Probiotics have been used therapeutically to modulate immunity, improve digestive processes, lower cholesterol, treat rheumatoid arthritis, and prevent cancer. The proposed research was designed to evaluate the changes in oxidative and antioxidative profile in addition to metabolic-related hormones of living animal model, which may generally affect the health status. Two groups of rabbits (10 animals each)

were allocated in hygienic cages of controlled animal house. Control group received standard diet, and the other group received the same diet containing one probiotic for 30 days. Lactate dehydrogenase (LDH) activity in leukocytes, blood glucose, reduced glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) were estimated in different tissues. Malondialdehyde (MDA) and total proteins were also determined in different tissues. Certain hormones related to metabolism and growth were also evaluated. Leukocytic LDH activity was significantly increased along with nonsignificant increase of blood glucose in probiotics-fed animals. Results showed significant decreases in the levels of triiodothyronine and thyroid-stimulating hormone but showed significant elevations in thyroxine, insulin, growth hormone, and testosterone levels in animals fed with probiotics. Total proteins content was highly significantly elevated in liver, kidneys, and muscles of probiotic-administered animals. Microsomal GSH level was significantly decreased only in skeletal muscles of probiotic-treated animals. MDA was significantly lowered in animal tissues fed with probiotics. GSH-Px activity was elevated in hepatic and muscular microsomes of probiotic-supplemented animals while it was nonsignificantly increased in renal microsomes. Microsomal SOD activity was elevated in liver, kidneys, and skeletal muscles of probiotics-administrated animals. It is concluded that supplementation of probiotic may enhance antioxidant efficacy and scavenge free radicals and thus may be used as a preventive measure for protection against free radicals-induced disorders.

Ghorbani, Z., Hajizadeh, M., and Hekmatdoost, A. Dietary supplementation in patients with alcoholic liver disease: a review on current evidence. Hepatobiliary.Pancreat.Dis.Int. 2016; 15(4):348-360.

ABSTRACT: BACKGROUND: Alcoholic liver disease (ALD) is one of the main causes of liver disease worldwide. Although the pathogenesis of ALD has not yet been well elucidated, the oxidative metabolites of ethanol such as acetaldehyde and reactive oxygen species play a pivotal role in the clinical and pathological spectrum of the disease. This review summarizes the existing evidences on dietary supplements considered to have antioxidant, and/or anti-inflammatory properties, and their role in the management of ALD and the proposed mechanisms. DATA SOURCES: The present study reviewed all studies published in PubMed, ScienceDirect and Scopus, from 1959 to 2015, indicating the role of different dietary supplementation in attenuation of many pathophysiological processes involved in development and progression of ALD. Full-texts of citations were used except for those that were published in languages other than English. RESULTS: Significant progress has been made to understand the key events and molecular players for the onset and progression of ALD from both experimental and clinical studies; however, there is no successful treatment currently available. The present review discussed the role of a variety of dietary supplements (e.g. vitamin A, carotenoids, vitamins B3, C and E, in addition to antioxidants and anti-inflammatory agents) in treating ALD. It has been shown that supplementation with some carotenoids, vitamin B3, vitamin C, silymarin, curcumin, probiotics, zinc, S-adenosylmethionine and garlic may have potential beneficial effects in animal models of ALD; however, the number of clinical studies is very limited. In addition, supplementation should be accompanied with alcohol cessation. CONCLUSIONS: Since oxidative stress and inflammation are involved in the pathogenesis of ALD, dietary supplements that can modulate these pathologies could be useful in the treatment of ALD. In addition to alcohol cessation, these supplements have shown beneficial effects on animal models of ALD. Clinical trials are needed to validate the beneficiary role of these supplements in patients with ALD.

Giannetti, E., Maglione, M., Alessandrella, A., Strisciuglio, C., De, Giovanni D., Campanozzi, A., Miele, E., and Staiano, A. A Mixture of 3 Bifidobacteria Decreases Abdominal Pain and Improves the Quality of Life in Children With Irritable Bowel Syndrome: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J.Clin.Gastroenterol. 6-15-2016;

ABSTRACT: GOALS: We assessed the efficacy of a probiotic mixture of Bifidobacterium infantis M-63, breve M-16V, and longum BB536 in improving abdominal pain (AP) and quality of life (QoL) in children with irritable bowel syndrome (IBS) and functional dyspepsia (FD). BACKGROUND: AP-associated functional gastrointestinal disorders, particularly IBS and FD, are common in pediatrics, and no well-established treatment is currently available. Although probiotics have shown promising results in adults, data in children are heterogeneous. STUDY: Forty-eight children with IBS (median age, 11.2 y; range, 8 to 17.9 y) and 25 with FD (age, 11.6 y; range, 8 to 16.6 y) were randomized to receive either a mixture of 3 Bifidobacteria or a placebo for 6 weeks. After a 2-week "washout" period, each patient was switched to the other group and followed up for further 6 weeks. At baseline and follow-up, patients completed a symptom diary and a QoL questionnaire. AP resolution represented the primary outcome parameter. RESULTS: In IBS, but not in FD, Bifidobacteria determined a complete resolution of AP in a significantly higher proportion of children, when compared with placebo (P=0.006), and significantly improved AP frequency (P=0.02). The proportion of IBS children with an improvement in QoL was significantly higher after probiotics than after placebo (48% vs. 17%, P=0.001), but this finding was not confirmed in FD. CONCLUSIONS: In children with IBS a mixture of Bifidobacterium infantis M-63, breve M-16V, and longum BB536 is associated with improvement in AP and QoL. These findings were not confirmed in FD subjects. Trial identifier: NCT02566876 (http://www.clinicaltrial.gov).

Giannetti, E. and Staiano, A. Probiotics for Irritable Bowel Syndrome: Clinical Data in Children. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S25-S26.

ABSTRACT: PURPOSE OF REVIEW: The purpose of this review was to summarize the evidence regarding probiotics treatment for pediatric IBS. RECENT FINDINGS: The overall management of children with IBS should be tailored to the patient's specific symptoms and identifiable triggers. The four major therapeutic approaches include: pharmacologic, dietary, psychosocial, and complementary/alternative medicine interventions.Although there is limited evidence for efficacy of pharmacological therapies such as antispasmodics and anti-diarrheals, these may have a role in severe cases. A Cochrane review concluded that only weak evidence exists regarding beneficial effects of pharmacological agents in providing relief from symptoms in functional abdominal pain (AP) in children. Role of antibiotics in treatment of children with IBS remains controversial. Various non-pharmacologic treatments are available for pediatric IBS. In a recent systematic review including 24 studies some evidence was found indicating beneficial effects of partially hydrolyzed guar gum (PHGG), cognitive behavioral therapy, hypnotherapy, and probiotics (LGG and VSL#3).Few randomized clinical trials (RCTs) are available in children. A meta-analysis including 9 trials which tested different probiotics as a treatment for Functional Gastrointestinal Disorders (FGIDs) in children and adolescents concluded that Lactobacillus GG, Lactobacillus reuteri DSM 17938 and VSL#3 significantly increased treatment success. We recently showed that, in children with IBS, a mixture of Bifidobacterium infantis M-63(R), breve M-16V(R) and longum BB536(R) is safe and is associated with better AP control and improved quality of

life when compared to placebo. SUMMARY: Probiotics are emerging as new therapeutic tools in FGIDs, due to the recognition of the importance of gut microbiota in influencing brain-gut interactions, and of the role played by intestinal infections in the genesis of AP-FGIDs. Preclinical data suggest that changes in the gut microbiota can affect brain signaling systems related to pain and associated emotional behavior. Therefore, probiotics could play a relevant role in the management of FGIDs, by affecting the gut microbiota or by altering brain function and pain perception centrally.

Giblot Ducray, H. A., Globa, L., Pustovyy, O., Reeves, S., Robinson, L., Vodyanoy, V., and Sorokulova, I. Mitigation of heat stress-related complications by a yeast fermentate product. J.Therm.Biol. 2016; 60:26-32.

ABSTRACT: Heat stress results in a multitude of biological and physiological responses which can become lethal if not properly managed. It has been shown that heat stress causes significant adverse effects in both human and animals. Different approaches have been proposed to mitigate the adverse effects caused by heat stress, among which are special diet and probiotics. We characterized the effect of the yeast fermentate EpiCor (EH) on the prevention of heat stress-related complications in rats. We found that increasing the body temperature of animals from 37.1+/-0.2 to 40.6+/-0.2 degrees C by exposure to heat (45 degrees C for 25min) resulted in significant morphological changes in the intestine. Villi height and total mucosal thickness decreased in heat-stressed rats pre-treated with PBS in comparison with control animals not exposed to the heat. Oral treatment of rats with EH before heat stress prevented the traumatic effects of heat on the intestine. Changes in intestinal morphology of heat-stressed rats, pre-treated with PBS resulted in significant elevation of lipopolysaccharides (LPS) level in the serum of these animals. Pre-treatment with EH was effective in the prevention of LPS release into the bloodstream of heat-stressed rats. Our study revealed that elevation of body temperature also resulted in a significant increase of the concentration of vesicles released by erythrocytes in rats, pre-treated with PBS. This is an indication of a pathological impact of heat on the erythrocyte structure. Treatment of rats with EH completely protected their erythrocytes from this heat-induced pathology. Finally, exposure to heat stress conditions resulted in a significant increase of white blood cells in rats. In the group of animals pre-treated with EH before heat stress, the white blood cell count remained the same as in non-heated controls. These results showed the protective effect of the EH product in the prevention of complications, caused by heat stress.

Giddings, S. L., Stevens, A. M., and Leung, D. T. Traveler's Diarrhea. Med.Clin.North Am. 2016; 100(2):317-330.

ABSTRACT: Traveler's diarrhea (TD) is the most common travel-related illness, and it can have a significant impact on the traveler. Pretravel consultation provides an excellent opportunity for the clinician to counsel the traveler and discuss strategies such as food and water hygiene, vaccinations, and medications for prophylaxis or self-treatment that may decrease the incidence and impact of TD. Postinfectious sequelae, such as postinfectious irritable bowel syndrome, reactive arthritis, and Guillain-Barre syndrome, may develop weeks or months after return.

Gille, C., Boer, B., Marschal, M., Urschitz, M. S., Heinecke, V., Hund, V., Speidel, S., Tarnow, I., Mylonas, I., Franz, A., Engel, C., and Poets, C. F. Effect of probiotics on vaginal health in pregnancy. EFFPRO, a randomized controlled trial. Am.J.Obstet.Gynecol. 6-21-2016;

ABSTRACT: BACKGROUND: Preterm delivery is a leading cause of neonatal morbidity and death. It often results from chorioamnionitis, which is a complication of bacterial vaginosis. Probiotics are effective in the treatment of bacterial vaginosis in women who were not pregnant; studies in pregnant woman are missing. OBJECTIVE: The purpose of this study was to evaluate whether an oral probiotic food supplement supports the maintenance or restoration of a normal vaginal microbiota during pregnancy. STUDY DESIGN: We conducted a randomized, placebo-controlled, triple-blind, parallel group trial. Oral Lactobacillus rhamnosus GR-1and L reuteri RC-14 (109 colony-forming units) or placebo were administered for 8 weeks to women with <12 completed weeks of pregnancy. Participants were enrolled at Tuebingen University Hospital and 10 recruiting gynecologic practices. Vaginal swabs were taken before and after intervention and analyzed according to the Nugent scoring system. Telephone interviews were performed before and after intervention and after delivery. Primary outcome was the proportion of swabs with normal Nugent score (<4) after intervention, compared by Fisher's exact test in an intention-to-treat analysis. RESULTS: Three hundred twenty pregnant women were enrolled. Vaginal swabs were analyzed from 290 women before and 271 women after intervention. The proportion of normal vaginal microbiota decreased from 82.6 to 77.8% in the treatment group and from 79.1 to 74.3% in the placebo group, with no significant difference across groups after intervention (P=.297). CONCLUSION: Oral probiotics may be suitable for implementation in antenatal care but, as administered here, had no effect on vaginal health during mid gestation. Other application routes or probiotic preparations may be more effective in supporting vaginal microbiota during pregnancy.

Gleeson, M. and Pyne, D. B. Respiratory inflammation and infections in high-performance athletes. Immunol.Cell Biol. 2016; 94(2):124-131.

ABSTRACT: Upper respiratory illness is the most common reason for non-injury-related presentation to a sports medicine clinic, accounting for 35-65% of illness presentations. Recurrent or persistent respiratory illness can have a negative impact on health and performance of athletes undertaking high levels of strenuous exercise. The cause of upper respiratory symptoms (URS) in athletes can be uncertain but the majority of cases are related to common respiratory viruses, viral reactivation, allergic responses to aeroallergens and exercise-related trauma to the integrity of respiratory epithelial membranes. Bacterial respiratory infections are uncommon in athletes. Undiagnosed or inappropriately treated asthma and/or allergy are common findings in clinical assessments of elite athletes experiencing recurrent URS. High-performance athletes with recurrent episodes of URS should undergo a thorough clinical assessment to exclude underlying treatable conditions of respiratory inflammation. Identifying athletes at risk of recurrent URS is important in order to prescribe preventative clinical, training and lifestyle strategies. Monitoring secretion rates and falling concentrations of salivary IgA can identify athletes at risk of URS. Therapeutic interventions are limited by the uncertainty of the underlying cause of inflammation. Topical anti-inflammatory sprays can be beneficial for some athletes. Dietary supplementation with bovine colostrum, probiotics and selected antioxidants can reduce the incidence or severity of URS in some athletes. Preliminary studies on athletes prone to URS indicate a genetic predisposition to a pro-inflammatory response and a dysregulated anti-inflammatory cytokine response to

intense exercise as a possible mechanism of respiratory inflammation. This review focuses on respiratory infections and inflammation in elite/professional athletes.

Gleeson, M. Immunological aspects of sport nutrition. Immunol.Cell Biol. 2016; 94(2):117-123.

ABSTRACT: Prolonged bouts of exercise and heavy training regimens are associated with depression of immune system functions that can increase the risk of picking up opportunistic infections such as the common cold and influenza. Some common sport nutrition practices including high-carbohydrate diets and carbohydrate ingestion during exercise, training with low-glycogen stores, intentional dieting for weight loss, ingestion of high-dose antioxidant supplements and protein ingestion post exercise may influence immune system status in athletes. In order to maintain robust immunity, athletes need to consume a well-balanced diet that is sufficient to meet their requirements for energy, carbohydrate, protein and micronutrients. Dietary deficiencies of protein and specific micronutrients are well known to be potential causes of immune dysfunction and an adequate intake of some essential minerals including iron and zinc and the vitamins A, D, E, B6 and B12 are important to maintain a healthy immune function. Vitamin D may be a particular concern as recent studies have emphasised its importance in limiting infection episode incidence and duration in both the general population and in athletes and many individuals exhibit inadequate vitamin D status during the winter months. There is only limited evidence that individual amino acids, beta-glucans, herbal extracts and zinc are capable of boosting immunity or reducing infection risk in athletes. The ingestion of carbohydrate during exercise and daily consumption of probiotics, vitamin D3, bovine colostrum and plant polyphenol containing supplements or foodstuffs currently offer the best chance of success, particularly for those individuals who are prone to illness.

Gloor, G. B. and Reid, G. Compositional analysis: a valid approach to analyze microbiome high-throughput sequencing data. Can.J.Microbiol. 2016; 62(8):692-703.

ABSTRACT: A workshop held at the 2015 annual meeting of the Canadian Society of Microbiologists highlighted compositional data analysis methods and the importance of exploratory data analysis for the analysis of microbiome data sets generated by high-throughput DNA sequencing. A summary of the content of that workshop, a review of new methods of analysis, and information on the importance of careful analyses are presented herein. The workshop focussed on explaining the rationale behind the use of compositional data analysis, and a demonstration of these methods for the examination of 2 microbiome data sets. A clear understanding of bioinformatics methodologies and the type of data being analyzed is essential, given the growing number of studies uncovering the critical role of the microbiome in health and disease and the need to understand alterations to its composition and function following intervention with fecal transplant, probiotics, diet, and pharmaceutical agents.

Gohel, M. K., Prajapati, J. B., Mudgal, S. V., Pandya, H. V., Singh, U. S., Trivedi, S. S., Phatak, A. G., and Patel, R. M. Effect of Probiotic Dietary Intervention on Calcium and Haematological Parameters in Geriatrics. J.Clin.Diagn.Res. 2016; 10(4):LC05-LC09.

ABSTRACT: INTRODUCTION: Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host. Sufficient calcium intake has been reported to support bone growth and prevent bone loss during the ageing

process. AIM: To determine the effect of Lactobacillus helveticus MTCC 5463 probiotic dietary intervention on serum calcium & haematological parameters in geriatric population. MATERIALS AND METHODS: Healthy volunteers with age ranging from 64-74 years were recruited from the nearby residential areas in and around Anand, Gujarat. Study duration was from 2012 to 2015. Of the 112 subjects initially enrolled in the trial, 36 withdrew before the intervention because of not matching with criterias. Of the 76 participants, 5 subjects (4%) under test group and 12 subjects (11%) under placebo left the study. We had 59 subjects who successfully completed a double blind cross over trial. Probiotic fermented milk products (in form of "Lassi") was prepared by supplementing toned milk with honey and fermenting with probiotic Lactobacillus helveticus MTCC 5463 and Streptococcus thermophilus MTCC 5460. The final product had at least 10(8) CFU/ml of viable Lactobacillus helveticus MTCC 5463 at the time of feeding. During feeding period, 200 ml of fermented product containing the test strain to one group and a similar product but without the test strain as placebo were fed regularly at the time of breakfast in morning for 4 weeks. Subjects of each group were given a washout period of 4 weeks before they were crossed over and included to the other group. The study was approved by institutional ethics committee. RESULTS: The socio-demographic and clinical profiles were similar at baseline. The mean (SD) calcium level improved significantly in test {9.36 (0.45) vs 8.45 (0.61), p<0.001}. No significant effect was observed with respect to haemoglobin & haematological parameters. CONCLUSION: The well-documented probiotic Lactobacillus helveticus MTCC 5463 confirmed increase in serum calcium level but no effect on haematological parameters when administered to geriatrics.

Goli, Y. D. and Moniri, R. Efficacy of probiotics as an adjuvant agent in eradication of Helicobacter pylori infection and associated side effects. Benef.Microbes. 5-31-2016; 1-10.

ABSTRACT: The intestinal tract is a host to various types of bacteria that are essential to health. Interactions between intestinal bacteria, i.e. the normal microbiota of the host's intestine, have been a subject of intensive research, as they may influence disease cycles. Recent studies of selected probiotic species and their therapeutic benefits have suggested a potential efficacy in treatment of several gastrointestinal illnesses, including Helicobacter pylori infection. The increasing evidence from these clinical studies supports the promising role of probiotics in improving the treatment of H. pylori by increasing eradication rates as well as decreasing the adverse effects of current medication therapy. However, many unsolved questions remain which require high quality trials on specific probiotic strains in the future. The main part of this review will focus on the effects of supplementary probiotic products during standard triple H. pylori therapy.

Gong, Y., Li, T., Li, S., Jiang, Z., Yang, Y., Huang, J., Liu, Z., and Sun, H. Achieving High Yield of Lactic Acid for Antimicrobial Characterization in Cephalosporin-Resistant Lactobacillus by the Co-Expression of the Phosphofructokinase and Glucokinase. J.Microbiol.Biotechnol. 6-28-2016; 26(6):1148-1161.

ABSTRACT: Lactobacilli are universally recognized as probiotics that are widely used in the adjuvant treatment of inflammatory diseases, such as vaginitis and enteritis. With the overuse of antibiotics in recent years, the lactobacilli in the human body are killed, which could disrupt the microecological balance in the human body and affect health adversely. In this work, cephalosporin-resistant Lactobacillus casei RL20 was obtained successfully from the feces of healthy volunteers, which possessed a stable genetic set.

However, the shortage of lactic acid (72.0 g/l at 48 h) by fermentation did not meet the requirement for its use in medicine. To increase the production of lactic acid, the functional genes pfk and glk were introduced into the wild strain. A yield of 144.2 g/l lactic acid was obtained in the transgenic L. casei RL20-2 after fermentation for 48 h in 1 L of basic fermentation medium with an initial glucose concentration of 100 g/l and increasing antibacterial activity. These data suggested that L. casei RL20-2 that exhibited a high yield of lactic acid may be a potential probiotic to inhibit the spread of bacterial infectious diseases and may be used for vaginitis therapy.

Gordon, S. Elie Metchnikoff, the Man and the Myth. J.Innate.Immun. 2016; 8(3):223-227.

ABSTRACT: The year 2016 marks the centenary of the death of Elie Metchnikoff, the father of innate immunity and discoverer of the significance of phagocytosis in development, homeostasis and disease. Through a series of intravital experiments on invertebrates and vertebrates, he described the role of specialised phagocytic cells, macrophages and microphages, subsequently renamed neutrophils and polymorphonuclear leucocytes, in the host response to injury, inflammation, infection and tissue repair. As a vigorous proponent of cellular immunity, he championed its importance versus humoral immunity in the so-called antibody wars. By 1908, when the Nobel Prize was awarded to Elie Metchnikoff and Paul Ehrlich, this debate was not yet resolved. Even earlier, Metchnikoff had turned his research interests to the process of ageing and the possible link to intestinal auto-intoxication, giving rise to the current interest in the microbiome of the gut and the use of probiotics to promote health and longevity. During the past century, Metchnikoff's reputation has waxed and waned, as lymphocyte heterogeneity, specificity and memory began to dominate the field of adaptive immunity, yet his benign visage continues to provide an iconic presence for specialists in innate immunology, whose studies have made a striking comeback in the past decade. In this review, I shall consider the nature of his studies and the person as well as the legendary description of his Eureka experience in Messina in 1882, a story loved by students and investigators alike, that marked, in his own words, his transformation from zoologist to pathologist.

Gorska, S., Buda, B., Brzozowska, E., Schwarzer, M., Srutkova, D., Kozakova, H., and Gamian, A. Identification of Lactobacillus proteins with different recognition patterns between immune rabbit sera and nonimmune mice or human sera. BMC.Microbiol. 2016; 16:17

ABSTRACT: BACKGROUND: The genus Lactobacillus belongs to a large heterogeneous group of low G + C Gram-positive anaerobic bacteria, which are frequently used as probiotics. The health-beneficial effects, in particular the immunomodulation effect, of probiotics depend on the strain and dose used. Strain variations may be related to diversity of the cell surface architecture of bacteria and the ability to express specific antigens or secrete compounds. The use of Lactobacillus as probiotic requires a comprehensive understanding of its effect on host immune system. To evaluate the potential immunoreactive properties of proteins isolated from four Lactobacillus strains: L. johnsonii 142 and L. johnsonii 151, L. rhamnosus LOCK 0900 and L. casei LOCK 0919, the polyclonal sera obtained from mouse and human have been tested as well as with sera from rabbits immunized with whole lactobacilli cells. RESULTS: The reactivity of isolated proteins detected by SDS-PAGE and Western blotting was heterogeneous and varied between different serum samples. The proteins with the highest immunoreactivity were isolated, purified and sequenced, in particular the fractions were identified as

phosphoglycerate kinase (L. johnsonii 142), glyceraldehyde 3-phosphate dehydrogenase (L. johnosnii 142, L. rhamnosus LOCK 0900), hypothetic protein JDM1_1307 (L. johnsonii 151) and fructose/tagatose-bisphosphate-aldolase (L. casei LOCK 0919). CONCLUSION: The different prevalence of reactions against tested antigens in rabbit, mouse and human sera may indicate significant differences in immune system and commensal cross-talk in these groups. The identification of immunoreactive lactobacilli proteins opens the possibility to use them as an antigens for development of vaccines.

Gracia, M. I., Millan, C., Sanchez, J., Guyard-Nicodeme, M., Mayot, J., Carre, Y., Csorbai, A., Chemaly, M., and Medel, P. Efficacy of feed additives against Campylobacter in live broilers during the entire rearing period: Part B. Poult.Sci. 2016; 95(4):886-892.

ABSTRACT: A total of 636 day-of-hatch Ross 308 broilers chicks were used in 4 independent trials carried out to screen the effect of 12 feed additives on reducing cecal colonization of Campylobacterin broilers. The tested additives were probiotics based on B. subtilis and S. cerevisae, a garlic extract, a blend of herbal substances and essential oils, two different combinations of essential oils and organic acids (OA), two mixtures of flavoring compounds, medium chain fatty acids (MCFA), monoglycerides (MG) of MCFA and MG-MCFA+OA. At 14 days of age, all the birds were orally infected with 0.1 mL of a bacterial suspension of C. jejuni ST-45 diluted at 10(5) cfu/mL in tryptone salt broth. In each trial, there was a positive control group and 2 (Trials 1 and 2) or 4 (Trials 3 and 4) additional treatment groups supplemented with additives, which were added to feed or water only to the finisher (21 to 42 d) diet (Trials 1 and 2) or to the starter (0 to 21 d) and finisher diets (Trials 3 and 4). Feed and water were available ad libitum. On days 35 and 42 of age in Trials 1 and 2, and on days 21, 35 and 42 of age in Trials 3 and 4, 10 (Trials 1 and 2) or 12 birds (Trials 3 and 4) per group were euthanized for cecal sampling. In Trial 1, birds fed with MCFA and MG-MCFA had a significant ($P<0.05$) reduction in cecal Campylobacter colonization compared to control at 35 d, but only the group treated with MG-MCFA maintained the reduction at 42 d. In Trials 2 to 4, no significant differences ($P>0.05$) in cecal Campylobacter counts were found between the treated and control animals. In conclusion, although none of the treatments were able to completely prevent the colonization of chickens with C. jejuni, MCFA and MG-MCFAs could reduce the pathogen counts when supplemented from 21 days onwards.

Grady, N. G., Petrof, E. O., and Claud, E. C. Microbial therapeutic interventions. Semin.Fetal Neonatal Med. 4-25-2016;

ABSTRACT: The microbiome comprises all the microbes living in and on the human body. Human cells are greatly outnumbered by bacterial cells; thus human health depends on the health of the microbial ecosystem. For the immature preterm infant, the microbiome also influences intestinal and immune system development. This has implications for short term morbidities such as neonatal necrotizing enterocolitis and sepsis, but also long term health outcomes. Optimization of the preterm infant microbiome is a growing topic of interest. The microbial world is not one of good versus evil, but rather one of community; thus optimization includes not only minimizing pathogens, but also enhancing beneficial organisms. Options for optimization include judicious antibiotic use, administration of supplements such as prebiotics or probiotics, and transfaunation procedures such as fecal microbial transplant or microbial ecosystem therapeutics. Potential for benefit as well as risk for each of these options will be discussed.

Grant, M. C. and Baker, J. S. An Overview of the Effect of Probiotics and Exercise on Mood and Associated Health Conditions. Crit Rev.Food Sci.Nutr. 5-31-2016; 0

ABSTRACT: The present paper provides a review of the current knowledge relating to the health benefits of probiotics, specially focused on the effects they may have together with physical exercise on mood disorders and related chronic medical conditions. With both these conditions being a substantial contributor to the global disease burden any alternative therapy must be considered. Probiotics influence the gut microbiota through a complex network of events which can influence mechanisms leading to development of mood disorders such as depression and anxiety. Similarly, through a complex interaction between psychological and neurobiological mechanisms, exercise has been found to play a key role in mood enhancement.

Grazul, H., Kanda, L. L., and Gondek, D. Impact of probiotic supplements on microbiome diversity following antibiotic treatment of mice. Gut Microbes. 3-3-2016; 7(2):101-114.

ABSTRACT: Shifts in microbial populations of the intestinal tract have been associated with a multitude of nutritional, autoimmune, and infectious diseases. The limited diversity following antibiotic treatments creates a window for opportunistic pathogens, diarrhea, and inflammation as the microbiome repopulates. Depending on the antibiotics used, microbial diversity can take weeks to months to recover. To alleviate this loss of diversity in the intestinal microbiota, supplementation with probiotics has become increasingly popular. However, our understanding of the purported health benefits of these probiotic bacteria and their ability to shape the microbiome is significantly lacking. This study examined the impact of probiotics concurrent with antibiotic treatment or during the recovery phase following antibiotic treatment of mice. We found that probiotics did not appear to colonize the intestine themselves or shift the overall diversity of the intestinal microbiota. However, the probiotic supplementation did significantly change the types of bacteria which were present. In particular, during the recovery phase the probiotic caused a suppression of Enterobacteriaceae outgrowth (Shigella and Escherichia) while promoting a blooming of Firmicutes, particularly from the Anaerotruncus genus. These results indicate that probiotics have a significant capacity to remodel the microbiome of an individual recovering from antibiotic therapy.

Grimm, V. and Riedel, C. U. Manipulation of the Microbiota Using Probiotics. Adv.Exp.Med.Biol. 2016; 902:109-117.

ABSTRACT: A number of diseases are associated with alterations in the composition of the microbiota of various niches of the human body. Although, in most cases, it is unclear if these alterations are the cause or the consequence of disease, they provide a rationale for therapeutic or prophylactic manipulation of a dysbiotic microbiota. Approaches to manipulate the microbiome include administration of either live bacteria, which are underrepresented in the diseased individual, substances that aim at increasing the populations of these bacteria, or a combination of the two. This chapter summarizes the available data in therapeutic manipulation of a various diseased states including irritable bowel syndrome, inflammatory bowel disease, necrotizing enterocolitis, atopic and allergic diseases, and antibiotic-associated and infectious diarrhoea.

Grimshaw, K. E., Bryant, T., Oliver, E. M., Martin, J., Maskell, J., Kemp, T., Clare Mills, E. N., Foote, K. D., Margetts, B. M., Beyer, K., and Roberts, G. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. Clin.Transl.Allergy. 2015; 6:1

ABSTRACT: BACKGROUND: The prevalence of food hypersensitivity in the UK is still largely open to debate. Additionally its pathogenesis is also unclear although it is known that there are differing phenotypes. Determining its prevalence, along with identifying those factors associated with its development will help to assess its clinical importance within the national setting and also add to the debate on appropriate prevention strategies. METHODS: A population based birth cohort study conducted in Hampshire, UK as part of the EuroPrevall birth cohort study. 1140 infants were recruited with 823 being followed up until 2 years of age. Infants with suspected food reactions were assessed including specific IgE measurement and skin prick testing. Diagnosis of food hypersensitivity was by positive double-blind, placebo-controlled food challenge (DBPCFC) where symptoms up to 48 h after the end of the food challenge were considered indicative of a food hypersensitivity. Factors associated with food hypersensitivity and its two phenotypes of IgE-mediated and non-IgE-mediated disease were modelled in a multivariable logistic regression analysis. RESULTS: Cumulative incidence of food hypersensitivity by 2 years of age was 5.0 %. The cumulative incidence for individual food allergens were hens' egg 2.7 % (1.6-3.8); cows' milk 2.4 % (1.4-3.5); peanut 0.7 % (0.1-1.3); soy 0.4 % (0.0-0.8); wheat 0.2 % (0.0-0.5) and 0.1 % (0.0-0.32) for fish. The cumulative incidence of IgE-mediated food allergy was 2.6 % with 2.1 % reacting to hens' egg. For non-IgE-mediated food allergy the cumulative incidence was 2.4 % (cows' milk 1.7 %). Predictors for any food hypersensitivity were wheeze, maternal atopy, increasing gestational age, age at first solid food introduction and mean healthy dietary pattern score. Predictors for IgE mediated allergy were eczema, rhinitis and healthy dietary pattern score whereas for non-IgE-mediated food allergy the predictors were dog in the home, healthy dietary pattern score, maternal consumption of probiotics during breastfeeding and age at first solid food introduction. CONCLUSIONS: Just under half the infants with confirmed food hypersensitivity had no demonstrable IgE. In an exploratory analysis, risk factors for this phenotype of food hypersensitivity differed from those for IgE-mediated food allergy except for a healthy infant diet which was associated with less risk for both phenotypes.

Grotkjaer, T., tzon-Tilia, M., D'Alvise, P., Dourala, N., Nielsen, K. F., and Gram, L. Isolation of TDA-producing Phaeobacter strains from sea bass larval rearing units and their probiotic effect against pathogenic Vibrio spp. in Artemia cultures. Syst.Appl.Microbiol. 2016; 39(3):180-188.

ABSTRACT: Fish-pathogenic Vibrio can cause large-scale crashes in marine larval rearing units and, since the use of antibiotics can result in bacterial antibiotic resistance, new strategies for disease prevention are needed. Roseobacter-clade bacteria from turbot larval rearing facilities can antagonize Vibrio anguillarum and reduce mortality in V. anguillarum-infected cod and turbot larvae. In this study, it was demonstrated that antagonistic Roseobacter-clade bacteria could be isolated from sea bass larval rearing units. In addition, it was shown that they not only antagonized V. anguillarum but also V. harveyi, which is the major bacterial pathogen in crustaceans and Mediterranean sea bass larvae cultures. Concomitantly, they significantly improved survival of V. harveyi-infected brine shrimp. 16S rRNA gene sequence homology identified the antagonists as Phaeobacter sp., and in silico DNA-DNA hybridization indicated that they could belong to a new species. The genomes contained genes involved in synthesis of the antibacterial compound tropodithietic acid (TDA), and its production was confirmed by

UHPLC-TOFMS. The new Phaeobacter colonized live feed (Artemia) cultures and reduced Vibrio counts significantly, since they reached only 10(4)CFUmL(-1), as opposed to 10(8)CFUmL(-1) in non-Phaeobacter treated controls. Survival of V. anguillarum-challenged Artemia nauplii was enhanced by the presence of wild type Phaeobacter compared to challenged control cultures (89+/-1.0% vs 8+/-3.2%). In conclusion, TDA-producing Phaeobacter isolated from Mediterranean marine larviculture are promising probiotic bacteria against pathogenic Vibrio in crustacean live-feed cultures for marine fish larvae.

Gruner, D., Paris, S., and Schwendicke, F. Probiotics for managing caries and periodontitis: Systematic review and meta-analysis. J.Dent. 2016; 48:16-25.

ABSTRACT: OBJECTIVES: Probiotics might be beneficial to prevent or treat caries, gingivitis or periodontitis. We aimed to appraise trials assessing probiotics for managing caries and periodontal disease. DATA: We included randomized controlled trials comparing the efficacy of probiotics versus (placebo) control with regards to Streptococcus mutans [SM], lactobacilli [LB], periodontal pathogens numbers, gingivitis, oral hygiene, caries incidence/experience increment, or periodontitis. Meta-analysis and trial-sequential-analysis were performed. SOURCES: Three electronic databases (Medline, Embase, Central) were screened. STUDY SELECTION: 50 studies (3247 participants) were included. Studies were mainly performed in children and used lactobacilli (45); bifidobacteria (12) or other genus (3). Probiotics significantly increased the chance of reducing SM (OR: 2.20, 95% CI: 1.23/3.92) or LB (OR: 2.84; 1.34/6.03)<10(4)CFU/ml. Such reduction was confirmed for SM counts (standardized mean differences: -1.18, 95% CI: -1.64/-0.72), but not LB (SMD: 0.33; 0.15/0.52). For periodontal pathogens, no significant difference was found. Probiotics significantly reduced bleeding-on-probing (SMD: -1.15; -1.68/-0.62) and gingival index (SMD: -0.86; -1.52/-0.20), but not plaque index (SMD: -0.34; -0.89/0.21). Caries incidence was not significantly reduced (OR: 0.60; 0.35/1.04), neither was caries experience (SMD: -0.26; -0.55/0.03) or CAL (SMD: -0.46; -0.84/0.08). In contrast, probing-pocket depths (SMD: -0.86; -1.55/-0.17) were significantly reduced. Data was quantitatively insufficient for conclusive findings, and risk of bias was high. CONCLUSION: Current evidence is insufficient for recommending probiotics for managing dental caries, but supportive towards managing gingivitis or periodontitis. Future studies should only record bacterial numbers alongside accepted disease markers or indicators. CLINICAL SIGNIFICANCE: Probiotic therapy could be used for managing periodontal diseases. For caries, further studies should ascertain both efficacy and safety.

Gu, S., Chen, Y., Zhang, X., Lu, H., Lv, T., Shen, P., Lv, L., Zheng, B., Jiang, X., and Li, L. Identification of key taxa that favor intestinal colonization of Clostridium difficile in an adult Chinese population. Microbes.Infect. 2016; 18(1):30-38.

ABSTRACT: Fecal microbial transplantation provides a high curative rate for recurrent Clostridium difficile infection (CDI). However, limitations associated with FMT drive the need to identify key taxa for selective probiotic therapy for prevention, treatment and cure of human CDI. CDI-associated changes in gut microbiota were investigated in adult patients in the Western countries and among infant population in China. However, there has been no such study involving adult patients in China. Therefore, using high throughput sequencing of the 16S ribosomal RNA V3 region and real-time quantitative polymerase chain reaction, we identified CDI-associated key taxa by comparing the fecal microbiota composition of 15 adult patients with CDI with those of 18 individuals

with C. difficile-negative nosocomial diarrhea (CDN) and 25 healthy control subjects. Reduced fecal bacterial diversity and dramatic shifts of intestinal microbial composition in CDI and CDN groups were observed compared with healthy controls. Putative butyrate-producing anaerobic bacteria were significantly depleted whereas endotoxin-producing opportunistic pathogens and lactate-producing phylotypes increased dramatically in patients with CDI compared with healthy controls. Further screening of specific microbes causing diarrheal diseases and resistance against CDI is necessary.

Guardiola, F. A., Porcino, C., Cerezuela, R., Cuesta, A., Faggio, C., and Esteban, M. A. Impact of date palm fruits extracts and probiotic enriched diet on antioxidant status, innate immune response and immune-related gene expression of European seabass (Dicentrarchus labrax). Fish.Shellfish.Immunol. 2016; 52:298-308.

ABSTRACT: The application of additives in the diet as plants or extracts of plants as natural and innocuous compounds has potential in aquaculture as an alternative to antibiotics and immunoprophylactics. The aim of the current study was to evaluate the potential effects of dietary supplementation of date palm fruit extracts alone or in combination with Pdp11 probiotic on serum antioxidant status, on the humoral and cellular innate immune status, as well as, on the expression levels of some immune-related genes in head-kidney and gut of European sea bass (Dicentrarchus labrax) after 2 and 4 weeks of administration. This study showed for the first time in European sea bass an immunostimulation in several of the parameters evaluated in fish fed with date palm fruits extracts enriched diet or fed with this substance in combination with Pdp 11 probiotic, mainly after 4 weeks of treatment. In the same way, dietary supplementation of mixture diet has positive effects on the expression levels of immune-related genes, chiefly in head-kidney of Dicentrarchus labrax. Therefore, the combination of both could be considered of great interest as potential additives for farmed fish.

Guarino, A. and Canani, R. B. Probiotics in Childhood Diseases: From Basic Science to Guidelines in 20 Years of Research and Development. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S1-S2.

No abstract currently available.

Gueimonde, L., Vesterlund, S., Garcia-Pola, M. J., Gueimonde, M., Soderling, E., and Salminen, S. Supplementation of xylitol-containing chewing gum with probiotics: a double blind, randomised pilot study focusing on saliva flow and saliva properties. Food Funct. 2016; 7(3):1601-1609.

ABSTRACT: The aim of this study was to investigate the impact of daily chewing, for 12 weeks, of 2 different probiotic gums compared with placebo on saliva flow rate, saliva IgA levels and saliva pH. The intervention study included 54 adult volunteers with hyposalivation in a double-blind, randomised and placebo-controlled design with three parallel groups. Volunteers were randomly assigned to 3 different groups: subjects in group A (n = 19) were given placebo chewing gum, group B (n = 17) received Bifidobacterium animalis ssp. lactis Bb12 (ATCC 27536) and group C (n = 18) received Lactobacillus rhamnosus LGG (ATCC 53103), Bifidobacterium longum 46 (DSM 14583) and Bifidobacterium longum 2C (DSM 14579) gums, during 3 months. Two volunteers from group B left the study for personal reasons leaving 19, 15 and 18 volunteers, respectively,

for analyses. Clinical examinations, personal interviews, sialometries and saliva sampling were conducted at baseline and after 1, 2, 3 and 4 months. No statistically significant differences were found between probiotic and placebo groups for any of the parameters analysed. No side effects of probiotic or placebo chewing gums were observed. Chewing gum, with and without probiotics, had a positive impact on salivary flow rate and saliva pH and IgA levels.

Guo, S., Gillingham, T., Guo, Y., Meng, D., Zhu, W., Walker, W. A., and Ganguli, K. Secretions of Bifiodobacterium Infantis and Lactobacillus Acidophilus Protect Intestinal Epithelial Barrier Function. J.Pediatr.Gastroenterol.Nutr. 6-17-2016;

ABSTRACT: OBJECTIVES: The secreted metabolites of probiotics are cytoprotective to intestinal epithelium and have been shown to attenuate inflammation and reduce gut permeability. This study was designed to determine the protective effects of probiotic conditioned media (PCM) from Bifidobacterium infantis (BCM) and Lactobacillus acidophilus (LCM) on IL-1beta-induced intestinal barrier compromise. METHODS: The epithelial barrier was determined by measuring the transepithelial electrical resistance (TER) across a Caco-2 cell monolayer using a Transwell model. The paracellular permeability was determined by fluorescein isothiocyanate-labeled dextran flux. The expression of tight junction proteins (TJs) and NF-kappaB p65 were determined using Western blot and the distribution of NF-kappaB p65 was determined by immunofluorescence staining. RESULTS: BCM and LCM induced a dose-dependent increase in Caco-2 TER after 4 and 24 hours of incubation ($p < 0.05$). The maximal increase of Caco-2 TER occurred at 4 hours of treatment with a PCM concentration of 15%. Preincubation with BCM and LCM for 4 hours significantly prevented the decrease of Caco-2 TER induced by 24 hours of stimulation with 10 ng/mL IL-1beta. BCM and LCM decreased paracellular permeability in both stimulated and unstimulated Caco-2 monolayers ($p < 0.05$). IL-1beta stimulation decreased occludin expression and increased claudin-1 expression in Caco-2 cells ($p < 0.05$), which was prevented in cells treated with BCM or LCM. The changes of claudin-1 expression in H4 cells were similar to Caco-2 cells in response to PCM treatment and IL-1beta stimulation, however a similar response in occludin was not demonstrated. The IL-1beta-induced nuclear translocation of NF-kappaB p65 in Caco-2 cells was prevented by pretreatment with both PCM. CONCLUSIONS: BCM and LCM protected the intestinal barrier against IL-1beta stimulation by normalizing the protein expression of occludin and claudin-1 and preventing IL-1beta-induced NF-kappaB activation in Caco-2 cells, which may be partly responsible for the preservation of intestinal permeability.

Guo, X., Chen, D. D., Peng, K. S., Cui, Z. W., Zhang, X. J., Li, S., and Zhang, Y. A. Identification and characterization of Bacillus subtilis from grass carp (Ctenopharynodon idellus) for use as probiotic additives in aquatic feed. Fish.Shellfish.Immunol. 2016; 52:74-84.

ABSTRACT: Bacillus subtilis is widely used as probiotic species in aquaculture for water quality control, growth promoting, or immunity enhancing. The aim of this study is to find novel B. subtilis strains from fish as potential probiotics for aquaculture. Eleven B. subtilis isolates derived from the intestinal tract of grass carp were identified by gene sequencing and biochemical tests. These isolates were classified into 4 groups, and the representatives (GC-5, GC-6, GC-21 and GC-22) of each group were further investigated for antibiotic susceptibility, sporulation rate, biofilm formation, activity against pathogenic bacteria, resistance to stress conditions of intestinal tract (high percentage

of bile and low pH) and high temperature, which are important for probiotics to be used as feed additives. Additionally, the adhesion properties of the 4 characterized strains were assessed using Caco-2 cell and gut mucus models. The results showed that the 4 strains differed in their capacities to adhere to intestinal epithelial cells and mucus. Furthermore, the strains GC-21 and GC-22 up-regulated the expression levels of IL-10 and TGF-beta but down-regulated IL-1beta, suggesting their potential anti-inflammatory abilities. Based on physiological properties of the 4 characterized B. subtilis strains, one or more strains may have potential to be used as probiotics in aquaculture.

Gupta, A. and Paria, A. Etiology and medical management of NEC. Early Hum.Dev. 2016; 97:17-23.

ABSTRACT: Necrotising enterocolitis (NEC) is a serious infection of the bowel that predominantly affects preterm infants and is a leading cause for mortality and morbidity in preterm infants. It involves a spectrum of pathology including widespread inflammation of the intestinal mucosa, invasion of the immature gut by enteric gas forming bacteria, dissection of the gut wall and portal veins by this gas, often culminating in ischemic necrosis of the intestine. This article provides an overview of the incidence, etio-pathological risk factors, preventive strategies and medical management of NEC.

Guthmann, F., rlettaz Mieth, R. P., Bucher, H. U., and Buhrer, C. Short courses of dual-strain probiotics appear to be effective in reducing necrotising enterocolitis. Acta Paediatr. 2016; 105(3):255-259.

ABSTRACT: AIM: Prophylactic probiotics to reduce necrotising enterocolitis (NEC) are mostly given for at least 28 days or until discharge. We describe the effects of a shorter duration dosing strategy. METHODS: Retrospective cohort study of neonates (birthweight 400-1500 g) in three neonatal intensive care units in Switzerland and Germany that embarked on probiotic prophylaxis given for 10 or 14 days, employing a fixed combination (Lactobacillus acidophilus plus Bifidobacterium infantis, each 10(9) CFU/day) licensed as a drug in Switzerland. Probiotics were initiated upon discontinuation of antibiotics, or on day 1-3 in infants without antibiotics. Repeat probiotic courses were given whenever antibiotics had been instituted and were discontinued. RESULTS: Birthweight and gestational age were similar in the two 24-month pre- and postimplementation cohorts. NEC rates fell from 33 of 633 (5.2%) to 8 of 591 infants alive at three days (1.4%; risk ratio (RR) 0.26, 95% confidence interval (CI) 0.12-0.55). The drop in NEC was significant both for infants of 400-999 g (6.4% to 2.5%) and 1000-1500 g birthweight (4.4% to 0.6%). Mortality was 5.1% (32/633) without, as opposed to 3.5% (21/591) with probiotics, respectively (RR 0.69, 95% CI 0.41-1.19). CONCLUSION: Short courses of a dual-strain probiotics appear to be effective in reducing NEC.

Gutierrez, S., Martinez-Blanco, H., Rodriguez-Aparicio, L. B., and Ferrero, M. A. Effect of fermented broth from lactic acid bacteria on pathogenic bacteria proliferation. J.Dairy Sci. 2016; 99(4):2654-2665.

ABSTRACT: In this study, the effect that 5 fermented broths of lactic acid bacteria (LAB) strains have on the viability or proliferation and adhesion of 7 potentially pathogenic microorganisms was tested. The fermented broth from Lactococcus lactis C660 had a growth inhibitory effect on Escherichia coli K92 that reached of 31%, 19% to

Pseudomonas fluorescens, and 76% to Staphylococcus epidermidis. The growth of Staph. epidermidis was negatively affected to 90% by Lc. lactis 11454 broth, whereas the growth of P. fluorescens (25%) and both species of Staphylococcus (35% to Staphylococcus aureus and 76% to Staph. epidermidis) were inhibited when they were incubated in the presence of Lactobacillus casei 393 broth. Finally, the fermented broth of Lactobacillus rhamnosus showed an inhibitory effect on growth of E. coli K92, Listeria innocua, and Staph. epidermidis reached values of 12, 28, and 76%, respectively. Staphylococcus epidermidis was the most affected strain because the effect was detected from the early stages of growth and it was completely abolished. The results of bacterial adhesion revealed that broths from Lc. lactis strains, Lactobacillus paracasei, and Lb. rhamnosus caused a loss of E. coli K92 adhesion. Bacillus cereus showed a decreased of adhesion in the presence of the broths of Lc. lactis strains and Lb. paracasei. Listeria innocua adhesion inhibition was observed in the presence of Lb. paracasei broth, and the greatest inhibitory effect was registered when this pathogenic bacterium was incubated in presence of Lc. lactis 11454 broth. With respect to the 2 Pseudomonas, we observed a slight adhesion inhibition showed by Lactobacillus rhamnosus broth against Pseudomonas putida. These results confirm that the effect caused by the different LAB assayed is also broth- and species-specific and reveal that the broth from LAB tested can be used as functional bioactive compounds to regulate the adhesion and biofilm synthesis and ultimately lead to preventing food and clinical contamination and colonization of E. coli K92, B. cereus, and Ls. innocua.

Guvenc, I. A., Muluk, N. B., Mutlu, F. S., Eski, E., Altintoprak, N., Oktemer, T., and Cingi, C. Do probiotics have a role in the treatment of allergic rhinitis?: A comprehensive systematic review and meta analysis. Am.J.Rhinol.Allergy. 7-20-2016;

ABSTRACT: OBJECTIVE: To investigate clinical evidence for the efficacy of probiotics in the treatment of allergic rhinitis (AR). METHODS: A systematic search was conducted to review the results of all randomized, double-blind, placebo-controlled trials by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Primary outcome measurements were total nasal and ocular symptom scores (SS) and quality of life (QoL) questionnaires. Secondary outcome measurements were individual nasal SS and immunologic parameters. RESULTS: Twenty-two randomized, double-blind, placebo-controlled studies were included. Seventeen trials showed significant benefit of probiotics clinically, whereas eight trials showed significant improvement in immunologic parameters compared with placebo. All five studies with Lactobacillus paracasei (LP) strains demonstrated clinically significant improvements compared with placebo. Probiotics showed significant reduction in nasal and ocular SS (standardized mean difference [SMD], -1.23, $p < 0.001$; and SMD, -1.84, $p < 0.001$; respectively), total, nasal, and ocular QoL scores compared with placebo (SMD, -1.84, $p < 0.001$; SMD, -2.30, $p = 0.006$; and SMD, -3.11, $p = 0.005$; respectively). Although heterogeneity was high, in subgroup analysis, SMD for total nasal and ocular symptoms with patients with seasonal AR and for nasal QoL scores for studies with LP-33 strain were significant and homogenous. Scores of nasal blockage, rhinorrhea, and nasal itching were significantly lower in the probiotic group compared with placebo. The meta-analysis studies SS the Japanese guidelines revealed a significant, homogenous SMD score of -0.34 for individual nasal SS, above the minimal important clinical difference value of 0.3. The T-helper 1 to T-helper 2 ratio was significantly lower in the probiotic group compared with placebo (SMD,-0.78; $p = 0.045$). CONCLUSION: Despite high variability among the studies, synthesis of available data provided significant evidence of beneficial clinical and immunologic effects of probiotics in the treatment of AR, especially with seasonal AR and

LP-33 strains. With the rising pool of studies, the most promising strains in specific allergies can be revealed and adjuvant therapy with probiotics can be recommended for the treatment of AR.

Guyard-Nicodeme, M., Keita, A., Quesne, S., Amelot, M., Poezevara, T., Le, Berre B., Sanchez, J., Vesseur, P., Martin, A., Medel, P., and Chemaly, M. Efficacy of feed additives against Campylobacter in live broilers during the entire rearing period. Poult.Sci. 2016; 95(2):298-305.

ABSTRACT: Poultry meat is the major source of human campylobacteriosis, the most frequently reported zoonosis in the EU. The prevalence of Campylobacter colonization in European broiler flocks is 71%. Despite considerable efforts, there is still no effective strategy available to prevent or reduce Campylobacter colonization in broilers. This study tested a wide variety of feed additives to reduce Campylobacter shedding in primary poultry production. Twelve additives containing organic or fatty acids, monoglycerides, plant extracts, prebiotics, or probiotics were tested. For each additive, broilers contaminated with Campylobacter jejuni were fed with an additive free diet (control group) or with a supplemented diet (treated group) and Campylobacter loads compared at three sampling times. No treatment was able to prevent broiler colonization by Campylobacter, and there was a high degree of variation in contamination among the birds. At 14 d of age, eight treatments significantly decreased the colonization level compared to the control group by a maximum of 2 log10 CFU/g. At 35 d of age, three of these treatments still had a significant effect with a maximum reduction of 1.88 log10 CFU/g for a probiotic. At 42 d of age, only one short-chain fatty acid was still significantly efficient with a mean reduction over 2 log10 CFU/g. In addition, a probiotic and a prebiotic-like compound significantly decreased the contamination by a maximum of 3 log10 CFU/g, only at the 42-d sampling period. This study gives promising results regarding the use of feed additives to reduce Campylobacter infection in flocks. Nevertheless, a global approach, combining intervention measures at the different steps of the broiler meat production chain could have a greater impact on the reduction of public health risk.

Ha, E. M. Escherichia coli-Derived Uracil Increases the Antibacterial Activity and Growth Rate of Lactobacillus plantarum. J.Microbiol.Biotechnol. 5-28-2016; 26(5):975-987.

ABSTRACT: Lactobacillus plantarum (L. plantarum) is a representative probiotic. In particular, L. plantarum is the first commensal bacterium to colonize the intestine of infants. For this reason, the initial settlement of L. plantarum can play an important role in determining an infant's health as well as their eventual health status as an adult. In addition, L. plantarum combats pathogenic infections (such as Escherichia coli (E. coli), one of the early pathogenic colonizers in an unhealthy infant gut) by secreting antimicrobial substances. The aim of this research was to determine how L. plantarum combats E. coli infection and why it is a representative probiotic in the intestine. Consequently, this research observed that E. coli releases uracil. L. plantarum specifically recognizes E. coli-derived uracil, which increases the growth rate and production of antimicrobial substance of L. plantarum. In addition, through the inhibitory activity test, this study postulates that the antimicrobial substance is a protein and can be considered a bacteriocin-like substance. Therefore, this research assumes that L. plantarum exerts its antibacterial ability by recognizing E. coli and increasing its growth rate as a result, and

this phenomenon could be one of the reasons for L. plantarum settling in the intestine of infants as a beneficial bacterium.

Ha, H. K., Jeon, N. E., Kim, J. W., Han, K. S., Yun, S. S., Lee, M. R., and Lee, W. J. Physicochemical Characterization and Potential Prebiotic Effect of Whey Protein Isolate/Inulin Nano Complex. Korean J.Food Sci.Anim Resour. 2016; 36(2):267-274.

ABSTRACT: The purposes of this study were to investigate the impacts of concentration levels of whey protein isolate (WPI) and inulin on the formation and physicochemical properties of WPI/inulin nano complexes and to evaluate their potential prebiotic effects. WPI/inulin nano complexes were produced using the internal gelation method. Transmission electron microscopy (TEM) and particle size analyzer were used to assess the morphological and physicochemical characterizations of nano complexes, respectively. The encapsulation efficiency of resveratrol in nano complexes was studied using HPLC while the potential prebiotic effects were investigated by measuring the viability of probiotics. In TEM micrographs, the globular forms of nano complexes in the range of 10 and 100 nm were successfully manufactured. An increase in WPI concentration level from 1 to 3% (w/v) resulted in a significant ($p<0.05$) decrease in the size of nano complexs while inulin concentration level did not affect the size of nano complexes. The polydispersity index of nano complexes was below 0.3 in all cases while the zeta-potential values in the range of -2 and -12 mV were observed. The encapsulation efficiency of resveratrol was significantly ($p<0.05$) increased as WPI and inulin concentration levels were increased from 1 to 3% (w/v). During incubation at 37 for 24 h, WPI/inulin nano complexes exhibited similar viability of probiotics with free inulin and had significantly ($p<0.05$) higher viability than negative control. In conclusions, WPI and inulin concentration levels were key factors affecting the physicochemical properties of WPI/inulin nano complexes and had potential prebiotic effect.

Haahr, T., Ersboll, A. S., Karlsen, M. A., Svare, J., Sneider, K., Hee, L., Weile, L. K., Ziobrowska-Bech, A., Ostergaard, C., Jensen, J. S., Helmig, R. B., and Uldbjerg, N. Treatment of bacterial vaginosis in pregnancy in order to reduce the risk of spontaneous preterm delivery - a clinical recommendation. Acta Obstet.Gynecol.Scand. 2016; 95(8):850-860.

ABSTRACT: INTRODUCTION: Bacterial vaginosis (BV) is characterized by a dysbiosis of the vaginal microbiota with a depletion of Lactobacillus spp. In pregnancy, prevalence's between 7 and 30% have been reported depending on the study population and the definition. BV may be associated with an increased risk of spontaneous preterm delivery (sPTD). However, it is controversial whether or not BV-positive pregnant women will benefit from treatment to reduce the risk of sPTD. We could not identify any good-quality guideline addressing this issue. Consequently we aimed to produce this clinical recommendation based on GRADE. MATERIAL AND METHODS: Systematic literature searches were conducted in the following databases: Guidelines International Network: G-I-N, Medline, Embase, The Cochrane Database of Systematic Reviews, Web of Science and http://www.clinicaltrials.gov from 1999 to 3 October 2014. Hence, nine guidelines, 34 reviews, 18 randomized controlled trials and 12 observational studies were included. RESULTS: The GRADE quality of evidence was consistently low or very low, primarily because none of the risk ratios (RR) for the risk of sPTD at <37 weeks were statistically significant. Concerning treatment with metronidazole, RR was 1.11 (95% CI 0.93-1.34) in low-risk pregnancies and 0.96 (95% CI 0.78-1.18) in high risk pregnancies. Concerning treatment with clindamycin at any gestational age, the RR was 0.87 (95% CI 0.73-1.05).

CONCLUSION: This systematic review gives a strong recommendation against treatment with metronidazole and a weak recommendation against treatment with clindamycin to reduce the sPTD rate in both high-risk and low-risk pregnancies with BV.

Haghshenas, B., Haghshenas, M., Nami, Y., Yari, Khosroushahi A., Abdullah, N., Barzegari, A., Rosli, R., and Hejazi, M. S. Probiotic Assessment of Lactobacillus plantarum 15HN and Enterococcus mundtii 50H Isolated from Traditional Dairies Microbiota. Adv.Pharm.Bull. 2016; 6(1):37-47.

ABSTRACT: PURPOSE: Probiotics are microorganisms, which show beneficial health effects on hosts once consumed in sufficient amounts. Among probiotic bacteria, the bioactive compounds from lactic acid bacteria (LAB) group can be utilized as preservative agents. LAB group can be isolated and characterized from traditional dairy sources. This study aimed to isolate, identify, and biologically characterize probiotic LAB strains from Iranian traditional dairy products. METHODS: A total of 19 LAB strains were identified by sequencing of their 16S rRNA genes. They were examined for adherence to human intestinal Caco-2 cells and tolerance to low pH/high bile salts and simulated in vitro digestion conditions. Moreover, they were evaluated further to assess their ability to prevent the adhesion of Escherichia coli 026 to the intestinal mucosa, inhibitory functions against pathogens, and sensitivity to conventional antibiotics. RESULTS: L. plantarum 15HN and E. mundtii 50H strains displayed >/= 71% survival rates at low pH/high bile salts and >/= 40% survival rates in digestive conditions. Their adherences to Caco-2 cells were 3.2x105 and 2.6x105 CFU mL-1 respectively and high values of anti-adhesion capability were observed (>/=36%). They inhibited the growth of 13 and 11 indicator pathogens respectively. Moreover, they were sensitive or semi-sensitive to seven and three out of eight antibiotics respectively. CONCLUSION: L. plantarum 15HN and E. mundtii 50H, which were isolated from shiraz product, displayed above-average results for all of the criteria. Therefore, they can be introduced as novel candidate probiotics that could be used in the food industry.

Haileselassie, Y., Navis, M., Vu, N., Qazi, K. R., Rethi, B., and Sverremark-Ekstrom, E. Postbiotic Modulation of Retinoic Acid Imprinted Mucosal-like Dendritic Cells by Probiotic Lactobacillus reuteri 17938 In Vitro. Front Immunol. 2016; 7:96

ABSTRACT: Lactobacilli are widely used as probiotics with beneficial effects on infection-associated diarrhea, but also used in clinical trials of e.g., necrotizing enterocolitis and inflammatory bowel diseases. The possibility of using probiotic metabolic products, so-called postbiotics, is desirable as it could prevent possible side effects of live bacteria in individuals with a disturbed gut epithelial barrier. Here, we studied how Lactobacillus reuteri DSM 17938 cell-free supernatant (L. reuteri-CFS) influenced retinoic acid (RA)-driven mucosal-like dendritic cells (DC) and their subsequent effect on T regulatory cells (Treg) in vitro. RA clearly imprinted a mucosal-like DC phenotype with higher IL10 production, increased CD103 and CD1d expression, and a downregulated mRNA expression of several inflammatory-associated genes (NFkappaB1, RELB, and TNF). Treatment with L. reuteri-CFS further influenced the tolerogenic phenotype of RA-DC by downregulating most genes involved in antigen uptake, antigen presentation, and signal transduction as well as several chemokine receptors, while upregulating IL10 production. L. reuteri-CFS also augmented CCR7 expression on RA-DC. In cocultures, RA-DC increased IL10 and FOXP3 expression in Treg, but pre-treatment with L. reuteri-CFS did not further influence the Treg phenotype. In conclusion, L. reuteri-CFS modulates the

phenotype and function of mucosal-like DC, implicating its potential application as postbiotic.

Hakobyan, L., Harutyunyan, K., Harutyunyan, N., Melik-Andreasyan, G., and Trchounian, A. Adhesive Properties and Acid-Forming Activity of Lactobacilli and Streptococci Under Inhibitory Substances, Such as Nitrates. Curr.Microbiol. 2016; 72(6):776-782.

ABSTRACT: One of the main requirements for probiotics is their ability to survive during passage through gastrointestinal tract and to maintain their activity at different adverse conditions. The aim of the study was to look for the strains of lactobacilli and streptococci with high adhesive properties even affected by inhibitory substances, such as nitrates (NO3 (-)). To study the adhesion properties hemagglutination reaction of bacterial cells with red blood cells of different animals and humans was used. The acid formation ability of bacteria was determined by the method of titration after 7 days of incubation in the sterile milk. These properties were investigated at different concentrations of NO3 (-). The high concentration (mostly >/=2.0 %) NO3 (-) inhibited the growth of both lactobacilli and streptococci, but compared with streptococcal cultures lactobacilli, especially Lactobacillus acidophilus Ep 317/402, have shown more stability and higher adhesive properties. In addition, the concentrations of NO3 (-) of 0.5-2.0 % decreased the acid-forming activity of the strains, but even under these conditions they coagulated milk and, in comparison to control, formed low acidity in milk. Thus, the L. acidophilus Ep 317/402 with high adhesive properties has demonstrated a higher activity of NO3 (-) transformation.

Halpern, R. and Coelho, R. Excessive crying in infants. J.Pediatr.(Rio J.). 2016; 92(3 Suppl 1):S40-S45.

ABSTRACT: OBJECTIVE: Review the literature on excessive crying in young infants, also known as infantile colic, and its effects on family dynamics, its pathophysiology, and new treatment interventions. DATA SOURCE: The literature review was carried out in the Medline, PsycINFO, LILACS, SciELO, and Cochrane Library databases, using the terms "excessive crying," and "infantile colic," as well technical books and technical reports on child development, selecting the most relevant articles on the subject, with emphasis on recent literature published in the last five years. SUMMARY OF THE FINDINGS: Excessive crying is a common symptom in the first 3 months of life and leads to approximately 20% of pediatric consultations. Different prevalence rates of excessive crying have been reported, ranging from 14% to approximately 30% in infants up to 3 months of age. There is evidence linking excessive crying early in life with adaptive problems in the preschool period, as well as with early weaning, maternal anxiety and depression, attention deficit hyperactivity disorder, and other behavioral problems. Several pathophysiological mechanisms can explain these symptoms, such as circadian rhythm alterations, central nervous system immaturity, and alterations in the intestinal microbiota. Several treatment alternatives have been described, including behavioral measures, manipulation techniques, use of medication, and acupuncture, with controversial results and effectiveness. CONCLUSION: Excessive crying in the early months is a prevalent symptom; the pediatrician's attention is necessary to understand and adequately manage the problem and offer support to exhausted parents. The prescription of drugs of questionable action and with potential side effects is not a recommended treatment, except in extreme situations. The effectiveness of dietary treatments and use of probiotics still require confirmation. There is incomplete evidence regarding alternative

treatments such as manipulation techniques, acupuncture, and use of the herbal supplements and behavioral interventions.

Hamza, A., Fdhila, K., Zouiten, D., and Masmoudi, A. S. Virgibacillus proomii and Bacillus mojavensis as probiotics in sea bass (Dicentrarchus labrax) larvae: effects on growth performance and digestive enzyme activities. Fish.Physiol Biochem. 2016; 42(2):495-507.

ABSTRACT: This study examined the effects of two probiotics (Virgibacillus proomii and Bacillus mojavensis) on the digestive enzyme activity, survival and growth of Dicentrarchus labrax at various ontogenetic stages in three separate experiments. These probiotics were incorporated as single or mixed into fish feed for a period of 60 days. The growth parameters, proximate composition of whole body, digestive enzymes and gut microbiology were monitored at regular. The increments in length and weight and the survival were significantly higher ($P < 0.05$), and the values of food conversions were significantly lower ($P < 0.05$) in fishes fed the probiotic. The administration of V. proomii and B. mojavensis in diet resulted in an increase ($P > 0.05$) in body ash and protein content and in the specific activity of phosphatase alkaline and amylase in the digestive tract of all the fishes. V. proomii and B. mojavensis persisted in the fish intestine and in the feed in high numbers during the feeding period (group 1: 5.8 x 10(4) CFU/ml, group 2: 9.6 x 10(4) CFU/ml, and group 3: 9.8 x 10(4) CFU/ml day 60). The two probiotics V. proomii and B. mojavensis were adequate for improved growth performance and survival and for healthy gut microenvironment of the host.

Han, C., Ding, Z., Shi, H., Qian, W., Hou, X., and Lin, R. The Role of Probiotics in Lipopolysaccharide-Induced Autophagy in Intestinal Epithelial Cells. Cell Physiol Biochem. 2016; 38(6):2464-2478.

ABSTRACT: BACKGROUND/AIMS: Dysfunction of autophagy has been associated with loss of intestinal homeostasis. Lipopolysaccharide (LPS) from Gram-negative bacteria is known to be a major initiator of intestinal epithelial cell (IEC) autophagy. Although probiotics have been recognized to be involved in many therapeutic properties and participate in host defense responses, the molecular mechanisms by which probiotics exert these positive effects remain unknown. This study assessed the effect of probiotics on LPS-induced physical barrier dysfunction and the underlying mechanism of probiotic action in IECs with a focus on autophagy. METHODS: A LPS-induced autophagic model was established in rat IEC18 cells wherein cells were treated with culture medium supernatants of Bifidobacteria following LPS intervention at indicated times. Autophagosomes in IEC18 cells were visualized by confocal microscopy after transfection with a tandem GFP-mCherry-LC3 construct and also by transmission electron microscopy. Autophagy-associated protein levels were analyzed by western blot and transepithelial electrical resistance (TEER) was measured using an epithelial voltohmmeter. RESULTS: Probiotic treatment could effectively inhibit LPS-induced autophagy, as evidenced by the decreased ratio of microtubule-associated light chain 3 (LC3)-II/LC3-I, fewer autophagic vacuoles, and reduced punctate distribution of GFP-mCherry-LC3. In addition, probiotics prevented chloroquine (CQ) inhibition of autophagic flux and autophagolysosomal fusion as indicated by a failure to recruit LAMP1 and cathepsin D to lysosomes. Interestingly, ATG16L1 knockdown did not inhibit the effect of probiotics on LPS-induced autophagy. Furthermore, the diminished barrier function could be prevented by probiotics. CONCLUSIONS: We provide evidence that autophagy mediation by probiotics may be involved in enteroprotection against LPS-

induced intestinal epithelial toxicity, and could serve as a novel mechanism through which probiotics promote and maintain gut homeostasis.

Han, K., Wang, J., Seo, J. G., and Kim, H. Efficacy of double-coated probiotics for irritable bowel syndrome: a randomized double-blind controlled trial. J.Gastroenterol. 5-13-2016;

ABSTRACT: BACKGROUND: The purpose of this study was to elucidate the effects of a dual-coated probiotic supplement (Duolac Care) on symptoms of diarrhea-predominant irritable bowel syndrome in a randomized double-blind clinical trial. METHODS: Fifty subjects with diarrhea-predominant irritable bowel syndrome were randomly assigned to either the non-coating group or the dual-coating group in order to receive two capsules per day of multi-species probiotics containing 5 billion bacteria per capsule for 4 weeks. Data from an adequate relief questionnaire were used in assessment of primary outcome. Daily records of stool frequencies and the Bristol stool scale, a weekly symptom diary using 100-mm visual analog scale, and Beck depression inventories were collected. Blood tests including blood cell counts, interleukin-10, tumor necrosis factor-alpha and inducible nitric oxide synthase, and regulatory T cells-CD4 + CD25high T cells, CD4 + LAP + T cells and CD25high + LAP + T cells-were analyzed before and after the study. The shift of gut microbiota was investigated using a quantitative real-time polymerase chain reaction assay. RESULTS: Responses to the adequate relief questionnaire indicated significant improvement in overall discomfort in the dual-coating group and the ratio of normal stools to hard or watery stools had a better effect from dual-coated probiotics compared to non-coated probiotics. This may be due to a shift of intestinal microbiota, as our correlation analysis showed significant negative correlation between Bifidobacterium and urgency of defecation. CONCLUSIONS: Our result implies that dual-coating layers of probiotic supplement can be a candidate for treatment of diarrhea-predominant irritable bowel syndrome.

Hannah, W. N., Jr. and Harrison, S. A. Lifestyle and Dietary Interventions in the Management of Nonalcoholic Fatty Liver Disease. Dig.Dis.Sci. 2016; 61(5):1365-1374.

ABSTRACT: NAFLD is the leading cause of chronic liver disease in the Western world with an estimated prevalence of 20-30 %. Lifestyle interventions targeted at weight loss through dietary interventions and exercise are the most effective treatment, but only a minority of patients are able to achieve and sustain the necessary intervention targets. Weight loss of 3-5 % has been associated with a reduction of hepatic steatosis while weight loss of >/=5-7 % has correlated with resolution of NASH in some studies. Greater reductions in weight loss (>/=10 %) may improve hepatic fibrosis. In the absence of weight loss, no specific diet has demonstrated superiority. Physical activity can improve hepatic steatosis and metabolic indices even without weight loss. Diet coupled with exercise can produce significant weight loss and may improve histologic components of the NAFLD activity score. While formal guidelines for diet and exercise in NAFLD are lacking, adherence to diet and exercise recommendations similar to those from the American Diabetes Association for diabetic care seems reasonable. Dietary supplementation with vitamin E in non-diabetics with biopsy-proven NASH has been shown to improve NAFLD activity score. The role for other macronutrients, micronutrients, antioxidants, and probiotics in the treatment of NAFLD remains limited.

Hanson, L., VandeVusse, L., Jerme, M., Abad, C. L., and Safdar, N. Probiotics for Treatment and Prevention of Urogenital Infections in Women: A Systematic Review. J.Midwifery Womens Health. 2016; 61(3):339-355.

ABSTRACT: INTRODUCTION: Probiotics are a complementary and integrative therapy useful in the treatment and prevention of urogenital infections in women. This study extends the work of researchers who systematically investigated the scientific literature on probiotics to prevent or treat urogenital infections. METHODS: A systematic review was conducted to determine the efficacy of probiotics for prevention and/or treatment of urogenital infections in adult women from January 1, 2008, through June 30, 2015. We searched in CINAHL, MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, Dissertations and Theses, and Alt-HealthWatch. After removing duplicates and studies that did not meet inclusion criteria, 20 studies were reviewed. All included at least one species of Lactobacillus probiotic as an intervention for treatment or prevention of urogenital infections. Data extracted included samples, settings, study designs, intervention types, reported outcomes, follow-up periods, and results. We evaluated all randomized controlled trials for risk of bias and made quality appraisals on all studies. RESULTS: Fourteen of the studies focused on bacterial vaginosis (BV), 3 on urinary tract infections (UTIs), 2 on vulvovaginal candidiasis, and one on human papillomavirus (HPV) as identified on Papanicolaou test. Studies were heterogeneous in terms of design, intervention, and outcomes. Four studies were of good quality, 9 of fair, and 7 poor. Probiotic interventions were effective for treatment and prevention of BV, prevention of recurrences of candidiasis and UTIs, and clearing HPV lesions. No study reported significant adverse events related to the probiotic intervention. DISCUSSION: The quality of the studies in this systematic review varied. Although clinical practice recommendations were limited by the strength of evidence, probiotic interventions were effective in treatment and prevention of urogenital infections as alternatives or co-treatments. More good quality research is needed to strengthen the body of evidence needed for application by clinicians.

Harata, G., Kumar, H., He, F., Miyazawa, K., Yoda, K., Kawase, M., Kubota, A., Hiramatsu, M., Rautava, S., and Salminen, S. Probiotics modulate gut microbiota and health status in Japanese cedar pollinosis patients during the pollen season. Eur.J.Nutr. 7-13-2016;

ABSTRACT: BACKGROUND: Japanese cedar pollinosis (JCP) is a challenging public health problem in Japan. Altered gut microbiota is associated with several diseases, including allergic diseases. However, only a few studies have focused on JCP and the underlying mechanisms for probiotic effects remain unclear. In addition, this study is the first observation of the correlation between the gut microbiota and blood lipid in JCP. METHODS: Faecal samples from JCP subjects were collected before and after treatment with (n = 14) and without (n = 11) LGG-TMC0356-fermented milk for 10 weeks. Gut microbiota composition was characterized from faecal DNA using sequencing of 16S rRNA genes. RESULTS: 16S rRNA-based operational taxonomic unit clustering of the microbiota revealed that LGG-TMC0356-fermented milk significantly altered gut microbiota after 10 weeks of milk consumption, and eight dominant genera of microbes were detected. During the JCP season, the Bacteroidetes/Firmicutes ratio, when compared to baseline, was significantly decreased in subjects at end of the study. Bacteroidetes showed positive correlation with LDL- and HDL-cholesterol levels, whereas Firmicutes showed negative correlation with total cholesterol, LDL- and HDL- cholesterol. CONCLUSIONS: The altered gut microbiota through supplementation of fermented milk

containing the study probiotics may be a prospective target for protection against JCP, with beneficial effects on blood lipid levels.

Harb, T., Matsuyama, M., David, M., and Hill, R. J. Infant Colic-What works: A Systematic Review of Interventions for Breast-fed Infants. J.Pediatr.Gastroenterol.Nutr. 2016; 62(5):668-686.

ABSTRACT: OBJECTIVES: To determine the strength of evidence for commonly used interventions for colic in breast-fed and mixed-fed infants younger than 6 months. METHODS: Searches of PubMed, CINAHL, Embase, AMED, and Web of Science databases were conducted from July 2014 to July 2015. Included studies were randomised controlled trials involving mothers and their colicky infants younger than 6 months; assessed colic against the Wessel or modified Wessel criteria; and included phytotherapies, prescription medicines, and maternal dietary interventions. Studies with <16 participants were excluded. Meta-analyses were conducted where data were sufficient to enable pooling. Quality was assessed against the Cochrane Risk Bias Assessment Tool. RESULTS: A total of 17 articles met the inclusion criteria for this review. The 6 studies included for subgroup meta-analysis on probiotic treatment, notably Lactobacillus reuteri, demonstrated that probiotics appear an effective treatment, with an overall mean difference in crying time at day 21 of -55.8 min/day (95% CI -64.4 to -47.3, P = 0.001). The 3 studies included for subgroup meta-analysis on preparations containing fennel suggest it to be effective, with an overall mean difference of -72.1 min/day (95% CI -126.4 to -17.7, P < 0.001). CONCLUSIONS: Probiotics, in particular L reuteri, and preparations containing fennel oil appear effective for reducing colic, although there are limitations to these findings. The evidence for maternal dietary manipulation, lactase, sucrose, glucose, and simethicone is weak. Further well-designed clinical trials are required to strengthen the evidence for all of these interventions.

Haron, M. H., Tyler, H. L., Pugh, N. D., Moraes, R. M., Maddox, V. L., Jackson, C. R., and Pasco, D. S. Activities and Prevalence of Proteobacteria Members Colonizing Echinacea purpurea Fully Account for Macrophage Activation Exhibited by Extracts of This Botanical. Planta Med. 6-10-2016;

ABSTRACT: Evidence supports the theory that bacterial communities colonizing Echinacea purpurea contribute to the innate immune enhancing activity of this botanical. Previously, we reported that only about half of the variation in in vitro monocyte stimulating activity exhibited by E. purpurea extracts could be accounted for by total bacterial load within the plant material. In the current study, we test the hypothesis that the type of bacteria, in addition to bacterial load, is necessary to fully account for extract activity. Bacterial community composition within commercial and freshly harvested (wild and cultivated) E. purpurea aerial samples was determined using high-throughput 16S rRNA gene pyrosequencing. Bacterial isolates representing 38 different taxa identified to be present within E. purpurea were acquired, and the activity exhibited by the extracts of these isolates varied by over 8000-fold. Members of the Proteobacteria exhibited the highest potency for in vitro macrophage activation and were the most predominant taxa. Furthermore, the mean activity exhibited by the Echinacea extracts could be solely accounted for by the activities and prevalence of Proteobacteria members comprising the plant-associated bacterial community. The efficacy of E. purpurea material for use against respiratory infections may be determined by the Proteobacterial community composition of this plant, since ingestion of bacteria (probiotics) is reported to have a protective effect against this health condition.

Hashemi, A., Villa, C. R., and Comelli, E. M. Probiotics in early life: a preventative and treatment approach. Food Funct. 4-20-2016; 7(4):1752-1768.

ABSTRACT: Microbial colonization of the infant gut plays a key role in immunological and metabolic pathways impacting human health. Since the maturation of the gut microbiota coincides with early life development, failure to develop a health compatible microbiota composition may result in pathology and disease in later life. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Maternal transfer of microorganisms is possible during pregnancy and lactation, and the mother's diet and microbiota can influence that of her offspring. Furthermore, pre-term birth, Caesarean section birth, formula feeding, antibiotic use, and malnutrition have been linked to dysbiosis, which in turn is associated with several pathologies such as necrotizing enterocolitis, inflammatory bowel diseases, antibiotic associated diarrhea, colic, and allergies. Thus, early life should represent a preferred stage of life for probiotic interventions. In this context, they could be regarded as a means to 'program' the individual for health maintenance, in order to prevent pathologies associated with dysbiosis. In order to elucidate the mechanisms underlying the benefits of probiotic administration, pre-clinical studies have been conducted and found an array of positive results such as improved microbial composition, intestinal maturation, decreased pathogenic load and infections, and improved immune response. Moreover, specific probiotic strains administered during the perinatal period have shown promise in attenuating severity of necrotizing enterocolitis. The mechanisms elucidated suggest that probiotic interventions in early life can be envisaged for disease prevention in both healthy offspring and offspring at risk of chronic disease.

Hassan, Z., Mustafa, S., Rahim, R. A., and Isa, N. M. Anti-breast cancer effects of live, heat-killed and cytoplasmic fractions of Enterococcus faecalis and Staphylococcus hominis isolated from human breast milk. In Vitro Cell Dev.Biol.Anim. 2016; 52(3):337-348.

ABSTRACT: Development of tumour that is resistant to chemotherapeutics and synthetic drugs, coupled with their life-threatening side effects and the adverse effects of surgery and hormone therapies, led to increased research on probiotics' anticancer potentials. The current study investigated the potential of live, heat-killed cells (HKC) and the cytoplasmic fractions (CF) of Enterococcus faecalis and Staphylococcus hominis as anti-breast cancer agents. MCF-7 cell line was treated with 25, 50, 100 and 200 mug/mL each of live, HKC and CF of the bacteria; and cytotoxicity was evaluated for 24, 48 and 72 h using MTT assay. The morphological features of the treated cells were examined by fluorescence microscopy. The stage of cell cycle arrest and apoptosis were quantified by flow cytometry. The bacterial effect on non-malignant breast epithelial cell line, MCF-10A, was assessed using MTT assay for 24, 48 and 72 h. All the three forms of the bacteria caused a significant decrease in MCF-7 (up to 33.29%) cell proliferation in concentration- and time-dependent manner. Morphological features of apoptosis like cell death, cell shrinkage and membrane blebbing were observed. Flow cytometry analyses suggested that about 34.60% of treated MCF-7 was undergoing apoptosis. A strong anti-proliferative activity was efficiently induced through sub-G1 accumulation (up to 83.17%) in treated MCF-7 and decreased number in the G0/G1 phase (74.39%). MCF-10A cells treated with both bacteria showed no significant difference with the untreated (>90% viability). These bacteria can be used as good alternative nutraceutical with promising therapeutic indexes for breast cancer because of their non-cytotoxic effects to normal cells.

Hastings, C. N., Sheridan, H., Pariante, C. M., and Mondelli, V. Does Diet Matter? The Use of Polyunsaturated Fatty Acids (PUFAs) and Other Dietary Supplements in Inflammation-Associated Depression. Curr.Top.Behav.Neurosci. 7-19-2016;

ABSTRACT: An increasingly pertinent issue in psychiatry in recent years is that of the limitations of conventional antidepressants, which are not effective in a large number of patients with major depressive disorder (MDD). Coupled with emerging hypotheses about the role of inflammation in depression, it would appear that it is time to look for alternative treatments for these symptoms.This review will examine an emerging area in psychiatry, that of dietary supplements and the diet in general to treat depressive symptoms, and inflammation in depression. In particular, polyunsaturated fatty acids (PUFAs), probiotics and folic acid are three supplements that demonstrate the ability to target inflammation and other underlying systems in depression. While there is a definite need for more research in all these supplements to determine true efficacy, dosage and target populations, they can be used as mono- or adjunctive therapies to good effect, and show superior safety profiles when compared with more traditional alternatives.

Hayakawa, T., Masuda, T., Kurosawa, D., and Tsukahara, T. Dietary administration of probiotics to sows and/or their neonates improves the reproductive performance, incidence of post-weaning diarrhea and histopathological parameters in the intestine of weaned piglets. Anim Sci.J. 3-28-2016;

ABSTRACT: Probiotics have gained considerable attention with respect to their beneficial effects on livestock performance and health. The most significant effects of probiotics on the gut microbiota and the host animals take place when they are included in diets during particularly stressful periods such as weaning and/or at the beginning of the lactation period. The probiotics Bacillus mesentericus strain TO-A at 1 x 108 colony forming units (CFU)/g, Clostridium butyricum strain TO-A at 1 x 108 CFU/g and Enterococcus faecalis strain T-110 at 1 x 109 CFU/g were used. Litter weight at delivery and ratio of return to estrous improved significantly (17% and 24% improvement, respectively) by probiotic administration to sows (0.2% (w/w)). Furthermore, the feed intake of the probiotics-administered sows was greater than that of the control sows during the late lactation period. Post-weaning diarrheal incidence and growth performance was improved by probiotics administration to neonates (0.02% (w/w)), while the combined use of probiotics in sows and their neonates induced the enlargement of villous height and prevented muscle layer thinning in the small intestine of weaning piglets. The administration of probiotics of three species of live bacteria improved the porcine reproductive performance around stressful periods of sows (farrowing) and piglets (weaning). [Corrections added on 26 April 2016, after first online publication: 'Enterococcus faecalis strain T-100' has been corrected to 'Enterococcus faecalis strain T-110' in the above paragraph and in the 'Probiotics' section under the Materials and Methods heading.].

Hays, S., Jacquot, A., Gauthier, H., Kempf, C., Beissel, A., Pidoux, O., Jumas-Bilak, E., Decullier, E., Lachambre, E., Beck, L., Cambonie, G., Putet, G., Claris, O., and Picaud, J. C. Probiotics and growth in preterm infants: A randomized controlled trial, PREMAPRO study. Clin.Nutr. 2016; 35(4):802-811.

ABSTRACT: BACKGROUND & AIMS: Recent studies have suggested that the gut microflora has metabolic effects. We aimed to evaluate postnatal growth in preterm infants who received different probiotic supplements, and to assess the safety of probiotic administration. METHODS: This prospective, randomized, double-blind, controlled trial was performed at three tertiary care neonatal units. Preterm infants were randomly assigned to receive daily supplementation over 4-6 weeks with placebo (group C) or probiotics (group P). Group P comprised three subgroups: P1 received Bifidobacterium lactis, P2 received Bifidobacterium longum, and P3 received B. lactis and B. longum. We assessed postnatal growth during the supplementation period and up to a corrected gestational age (GA) of 41 weeks when body composition was assessed using whole-body dual-energy X-ray absorptiometry. Aerobic and anaerobic blood cultures were performed on suspicion of late-onset sepsis. RESULTS: The study comprised 199 preterm infants with a mean GA of 29.1 +/- 1.4 weeks and a mean birth weight of 1173 +/- 210 g, who received a placebo (group C, n = 52) or probiotics (group P, n = 147) from the first week of life. At the end of the supplementation period, no statistically significant differences were seen between the groups in relation to the mean body weight (group C = 1906 +/- 23 g, group P = 1875 +/- 14 g, p = 0.25), length, or head circumference. The incidence rates of necrotizing enterocolitis and late-onset sepsis were similar in the two groups. At the corrected GA of 41 weeks, there were no differences between the groups with respect to anthropometric measurements or body composition analysis. CONCLUSIONS: Preterm infants receiving Bifidobacterium supplements did not exhibit better postnatal growth compared with those who received placebo treatment. No adverse effects were associated with probiotic administration. Registered under ClinicalTrials.gov Identifier no. NCT01379417.

Hecht, A. L., Casterline, B. W., Earley, Z. M., Goo, Y. A., Goodlett, D. R., and Bubeck, Wardenburg J. Strain competition restricts colonization of an enteric pathogen and prevents colitis. EMBO Rep. 7-18-2016;

ABSTRACT: The microbiota is a major source of protection against intestinal pathogens; however, the specific bacteria and underlying mechanisms involved are not well understood. As a model of this interaction, we sought to determine whether colonization of the murine host with symbiotic non-toxigenic Bacteroides fragilis could limit acquisition of pathogenic enterotoxigenic B. fragilis We observed strain-specific competition with toxigenic B. fragilis, dependent upon type VI secretion, identifying an effector-immunity pair that confers pathogen exclusion. Resistance against host acquisition of a second non-toxigenic strain was also uncovered, revealing a broader function of type VI secretion systems in determining microbiota composition. The competitive exclusion of enterotoxigenic B. fragilis by a non-toxigenic strain limited toxin exposure and protected the host against intestinal inflammatory disease. Our studies demonstrate a novel role of type VI secretion systems in colonization resistance against a pathogen. This understanding of bacterial competition may be utilized to define a molecularly targeted probiotic strategy.

Heida, F. H., van Zoonen, A. G., Hulscher, J. B., te Kiefte, B. J., Wessels, R., Kooi, E. M., Bos, A. F., Harmsen, H. J., and de Goffau, M. C. A Necrotizing Enterocolitis-Associated Gut Microbiota Is Present in the Meconium: Results of a Prospective Study. Clin.Infect.Dis. 4-1-2016; 62(7):863-870.

ABSTRACT: BACKGROUND: Anomalous intestinal microbiota development is supposedly associated with development of necrotizing enterocolitis (NEC). Our aim in this study was to identify the intestinal microbiota of patients at risk for NEC. METHODS: In a prospective trial that investigated prognostic factors for development of NEC in high-risk neonates (NTR4153), 11 NEC cases were gestational age/birthweight matched with controls (ratio of 1:2). Feces were collected twice a week. We used the first feces sample of each patient (meconium), as well as the last 2 feces samples prior to development of NEC. DNA was extracted, and the bacterial 16S rRNA genes were analyzed on a MiSeq sequencer. RESULTS: The presence and abundance of Clostridium perfringens (8.4%) and Bacteroides dorei (0.9%) in meconium were increased in neonates who developed NEC compared with controls (0.1% and 0.2%; both species, P < .001). In post-meconium samples, the abundance of staphylococci became negatively associated with NEC development (P = .1 and P = .01 for consecutive samples); Clostridium perfringens continued to be more prevalent in NEC cases. Early enteral feeding and, in particular, breast milk were correlated with an increase in lactate-producing bacilli in post-meconium samples (rho = -0.45; P = .004). CONCLUSIONS: A NEC-associated gut microbiota can be identified in meconium samples; C. perfringens continues to be associated with NEC from the first meconium till just before NEC onset. In contrast, in post-meconium, increased numbers of staphylococci were negatively associated with NEC. These findings suggest causality but this causality should be verified in trials of induced infection in animals, targeted antibiotics, and/or probiotics. CLINICAL TRIALS REGISTRATION: CALIFORNIA trial, registered under trial number NTR4153 in the Dutch Trial Registry.

Hendaus, M. A., Jomha, F. A., and Ehlayel, M. Allergic diseases among children: nutritional prevention and intervention. Ther.Clin.Risk Manag. 2016; 12:361-372.

ABSTRACT: Allergic diseases comprise a genetically heterogeneous group of chronic, immunomediated diseases. It has been clearly reported that the prevalence of these diseases has been on the rise for the last few decades, but at different rates, in various areas of the world. This paper discusses the epidemiology of allergic diseases among children and their negative impact on affected patients, their families, and societies. These effects include the adverse effects on quality of life and economic costs. Medical interest has shifted from tertiary or secondary prevention to primary prevention of these chronic diseases among high-risk infants in early life. Being simple, practical, and cost-effective are mandatory features for any candidate methods delivering these strategies. Dietary therapy fits this model well, as it is simple, practical, and cost-effective, and involves diverse methods. The highest priority strategy is feeding these infants breast milk. For those who are not breast-fed, there should be a strategy to maintain beneficial gut flora that positively influences intestinal immunity. We review the current use of probiotics, prebiotics, and synbiotics, and safety and adverse effects. Other dietary modalities of possible potential in achieving this primary prevention, such as a Mediterranean diet, use of milk formula with modified (hydrolyzed) proteins, and the role of micronutrients, are also explored. Breast-feeding is effective in reducing the risk of asthma, allergic rhinitis, and atopic eczema among children. In addition, breast milk constitutes a major source of support for gut microbe colonization, due to its bifidobacteria and galactooligosaccharide content. The literature lacks consensus in recommending the addition of probiotics to foods for prevention and treatment of allergic diseases, while prebiotics may prove to be effective in reducing atopy in healthy children. There is insufficient evidence to support soy formulas or amino acid formulas for prevention of allergic disease. A healthy diet, such as the Mediterranean diet, may have a protective

effect on the development of asthma and atopy in children. In children with asthma and allergic diseases, vitamin D deficiency correlates strongly with asthma, allergic rhinitis, and wheezing.

Hernandez, C. J., Guss, J. D., Luna, M., and Goldring, S. R. Links Between the Microbiome and Bone. J.Bone Miner.Res. 6-18-2016;

ABSTRACT: The human microbiome has been shown to influence a number of chronic conditions associated with impaired bone mass and bone quality, including obesity, diabetes, and inflammatory bowel disease. The connection between the microbiome and bone health, however, has not been well studied. The few studies available demonstrate that the microbiome can have a large effect on bone remodeling and bone mass. The gut microbiome is the largest reservoir of microbial organisms in the body and consists of more than a thousand different species interacting with one another in a stable, dynamic equilibrium. How the microbiome can affect organs distant from the gut is not well understood but is believed to occur through regulation of nutrition, regulation of the immune system, and/or translocation of bacterial products across the gut endothelial barrier. Here we review each of these mechanisms and discuss their potential effect on bone remodeling and bone mass. We discuss how preclinical studies of bone-microbiome interactions are challenging because the microbiome is sensitive to genetic background, housing environment, and vendor source. Additionally, although the microbiome exhibits a robust response to external stimuli, it rapidly returns to its original steady state after a disturbance, making it difficult to sustain controlled changes in the microbiome over time periods required to detect alterations in bone remodeling, mass, or structure. Despite these challenges, an understanding of the mechanisms by which the gut microbiome affects bone has the potential to provide insights into the dissociation between fracture risk and bone mineral density in patients including those with obesity, diabetes, or inflammatory bowel disease. In addition, alteration of the gut microbiome has the potential to serve as a biomarker of bone metabolic activity as well as a target for therapies to improve bone structure and quality using pharmaceutical agents or pre- or probiotics. (c) 2016 American Society for Bone and Mineral Research.

Hidalgo-Cantabrana, C., Algieri, F., Rodriguez-Nogales, A., Vezza, T., Martinez-Camblor, P., Margolles, A., Ruas-Madiedo, P., and Galvez, J. Effect of a Ropy Exopolysaccharide-Producing Bifidobacterium animalis subsp. lactis Strain Orally Administered on DSS-Induced Colitis Mice Model. Front Microbiol. 2016; 7:868

ABSTRACT: Exopolysaccharide (EPS)-producing bifidobacteria, particularly Bifidobacterium animalis subsp. lactis strains, are used in the functional food industry as promising probiotics with purported beneficial effects. We used three isogenic strains of B. animalis subsp. lactis, with different EPS producing phenotypes (mucoid-ropy and non-ropy), in order to determine their capability to survive the murine gastrointestinal tract transit, as well as to evaluate their role in improving clinical outcomes in a chemically-induced colitis model. The three strains were able to survive in the intestinal tract of C57BL/6J mice during the course of the intervention study. Furthermore, the disease activity index (DAI) of the animal group treated with the ropy strain was significantly lower than of the DAI of the placebo group at the end of the treatment. However, no significant differences were found among the three strains. The analysis of several immune parameters, such as TNFalpha and IL-10 quantified in blood plasma and lymphocyte populations enumerated in mesenteric nodes, showed some significant

variations among the four experimental animal groups. Remarkably, a higher capability of the ropy strain to increase regulatory T-cells in mesenteric lymphoid nodes was demonstrated, suggesting a higher ability of this strain to regulate inflammatory responses at mucosal level. Our data indicate that strains of B. animalis subsp. lactis producing EPS that confer a mucoid-ropy phenotype could represent promising candidates to perform further studies targeting intestinal inflammatory processes.

Hlinkova, J., Svobodova, H., Brachtlova, T., and Gardlik, R. Effect of DSS on Bacterial Growth in Gastrointestinal Tract. Folia Biol.(Praha). 2016; 62(1):40-46.

ABSTRACT: Inflammatory bowel disease is an idiopathic autoimmune disorder that is mainly divided into ulcerative colitis and Crohn's disease. Probiotics are known for their beneficial effect and used as a treatment option in different gastrointestinal problems. The aim of our study was to find suitable bacterial vectors for gene therapy of inflammatory bowel disease. Salmonella enterica serovar Typhimurium SL7207 and Escherichia coli Nissle 1917 were investigated as potential vectors. Our results show that the growth of Escherichia coli Nissle 1917 was inhibited in the majority of samples collected from dextran sodium sulphate-treated animals compared with control growth in phosphate-buffered saline. The growth of Salmonella enterica serovar Typhimurium SL7207 in all investigated samples was enhanced or unaffected in comparison with phosphate-buffered saline; however, it did not reach the growth rates of Escherichia coli Nissle 1917. Dextran sodium sulphate treatment had a stimulating effect on the growth of both strains in homogenates of distant small intestine and proximal colon samples. The gastrointestinal tract contents and tissue homogenates did not inhibit growth of Salmonella enterica serovar Typhimurium SL7207 in comparison with the negative control, and provided more suitable environment for growth compared to Escherichia coli Nissle 1917. We therefore conclude that Salmonella enterica serovar Typhimurium SL7207 is a more suitable candidate for a potential bacterial vector, even though it has no known probiotic properties.

Hojsak, I., Mocic, Pavic A., Kos, T., Dumancic, J., and Kolacek, S. Bifidobacterium animalis subsp. lactis in prevention of common infections in healthy children attending day care centers - Randomized, double blind, placebo-controlled study. Clin.Nutr. 2016; 35(3):587-591.

ABSTRACT: BACKGROUND & AIMS: The aim of our study was to investigate the role of Bifidobacterium animalis subsp. lactis (BB-12((R))) in the prevention of common (gastrointestinal and respiratory) infections in healthy children who attend day care centers. METHODS: We conducted a randomized, double-blind, placebo-controlled trial in 210 children who attend day care centers. They were randomly allocated to receive placebo (Placebo group, n = 106) or BB-12((R)) at a dose of 10(9) colony-forming units (CFU) (Intervention group, n = 104) during the 3-month intervention period. RESULTS: Intention to treat analysis was used. There were overall 99 infections in Placebo group and 97 in Intervention group (incidence rate ratio = 1.0014, p = 0.992, Poisson regression model). Overall 65 children (61.3%) in Placebo group and 67 (64.4%) in Intervention group had common infections (p = 0.642). Mean number of infections per child was 0.93 (range 0-3) in Placebo group and 0.93 (range 0-3) in Intervention group (p = 0.898). There was no difference in secondary (duration of symptoms, number of children with gastrointestinal and respiratory tract infections, absence from day care center due to infections, use of antibiotics) and exploratory (type of gastrointestinal and respiratory tract infection) endpoints between groups. CONCLUSION: Results of performed study show that BB-

12((R)) has no effect on the prevention of gastrointestinal and respiratory tract infections in healthy children who attend day care centers.

Holvoet, S., Doucet-Ladeveze, R., Perrot, M., Barretto, C., Nutten, S., and Blanchard, C. Beneficial effect of Lactococcus lactis NCC 2287 in a murine model of eosinophilic esophagitis. Allergy. 6-4-2016;

ABSTRACT: BACKGROUND: Eosinophilic esophagitis (EoE) is a severe inflammatory disease of the esophagus which is characterized histologically by an eosinophilic infiltration into the esophageal tissue. The efficacy of probiotics in the context of atopic diseases has been well investigated but, to date, there has been no study which has evaluated probiotic effects on EoE inflammation. This study sought to identify a probiotic which improves esophageal inflammation in experimental EoE. METHODS: Two candidate probiotics, Lactococcus lactis NCC 2287 and Bifidobacterium lactis NCC 2818, were tested in a murine model of EoE elicited by epicutaneous sensitization with Aspergillus fumigatus protein extract. Administration of bacterial strains in drinking water was used, respectively, as a preventive or treatment measure, or continuously throughout the study. Inflammatory parameters were assessed in the esophagus, skin, and lungs after allergen challenge. RESULTS: In this EoE model, supplementation with L. lactis NCC 2287 significantly decreased esophageal and bronchoalveolar eosinophilia but only when given as a therapeutic treatment. No significant effect on eosinophilia was observed when NCC 2287 was given as a preventive or a continuous intervention. NCC 2287 supplementation had no significant effect on immunoglobulin levels, skin symptom scores, or on transepidermal water loss. Supplementation with another probiotic, B. lactis NCC 2818, had no significant effect on esophageal eosinophilia. CONCLUSION: We identified a L. lactis strain, able to attenuate esophageal eosinophilic inflammation in a preclinical model of EoE. This effect is strain specific and depends on the timing and duration of bacterial supplementation. Confirmation of these observations in human clinical trials is warranted.

Homayoni, Rad A., Vaghef, Mehrabany E., Alipoor, B., and Vaghef, Mehrabany L. The Comparison of Food and Supplement as Probiotic Delivery Vehicles. Crit Rev.Food Sci.Nutr. 4-25-2016; 56(6):896-909.

ABSTRACT: Probiotics are live bacteria which have frequently been reported to be beneficial in preventing a wide range of diseases as well as playing a major role in treating the existing ailments. Thus far, a variety of probiotic products have been developed which can be categorized into two groups: probiotic foods and supplements. Both foods and supplements have been able to confer the health benefits claimed for them. However, it is not known which one can be clinically more efficient, and to the best of our knowledge, until now no research has been conducted to investigate this issue. The present review aims to discuss this matter, based on the evidence available in the literature. To do so, articles indexed in PubMed and ScienceDirect between 2000 and 2011 were reviewed. The articles included the clinical trials in which either foods or supplements were used to administer the probiotics to either patients suffering from different diseases or healthy subjects. Although both foods and supplements seem to have been efficient carriers for the beneficial bacteria, to generally promote public health in communities, probiotic foods appear to be preferred to probiotic supplements.

Hong, Y. F., Kim, H., Kim, H. S., Park, W. J., Kim, J. Y., and Chung, D. K. Lactobacillus acidophilus K301 Inhibits Atherogenesis via Induction of 24 (S), 25-Epoxycholesterol-Mediated ABCA1 and ABCG1 Production and Cholesterol Efflux in Macrophages. PLoS.One. 2016; 11(4):e0154302

ABSTRACT: Lactobacillus acidophilus species are well-known probiotics with the beneficial activity of regulating cholesterol levels. In this study, we showed that L. acidophilus K301 reduced the level of cholesterol through reverse transport in macrophages. L. acidophilus K301 upregulated the mRNA and protein levels of genes such as ATP-binding cassette A1 (ABCA1) and ATP-binding cassette G1 (ABCG1) under the control of liver X receptor (LXR), resulting in increased apoA-I-dependent cholesterol efflux in phorbol 12-myristate 13-acetate (PMA)-differentiated THP-1 cells. L. acidophilus K301 induced both ABCA1 and ABCG1 through the endogenous LXR agonist 24(S), 25-epoxcycholesterol, which is synthesized by intracellular cholesterol synthetic pathways. In vivo studies using L. acidophilus K301-treated ApoE-/- mice showed reduced accumulation of lipoproteins in the arterial lumen. The inhibitory effects of L. acidophilus K301 on accumulation of lipoprotein in atherosclerotic plaques were mediated by the induction of squalene reductase (SQLE) and oxidosqualene cyclase (OSC) and resulted in ABCA1-mediated cholesterol efflux. Taken together, our findings revealed that Lactobacillus acidophilus K301 regulates the expression of genes related to cholesterol reverse transport via the induction of endogenous LXR agonist, suggesting the therapeutic potential of Lactobacillus acidophilus K301 as an anti-atherosclerotic agent.

Hossain, N., Kanwar, P., and Mohanty, S. R. A Comprehensive Updated Review of Pharmaceutical and Nonpharmaceutical Treatment for NAFLD. Gastroenterol.Res.Pract. 2016; 2016:7109270

ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the western world with prevalence of 20-33%. NAFLD comprises a pathological spectrum. Nonalcoholic fatty liver (NAFL) is at one end and consists of simple hepatic steatosis. On the contrary, nonalcoholic steatohepatitis (NASH) consists of steatosis, inflammation, and ballooning degeneration and can progress to cirrhosis. Despite the rising incidence, definitive treatment for NAFLD, specifically NASH, has not yet been established. Lifestyle modification with dietary changes combined with regular aerobic exercise, along with multidisciplinary approach including cognitive behavior therapy, has been shown to be an effective therapeutic option, even without a significant weight loss. Pioglitazone and vitamin E have shown to be most effective in NASH patients. Surgery and weight loss medication are effective means of weight loss but can potentially worsen NASH related fibrosis. Other agents such as n-3 polyunsaturated fatty acids, probiotics, and pentoxifylline along with herbal agent such as milk thistle as well as daily intake of coffee have shown potential benefits, but further well organized studies are definitely warranted. This review focuses on the available evidence on pharmaceutical and nonpharmaceutical therapy in the treatment and the prevention of NAFLD, primarily NASH.

Hoy-Schulz, Y. E., Jannat, K., Roberts, T., Zaidi, S. H., Unicomb, L., Luby, S., and Parsonnet, J. Safety and acceptability of Lactobacillus reuteri DSM 17938 and Bifidobacterium longum subspecies infantis 35624 in Bangladeshi infants: a phase I randomized clinical trial. BMC.Complement Altern.Med. 2016; 16:44

ABSTRACT: BACKGROUND: Probiotics have rarely been studied in young healthy infants from low-income countries. This phase I study investigated the safety and acceptability of two probiotics in Bangladesh. METHODS: Healthy infants aged four to twelve weeks from urban slums in Bangladesh were randomized to one of three different intervention dosing arms (daily, weekly, biweekly - once every two weeks) of Lactobacillus reuteri DSM 17938 and Bifidobacterium longum subspecies infantis 35624 over one month or to a fourth arm that received no probiotics. All subjects were followed for two additional months. Reported gastrointestinal and respiratory symptoms as well as breastfeeding rates, hospitalizations, differential withdrawals, and caretakers' perception of probiotic use were compared among arms. RESULTS: In total, 160 infants were randomized (40 to each arm) with 137 (Daily n = 35, Weekly n = 35, Biweekly n = 35, Control n = 32) followed up for a median of twelve weeks; 113 completed the study. Illness and breastfeeding rates were similar across all arms. Ten hospitalizations unrelated to probiotic use occurred. Forty eight percent of the caretakers of infants in intervention arms believed that probiotics improved their baby's health. CONCLUSIONS: These two commonly used probiotics appeared safe and well-accepted by Bangladeshi families. TRIAL REGISTRATION: ClinicalTrials.gov NCT01899378 . Registered July 10, 2013.

Hu, L., Peng, X., Chen, H., Yan, C., Liu, Y., Xu, Q., Fang, Z., Lin, Y., Xu, S., Feng, B., Li, J., Wu, and Che, L. Effects of intrauterine growth retardation and Bacillus subtilis PB6 supplementation on growth performance, intestinal development and immune function of piglets during the suckling period. Eur.J.Nutr. 5-17-2016;

ABSTRACT: OBJECTIVES: The aim of this study was to investigate the effects of intrauterine growth retardation (IUGR) and Bacillus subtilis PB6 supplementation in formula milk (FORM) on growth performance, intestinal development and immune function of neonates using a porcine model. METHODS: Fourteen pairs of normal birth weight and IUGR piglets (7 days old) were randomly assigned to receive FORM or FORM supplemented with B. subtilis PB6 (FORM-BsPB6) for a period of 21 days. Blood samples, intestinal tissues and digesta were collected at necropsy and analysed for morphology, digestive enzyme activities, immune cell abundance, expression of genes associated with innate immunity and barrier function and microbial populations. RESULTS: Regardless of diet, IUGR significantly decreased average daily dry matter intake and average daily weight gain ($P < 0.05$). Moreover, IUGR significantly decreased plasma concentrations of immunoglobulin A, interleukin 1beta, count and percentage of blood lymphocytes ($P < 0.05$). Meanwhile, IUGR markedly decreased villous height and maltase activity, as well as mRNA abundance of Toll-like receptor 9 and Toll-interacting protein in the ileum ($P < 0.05$). Regardless of body weight, FORM-BsPB6 markedly decreased the feed conversion ratio ($P < 0.05$), due to better intestinal development, as indicated by increased villous height ($P < 0.05$), activities of maltase and sucrase in the intestine ($P < 0.10$). Moreover, both mRNA and protein abundances of zonula occludens-1 and claudin-1 in the ileum as well as the copy number of Bacillus in colonic digesta were increased ($P < 0.05$) in piglets fed FORM-BsPB6 relative to FORM. CONCLUSION: The results of this study indicate that IUGR delayed growth, intestinal development and immune function of piglets, while FORM-BsPB6 improved digestive capability and intestinal barrier function.

Hu, X., Zhang, H., Lu, H., Qian, G., Lv, L., Zhang, C., Guo, J., Jiang, H., Zheng, B., Yang, F., Gu, S., Chen, Y., Bao, Q., Yu, L., Jiang, X., Hu, Q., Shi, H., Gao, H., and Li, L. The Effect of Probiotic Treatment on Patients Infected with the H7N9 Influenza Virus. PLoS.One. 2016; 11(3):e0151976

ABSTRACT: BACKGROUND: A novel avian-origin influenza A (H7N9) virus emerged and spread among humans in Eastern China in 2013. Prophylactic treatment with antibiotics and probiotics for secondary infection is as important as antiviral treatment. This study aims to assess the ability of probiotic treatment to restore internal homeostasis under antibiotic pressure and to reduce/ameliorate the risk of secondary infections resulting from infection with the H7N9 virus. METHODS: This is a retrospective study in archival samples. Between April 1 and May 10, 2013, 113 stool, sputum, and blood specimens were collected and analyzed by denaturing gradient gel electrophoresis (DGGE) to determine the composition of the patient microbiomes. Microbial diversity was calculated using Gel-Pro analyzer and Past software. Cluster analysis of DGGE pattern profiles was employed to create a phylogenetic tree for each patient, and multidimensional scaling (MDS) and principal component analysis (PCA) were performed to visualize relationships between individual lanes. RESULTS: Five patients had secondary infections, including Klebsiella pneumonia, Acinetobacter baumanii and Candida albicans infection. The DGGE profiles of fecal samples obtained at different time points from the same individual were clearly different, particularly for patients with secondary infections. Shannon's diversity index and evenness index were lower in all infected groups compared to the control group. After B. subtilis and E. faecium or C. butyricum administration, the fecal bacterial profiles of patients who had not been treated with antibiotics displayed a trend of increasing diversity and evenness. C. butyricum failed to reduce/ameliorate secondary infection in H7N9-infected patients, but administration of B. subtilis and E. faecium appeared to reduce/ameliorate secondary infection in one patient. CONCLUSION: H7N9 infection might decrease intestinal microbial diversity and species richness in humans. C. butyricum failed to reduce/ameliorate secondary infection in H7N9-infected patients. B. subtilis and E. faecium may also play a role in reducing/ameliorating secondary infection in these patients.

Huang, K., Xia, H., Li, F., Wei, Y., Cui, G., Fu, X., and Chen, X. Optimal growth condition of earthworms and their vermicompost features during recycling of five different fresh fruit and vegetable wastes. Environ.Sci.Pollut.Res.Int. 2016; 23(13):13569-13575.

ABSTRACT: This study aimed to promote vermicomposting performance for recycling fresh fruit and vegetable wastes (FVWs) and to assess microbial population and community of final products. Five fresh FVWs including banana peels, cabbage, lettuce, potato, and watermelon peels were chosen as earthworms' food. The fate test of earthworms showed that 30 g fresh FVWs/day was the optimal loading and the banana peels was harmful for the survival of Eisenia fetida. The followed vermicomposting test revealed lower contents of total carbon and weaker microbial activity in final vermicomposts, relative to those in compared systems without earthworms worked. The leachate from FVWs carried away great amounts of nutrients from reactors. Additionally, different fresh FVWs displayed dissimilar stabilization process. Molecular biological approaches revealed that earthworms could broaden bacterial diversity in their products, with significant greater populations of actinobacteria and ammonia oxidizing bacteria than in control. This study evidences that vermicomposting efficiency differs with the types and loadings of fresh FVWs and vermicomposts are rich in agricultural probiotics.

Huang, S., Rabah, H., Jardin, J., Briard-Bion, V., Parayre, S., Maillard, M. B., Le, Loir Y., Chen, X. D., Schuck, P., Jeantet, R., and Jan, G. Hyperconcentrated Sweet Whey, a New Culture

Medium That Enhances Propionibacterium freudenreichii Stress Tolerance. Appl.Environ.Microbiol. 8-1-2016; 82(15):4641-4651.

ABSTRACT: Propionibacterium freudenreichii is used as a cheese-ripening starter and as a probiotic. Its reported physiological effects at the gut level, including modulation of bifidobacteria, colon epithelial cell proliferation and apoptosis, and intestinal inflammation, rely on active metabolism in situ Survival and activity are thus key factors determining its efficacy, creating stress adaptation and tolerance bottlenecks for probiotic applications. Growth media and growth conditions determine tolerance acquisition. We investigated the possibility of using sweet whey, a dairy by-product, to sustain P. freudenreichii growth. It was used at different concentrations (dry matter) as a culture medium. Using hyperconcentrated sweet whey led to enhanced multistress tolerance acquisition, overexpression of key stress proteins, and accumulation of intracellular storage molecules and compatible solutes, as well as enhanced survival upon spray drying. A simplified process from growth to spray drying of propionibacteria was developed using sweet whey as a 2-in-1 medium to both culture P. freudenreichii and protect it from heat and osmotic injury without harvesting and washing steps. As spray drying is far cheaper and more energy efficient than freeze-drying, this work opens new perspectives for the sustainable development of new starter and probiotic preparations with enhanced robustness. IMPORTANCE: In this study, we demonstrate that sweet whey, a dairy industry by-product, not only allows the growth of probiotic dairy propionibacteria, but also triggers a multitolerance response through osmoadaptation and general stress response. We also show that propionibacteria accumulate compatible solutes under these culture conditions, which might account for the limited loss of viability after spray drying. This work opens new perspectives for more energy-efficient production of dairy starters and probiotics.

Hutsko, S. L., Meizlisch, K., Wick, M., and Lilburn, M. S. Early intestinal development and mucin transcription in the young poult with probiotic and mannan oligosaccharide prebiotic supplementation. Poult.Sci. 2016; 95(5):1173-1178.

ABSTRACT: Alternative and adjunctive approaches to decreasing the use of dietary antibiotics are becoming popular areas of study. Supplemental probiotics (commensal microbes) and prebiotics (indigestible complex carbohydrates) are 2 dietary approaches to facilitating the intestinal colonization of beneficial bacteria to compete with potential pathogens, thus creating a healthy mucosal environment. The intestinal mucosa is composed of mucin glycoproteins, which play a key role in preventing the attachment of pathogenic bacteria. At hatch, the neonatal turkey intestine is relatively aseptic and vulnderable to bacterial colonization by both commensal and pathogenic microbes. In the current study, we determined the transcription of MUC2, the primary mucin protein produced by goblet cells within the small intestine, and we also measured intestinal morphology immediately post-hatch through d 11. Poults were fed a conventional starter diet, the starter diet supplemented with one of 2 commercial probiotics (A, B), or a commercial mannan oligosaccharide. MUC2 transcription increased from d zero to d 4 post-hatch ($P< 0.05$), but there was no effect of probiotic or prebiotic supplementation. Villus height and villus area both increased with Probiotic B and mannan oligosaccharide supplementation ($P<0.05$) and there was a significant d X treatment interaction effect for crypt depth ($P=0.007$). These results suggest that probiotic and prebiotic supplementation can positively alter the intestinal microenvironment.

Iqbal, J., Yuen, T., Sun, L., and Zaidi, M. From the gut to the strut: where inflammation reigns, bone abstains. J.Clin.Invest. 6-1-2016; 126(6):2045-2048.

ABSTRACT: In this issue of the JCI, Li et al. show that germ-free mice, when chemically castrated, do not lose bone - a finding that unequivocally establishes a role of gut microbiota in mediating hypogonadal bone loss. Additionally and not unexpectedly, probiotics reversed hypogonadal osteopenia in sex steroid-deficient mice by preventing the disruption of gut barrier function and dampening cytokine-induced inflammation. The authors propose that TNFalpha is a key mediator; however, it is very likely that other molecules - including IL-1, IL-6, IL-17, RANKL, OPG, and C.

Isa, K., Oka, K., Beauchamp, N., Sato, M., Wada, K., Ohtani, K., Nakanishi, S., McCartney, E., Tanaka, M., Shimizu, T., Kamiya, S., Kruger, C., and Takahashi, M. Safety assessment of the Clostridium butyricum MIYAIRI 588(R) probiotic strain including evaluation of antimicrobial sensitivity and presence of Clostridium toxin genes in vitro and teratogenicity in vivo. Hum.Exp.Toxicol. 2016; 35(8):818-832.

ABSTRACT: Probiotics are live microorganisms ingested for the purpose of conferring a health benefit on the host. Development of new probiotics includes the need for safety evaluations that should consider factors such as pathogenicity, infectivity, virulence factors, toxicity, and metabolic activity. Clostridium butyricum MIYAIRI 588((R)) (CBM 588((R))), an anaerobic spore-forming bacterium, has been developed as a probiotic for use by humans and food animals. Safety studies of this probiotic strain have been conducted and include assessment of antimicrobial sensitivity, documentation of the lack of Clostridium toxin genes, and evaluation of CBM 588((R)) on reproductive and developmental toxicity in a rodent model. With the exception of aminoglycosides, to which anaerobes are intrinsically resistant, CBM 588((R)) showed sensitivity to all antibiotic classes important in human and animal therapeutics. In addition, analysis of the CBM 588((R)) genome established the absence of genes for encoding for alpha, beta, or epsilon toxins and botulin neurotoxins types A, B, E, or F. There were no deleterious reproductive and developmental effects observed in mice associated with the administration of CBM 588((R)) These data provide further support for the safety of CBM 588((R)) for use as a probiotic in animals and humans.

Iweala, O. I. and Burks, A. W. Food Allergy: Our Evolving Understanding of Its Pathogenesis, Prevention, and Treatment. Curr.Allergy Asthma Rep. 2016; 16(5):37

ABSTRACT: Food allergy is defined as an IgE-mediated hypersensitivity response to ingested food with allergic symptoms ranging from urticaria to life-threatening anaphylaxis. Food allergy is thought to develop because of (1) failed induction of tolerance upon initial exposure to food antigen or (2) breakdown of established tolerance to food antigen. We review current understanding of the pathogenesis, epidemiology, and natural history of food allergy, including the unconventional IgE-mediated food allergy to mammalian meat known as alpha-gal food allergy. We highlight emerging data on food allergy treatment and prevention, emphasizing the growing appeal of manipulating the gut microenvironment using probiotics and helminth products to blunt systemic allergic responses to food.

Jafarnejad, S., Shab-Bidar, S., Speakman, J. R., Parastui, K., neshi-Maskooni, M., and Djafarian, K. Probiotics Reduce the Risk of Antibiotic-Associated Diarrhea in Adults (18-64 Years) but Not the Elderly (>65 Years): A Meta-Analysis. Nutr.Clin.Pract. 2016; 31(4):502-513.

ABSTRACT: BACKGROUND: Antibiotic-associated diarrhea (AAD) is a common problem in adults and elderly patients due to the widespread use of antibiotics in this population. Multiple previous systematic reviews have demonstrated an association between specific probiotics and decrease of AAD, especially in children. As there is no specific analysis concerning the elderly patients, we decided to focus on adults, especially elderly people. METHODS: We performed a systematic review of the literature regarding the use of probiotics in the treatment of AAD in adults (18-64 years old) and elderly subjects (>/=65 years old). We identified 436 articles that met the search criteria. Thirty randomized controlled trials met the predefined inclusion criteria and were included in the meta-analysis. RESULTS: There was considerable heterogeneity among the trials (P < .001); thus, subgroup analyses were performed. The meta-analysis resulted in a pooled relative risk (RR) of AAD of 0.69 (95% confidence interval [95% CI]: 0.62-0.76) in a fixed effects model and 0.58 (95% CI: 0.48-0.71) in a random effects model, as compared with placebo. The positive association between intake of probiotic and reduced risk of AAD was observed in adults (RR, 0.47; 95% CI: 0.4-0.56). In contrast, in elderly patients, there was no positive effect (RR, 0.94; 95% CI: 0.76-1.15) of probiotic use and AAD. CONCLUSION: In summary, the results emerging from our meta-analysis suggested that adjunct probiotic administration is associated with a reduced risk of AAD in adults but not in elderly people.

Jafarnejad, S., Saremi, S., Jafarnejad, F., and Arab, A. Effects of a Multispecies Probiotic Mixture on Glycemic Control and Inflammatory Status in Women with Gestational Diabetes: A Randomized Controlled Clinical Trial. J.Nutr.Metab. 2016; 2016:5190846

ABSTRACT: Objective. This trial aims to examine the effects of a Probiotic Mixture (VSL#3) on glycemic status and inflammatory markers, in women with GDM. Materials and Methods. Over a period of 8 weeks, 82 women with gestational diabetes were randomly assigned to either an intervention group (n = 41) which were given VSL#3 capsule or to a control group which were given placebo capsule (n = 41). Fasting plasma glucose, homeostatic model assessment of insulin resistance, glycosylated hemoglobin, high-sensitivity C-reactive protein, tumor necrosis factor-alpha, interleukin-6, Interferon gamma, and interleukin-10 were measured before and after the intervention. Results. After 8 wk of supplementation FPG, HbA1c, HOMA-IR, and insulin levels remained unchanged in the probiotic and placebo groups. The comparison between the two groups showed no significant differences with FPG and HbA1c, but there were significant differences in insulin levels and HOMA-IR (16.6 +/- 5.9; 3.7 +/- 1.5, resp.). Unlike the levels of IFN-g (19.21 +/- 16.6), there was a significant decrease in levels of IL-6 (3.81 +/- 0.7), TNF-alpha (3.10 +/- 1.1), and hs-CRP (4927.4 +/- 924.6). No significant increase was observed in IL-10 (3.11 +/- 5.7) in the intervention group as compared with the control group. Conclusions. In women with GDM, supplementation with probiotics (VSL#3) may help to modulate some inflammatory markers and may have benefits on glycemic control.

Jaffar, N., Ishikawa, Y., Mizuno, K., Okinaga, T., and Maeda, T. Mature Biofilm Degradation by Potential Probiotics: Aggregatibacter actinomycetemcomitans versus Lactobacillus spp. PLoS.One. 2016; 11(7):e0159466

ABSTRACT: The biofilm degradation of Aggregatibacter actinomycetemcomitans is essential as a complete periodontal disease therapy, and here we show the effects of potential probiotic bacteria such as Lactobacillus spp. for the biofilm of several serotypes of A. actinomycetemcomitans strains. Eight of the 13 species showed the competent biofilm degradation of >/= 90% reduction in biofilm values in A. actinomycetemcomitans Y4 (serotype b) as well as four of the seven species for the biofilm of A. actinomycetemcomitans OMZ 534 (serotype e). In contrast, the probiotic bacteria did not have a big impact for the degradation of A. actinomycetemcomitans SUNY 75 (serotype a) biofilm. The dispersed A. actinomycetemcomitans Y4 cells through the biofilm detachment were still viable and plausible factors for the biofilm degradation were not due to the lactic acid and low pH conditions. The three enzymes, protease, lipase, and amylase may be responsible for the biofilm degradation; in particular, lipase was the most effective enzyme for the biofilm degradation of A. actinomycetemcomitans Y4 along with the protease activity which should be also important for the other serotypes. Remarkable lipase enzyme activities were detected from some of the potential probiotics and a supporting result using a lipase inhibitor presented corroborating evidence that lipase activity is one of the contributing factors for biofilm degradation outside of the protease which is also another possible factor for the biofilm of the other serotype of A. actinomycetemcomitans strains. On the other hand, the biofilm of A. actinomycetemcomitans SUNY 75 (serotype a) was not powerfully degraded by the lipase enzyme because the lipase inhibitor was slightly functional for only two of potential probiotics.

James, K. M., MacDonald, K. W., Chanyi, R. M., Cadieux, P. A., and Burton, J. P. Inhibition of Candida albicans biofilm formation and modulation of gene expression by probiotic cells and supernatant. J.Med.Microbiol. 2016; 65(4):328-336.

ABSTRACT: Oral candidiasis is a disease caused by opportunistic species of Candida that normally reside on human mucosal surfaces. The transition of Candida from budding yeast to filamentous hyphae allows for covalent attachment to oral epithelial cells, followed by biofilm formation, invasion and tissue damage. In this study, combinations of Lactobacillus plantarum SD5870, Lactobacillus helveticus CBS N116411 and Streptococcus salivarius DSM 14685 were assessed for their ability to inhibit the formation of and disrupt Candida albicans biofilms. Co-incubation with probiotic supernatants under hyphae-inducing conditions reduced C. albicans biofilm formation by >75 % in all treatment groups. Likewise, combinations of live probiotics reduced biofilm formation of C. albicans by >67 %. When live probiotics or their supernatants were overlaid on preformed C. albicans biofilms, biofilm size was reduced by >63 and >65 % respectively. Quantitative real-time PCR results indicated that the combined supernatants of SD5870 and CBS N116411 significantly reduced the expression of several C. albicans genes involved in the yeast-hyphae transition: ALS3 (adhesin/invasin) by 70 % ($P < 0.0001$), EFG1 (hyphae-specific gene activator) by 47 % ($P = 0.0061$), SAP5 (secreted protease) by 49 % ($P < 0.0001$) and HWP1 (hyphal wall protein critical to biofilm formation) by >99 % ($P < 0.0001$). These findings suggest the combination of L. plantarum SD5870, L. helveticus CBS N116411 and S. salivarius DSM 14685 is effective at both preventing the formation of and removing preformed C. albicans biofilms. Our novel results point to the downregulation of several Candida genes critical to the yeast-hyphae transition, biofilm formation, tissue invasion and cellular damage.

Jasberg, H., Soderling, E., Endo, A., Beighton, D., and Haukioja, A. Bifidobacteria inhibit the growth of Porphyromonas gingivalis but not of Streptococcus mutans in an in vitro biofilm model. Eur.J.Oral Sci. 2016; 124(3):251-258.

ABSTRACT: There is growing interest in the use of probiotic bifidobacteria for enhancement of the therapy, and in the prevention, of oral microbial diseases. However, the results of clinical studies assessing the effects of bifidobacteria on the oral microbiota are controversial, and the mechanisms of actions of probiotics in the oral cavity remain largely unknown. In addition, very little is known about the role of commensal bifidobacteria in oral health. Our aim was to study the integration of the probiotic Bifidobacterium animalis subsp. lactis Bb12 and of oral Bifidobacterium dentium and Bifidobacterium longum isolates in supragingival and subgingival biofilm models and their effects on other bacteria in biofilms in vitro using two different in vitro biofilms and agar-overlay assays. All bifidobacteria integrated well into the subgingival biofilms composed of Porphyromonas gingivalis, Actinomyces naeslundii, and Fusobacterium nucleatum and decreased significantly only the number of P. gingivalis in the biofilms. The integration of bifidobacteria into the supragingival biofilms containing Streptococcus mutans and A. naeslundii was less efficient, and bifidobacteria did not affect the number of S. mutans in biofilms. Therefore, our results suggest that bifidobacteria may have a positive effect on subgingival biofilm and thereby potential in enhancing gingival health; however, their effect on supragingival biofilm may be limited.

Javed, N. H., Alsahly, M. B., and Khubchandani, J. Oral Feeding of Probiotic Bifidobacterium infantis: Colonic Morphological Changes in Rat Model of TNBS-Induced Colitis. Scientifica.(Cairo.). 2016; 2016:9572596

ABSTRACT: Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology. It has been proposed that modifying the bacterial flora in intestine with probiotics may decrease the inflammatory process and prevent relapses in UC. We investigated the possible protective and therapeutic effects of a single strand of probiotic, Bifidobacterium infantis (BI), on colonic inflammation, in rats with regular feedings. Two groups of Lewis rats were prepared (n = 8). The first group was the control, sham-fed group (n = 4). The other group was the experimental BI-fed group (n = 4). Colitis was induced in both groups by intrarectal administration of TNBS under light anesthesia. The sham-fed colitis induced groups received a daily oral gavage feeding of 1.0 mL distilled water, whereas the B. infantis-fed group received 0.205 g of B. infantis dissolved in 1.0 mL distilled water daily. The change in body weight and food and water intake was recorded over the course of each study and analyzed. The rats were euthanized and tissues from the descending colon were harvested and analyzed microscopically and histologically. Results of our study indicated significant reduction in inflammation, mucosal damage, and preservation of goblet cells, as compared to the control animals. Modulation of gastrointestinal (GI) flora suggests a promising field in developing strategies for prevention and treatment of inflammatory bowel diseases by dietary modifications.

Jawaro, T., Yang, A., Dixit, D., and Bridgeman, M. B. Management of Hepatic Encephalopathy: A Primer. Ann.Pharmacother. 2016; 50(7):569-577.

ABSTRACT: OBJECTIVE: To review the management of hepatic encephalopathy (HE), including lifestyle modifying strategies and pharmacological interventions. DATA

SOURCES: A literature search of PubMed through March 2016 was conducted utilizing the keywords hepatic encephalopathy, ammonia, and cirrhosis All published articles evaluating treatments for HE were considered. STUDY SELECTION AND DATA EXTRACTION: Available English-language data from reviews, abstracts, presentations, and clinical trials of the treatment of HE in humans were reviewed; relevant clinical data were selected and included. DATA SYNTHESIS: HE is a prevalent complication of portal hypertension and cirrhosis that results in altered mental status and neuropsychiatric impairment. Although the pathogenesis has not been elucidated, numerous treatment options exist. This review will explore the role of dietary interventions and supplements, including use of zinc, acetyl-l-carnitine, and probiotics, in the management of HE. Additionally, the use of various ammonia-lowering agents will be evaluated. The nonabsorbable disaccharides represent first-line therapies for the management and prophylaxis of HE; rifaximin use has been demonstrated to be effective for both treatment and prophylaxis of HE symptoms, with use relegated to those patients who fail to respond to or tolerate the nonabsorbable disaccharides. In light of toxicities associated with the use of neomycin and metronidazole, recent guidelines recommend both as alternatives for the treatment of HE, with the use of vancomycin discouraged. CONCLUSION: Although numerous treatment options are available, management of HE remains a clinical challenge. Additional research is needed to explore the pathogenesis and better understand the role of pharmacotherapy in managing this condition.

Jiang, M., Deng, K., Jiang, C., Fu, M., Guo, C., Wang, X., Wang, X., Meng, F., Yang, S., Deng, K., Chen, T., and Xin, H. Evaluation of the Antioxidative, Antibacterial, and Anti-Inflammatory Effects of the Aloe Fermentation Supernatant Containing Lactobacillus plantarum HM218749.1. Mediators.Inflamm. 2016; 2016:2945650

ABSTRACT: Little work is done to develop Aloe vera (AV) using probiotics. To explore the potential benefits, the antioxidant effects and the antibacterial effects on foodborne pathogens of Aloe fermentation supernatant were evaluated in vitro. Our results indicated that the Aloe fermentation supernatant fermented by Lactobacillus plantarum HM218749.1 had very strong scavenging capacities of the DPPH (86%), O2 (*-) (85%), (*)OH (76%), and Fe(2+) chelation (82%) and reducing powers (242.5 mg/L), and the inhibition zones for Salmonella typhimurium, Salmonella enteritidis, Shigella flexneri, Escherichia coli, Listeria monocytogenes, S. dysenteriae 301, Staphylococcus aureus Cowan1, and Propionibacterium acnes were 16, 15, 19, 20, 21, 20, and 27 mm. Moreover, the low concentration of Aloe fermentation supernatant had significantly reduced the production of IL-1beta, TNF-alpha, and IL-6 in both mRNA and protein levels ($P < 0.01$). Therefore, the Aloe fermentation supernatant can be used as functional beverage or cosmetic ingredients to guard human intestinal health, delaying senescence, and prevent chronic diseases.

Jiang, Q., Stamatova, I., Kainulainen, V., Korpela, R., and Meurman, J. H. Interactions between Lactobacillus rhamnosus GG and oral micro-organisms in an in vitro biofilm model. BMC.Microbiol. 2016; 16(1)::

BACKGROUND: Probiotics have shown favourable properties in maintaining oral health. By interacting with oral microbial communities, these species could contribute to healthier microbial equilibrium. This study aimed to investigate in vitro the ability of probiotic Lactobacillus rhamnosus GG (L.GG) to integrate in oral biofilm and affect its species composition. Five oral strains, Streptococcus mutans, Streptococcus sanguinis,

Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum and Candida albicans were involved. The group setup included 6 mono-species groups, 3 dual-species groups (L.GG + S. mutans/S. sanguinis/C. albicans), and 4 multi-species groups (4/5 species and 4/5 species + L.GG, 4 species were all the tested strains except S. mutans). Cell suspensions of six strains were pooled according to the group setup. Biofilms were grown on saliva-coated hydroxyapatite (HA) discs at 37 degrees C in anaerobic conditions for 64.5 h. Biofilm medium was added and refreshed at 0, 16.5, and 40.5 h. The pH of spent media was measured. Viable cells of the 16.5 h and 64.5 h biofilms were counted. 64.5 h biofilms were stained and scanned with confocal laser scanning microscopy. RESULTS: Our results showed that L.GG and S. mutans demonstrated stronger adhesion ability than the other strains to saliva-coated HA discs. L.GG, C. albicans, S. mutans and F. nucleatum, with poor ability to grow in mono-species biofilms demonstrated better abilities of adhesion and reproduction in dual- and/or multi-species biofilms. L.GG slightly suppressed the growth of C. albicans in all groups, markedly weakened the growth of S. sanguinis and F. nucleatum in 4sp + L.GG group, and slightly reduced the adhesion of S. mutans in L.GG+ S. mutans group. CONCLUSIONS: To conclude, in this in vitro model L.GG successfully integrated in all oral biofilms, and reduced the counts of S. sanguinis and C. albicans and lowered the biofilm-forming ability of F. nucleatum, but only slightly reduced the adhesion of S. mutans. C. albicans significantly promoted the growth of L.GG.

Jiang, Y., Yang, G., Meng, F., Yang, W., Hu, J., Ye, L., Shi, C., and Wang, C. Immunological mechanisms involved in probiotic-mediated protection against Citrobacter rodentium-induced colitis. Benef.Microbes. 2016; 7(3):397-407.

ABSTRACT: Inflammatory bowel disease is a group of chronic, incurable inflammatory disorders of the gastrointestinal tract that cause severe diarrhoea, intestinal inflammation, pain, fatigue and weight loss. In this study, we first developed a model of Citrobacter rodentium-induced colitis and then evaluated the protective effects of selected probiotics on inflammation. The results showed that administration of a combination of probiotics including Lactobacillus rhamnosus ATCC 53103, Lactobacillus acidophilus ATCC 4356 and Lactobacillus plantarum A significantly increased the production of CD11c(+) dendritic cells in the spleen (3.62% vs phosphate buffered saline (PBS)-treated control, P<0.01) and mesenteric lymph nodes (MLNs). In addition, the presence of probiotics significantly up-regulated the development of CD4(+)/CD25(+)/Foxp3(+) regulatory T cells in MLNs by approximately 2.07% compared to the effect observed in the PBS-treated control (P<0.01) and down-regulated the expression of inflammatory cytokines, including interleukin-17, tumour necrosis factor-alpha and interferon-gamma, by 0.11, 0.11 and 0.15%, respectively, compared to the effect observed in the PBS-treated control (P<0.01).These effects conferred protection against colitis, as shown by histopathological analyses.

Jiang, Y., Zheng, Z., Zhang, T., Hendricks, G., and Guo, M. Microencapsulation of Lactobacillus acidophilus NCFM using polymerized whey proteins as wall material. Int.J.Food Sci.Nutr. 2016; 67(6):670-677.

ABSTRACT: Survivability of probiotics in foods is essential for developing functional food containing probiotics. We investigated polymerized whey protein (PWP)-based microencapsulation process which is developed for protecting probiotics like Lactobacillus acidophilus NCFM and compared with the method using sodium alginate

(SA). The entrapment rate was 89.3 +/- 4.8% using PWP, while it was 73.2 +/- 1.4% for SA. The microencapsulated NCFM by PWP and SA were separately subjected to digestion juices and post-fermentation storage of fermented cows' and goats' milk using the encapsulated culture. The log viable count of NCFM in PWP-based microencapsulation was 4.56, compared with that of 4.26 in SA-based ones and 3.13 for free culture. Compared with using SA as wall material, PWP was more effective in protecting probiotic. Microencapsulation of L. acidophilus NCFM using PWP as wall material can be exploited in the development of fermented dairy products with better survivability of probiotic organism.

Jo, S. G., Noh, E. J., Lee, J. Y., Kim, G., Choi, J. H., Lee, M. E., Song, J. H., Chang, J. Y., and Park, J. H. Lactobacillus curvatus WiKim38 isolated from kimchi induces IL-10 production in dendritic cells and alleviates DSS-induced colitis in mice. J.Microbiol. 2016; 54(7):503-509.

ABSTRACT: Probiotics such as lactobacilli and bifidobacteria have healthpromoting effects by immune modulation. In the present study, we examined the immunomodulatory properties of Lactobacillus curvatus WiKim38, which was newly isolated from baechu (Chinese cabbage) kimchi. The ability of L. curvatus WiKim38 to induce cytokine production in bone marrow-derived dendritic cells (BMDCs) was determined by enzyme-linked immunosorbent assay. To evaluate the molecular mechanisms underlying L. curvatus Wikim38-mediated IL-10 production, Western blot analyses and inhibitor assays were performed. Moreover, the in vivo anti-inflammatory effects of L. curvatus WiKim38 were examined in a dextran sodium sulfate (DSS)-induced colitis mouse model. L. curvatus WiKim38 induced significantly higher levels of IL-10 in BMDCs compared with that induced by LPS. NF-kappaB and ERK were activated by L. curvatus WiKim38, and an inhibitor assay revealed that these pathways were required for L. curvatus WiKim38-induced production of IL-10 in BMDCs. An in vivo experiment showed that oral administration of L. curvatus WiKim38 increased the survival rate of mice with DSS-induced colitis and improved clinical signs and histopathological severity in colon tissues. Taken together, these results indicate that L. curvatus Wikim38 may have health-promoting effects via immune modulation, and may thus be applicable for therapy of various inflammatory diseases.

Johansson, M. A., Bjorkander, S., Mata, Forsberg M., Qazi, K. R., Salvany, Celades M., Bittmann, J., Eberl, M., and Sverremark-Ekstrom, E. Probiotic Lactobacilli Modulate Staphylococcus aureus-Induced Activation of Conventional and Unconventional T cells and NK Cells. Front Immunol. 2016; 7:273

ABSTRACT: Lactobacilli are probiotic commensal bacteria and potent modulators of immunity. When present in the gut or supplemented as probiotics, they beneficially modulate ex vivo immune responsiveness. Further, factors derived from several lactobacilli strains act immune regulatory in vitro. In contrast, Staphylococcus aureus (S. aureus) is known to induce excessive T cell activation. In this study, we aimed to investigate S. aureus-induced activation of human mucosal-associated invariant T cells (MAIT cells), gammadelta T cells, NK cells, as well as of conventional CD4(+) and CD8(+) T cells in vitro. Further, we investigated if lactobacilli-derived factors could modulate their activation. PBMC were cultured with S. aureus 161:2 cell-free supernatants (CFS), staphylococcal enterotoxin A or CD3/CD28-beads alone, or in combination with Lactobacillus rhamnosus GG-CFS or Lactobacillus reuteri DSM 17938-CFS and activation

of T and NK cells was evaluated. S. aureus-CFS induced IFN-gamma and CD107a expression as well as proliferation. Costimulation with lactobacilli-CFS dampened lymphocyte-activation in all cell types analyzed. Preincubation with lactobacilli-CFS was enough to reduce subsequent activation, and the absence of APC or APC-derived IL-10 did not prevent lactobacilli-mediated dampening. Finally, lactate selectively dampened activation of unconventional T cells and NK cells. In summary, we show that molecules present in the lactobacilli-CFS are able to directly dampen in vitro activation of conventional and unconventional T cells and of NK cells. This study provides novel insights on the immune-modulatory nature of probiotic lactobacilli and suggests a role for lactobacilli in the modulation of induced T and NK cell activation.

John, G. K. and Mullin, G. E. The Gut Microbiome and Obesity. Curr.Oncol.Rep. 2016; 18(7):45

ABSTRACT: The gut microbiome consists of trillions of bacteria which play an important role in human metabolism. Animal and human studies have implicated distortion of the normal microbial balance in obesity and metabolic syndrome. Bacteria causing weight gain are thought to induce the expression of genes related to lipid and carbohydrate metabolism thereby leading to greater energy harvest from the diet. There is a large body of evidence demonstrating that alteration in the proportion of Bacteroidetes and Firmicutes leads to the development of obesity, but this has been recently challenged. It is likely that the influence of gut microbiome on obesity is much more complex than simply an imbalance in the proportion of these phyla of bacteria. Modulation of the gut microbiome through diet, pre- and probiotics, antibiotics, surgery, and fecal transplantation has the potential to majorly impact the obesity epidemic.

Jonkers, D. M. Microbial perturbations and modulation in conditions associated with malnutrition and malabsorption. Best.Pract.Res.Clin.Gastroenterol. 2016; 30(2):161-172.

ABSTRACT: The intestinal microbiota is a complex ecosystem, which can be considered an accessory organ. It involves complex microbe-microbe and host-microbe interactions with indispensable functions for the human host with regard to the intestinal epithelium and barrier function, the innate and adaptive immune system, and its large metabolic capacity. Saccharolytic fermentation results in the production of short chain fatty acids, which exert an array of beneficial effects, while proteolytic fermentation leads to an increase in potentially harmful metabolites. In addition, numerous other microbial metabolites are being produced with various intestinal as well as extra-intestinal effects. Their generation depends on the composition of the microbiota as well as the availability of substrates, which both vary along the GI tract. Diet impacts the intestinal microbiota composition and activity in early infancy as well as in adults. Microbial perturbations have been demonstrated in subjects with under-nutrition and/or malabsorption. The bidirectional interactions between the microbiome, nutrient availability and GI function, can contribute to a vicious circle, further impairing health outcome in conditions associated with malnutrition and/or malabsorption. Integrated multivariate approaches are needed to further unravel the complex interaction between microbiome, diet and host factors, as well as possible modulation thereof by prebiotics or probiotics. The present overview will briefly outline the composition and function of the intestinal microbiota, its association with nutrient intake and availability, and will address the role of the intestinal microbiota in malnutrition and malabsorption.

Jorgensen, M. R., Keller, M. K., Kragelund, C., Hamberg, K., Ericson, D., Nielsen, C. H., and Twetman, S. Lactobacillus reuteri supplements do not affect salivary IgA or cytokine levels in healthy subjects: A randomized, double-blind, placebo-controlled, cross-over trial. Acta Odontol.Scand. 2016; 74(5):399-404.

ABSTRACT: OBJECTIVES: To evaluate the effect of daily ingestion of probiotic lactobacilli on the levels of secretory IgA (sIgA) and selected cytokines in whole saliva of healthy young adults. MATERIALS AND METHODS: The study group consisted of 47 healthy adults (18-32 years) who volunteered for a randomized, double-blind, placebo-controlled, cross-over trial after informed consent. During intervention, the subjects ingested two lozenges per day containing two strains of the probiotic bacterium Lactobacillus reuteri (DSM 17938 and ATCC PTA 5289) or placebo lozenges. The intervention and wash-out periods were 3 weeks. Saliva samples were collected at baseline, immediately after each intervention period and 3 weeks post-intervention. ELISA was used to measure sIgA and luminex technology was used to measure the interleukins (IL)-1beta, IL-6, IL-8 and IL-10. For statistical analyses a mixed ANOVA model was employed to calculate changes in the salivary outcome variables. RESULTS: Forty-one subjects completed the study and reported a good compliance. No significant differences in the concentrations of salivary sIgA or cytokines were recorded between the L. reuteri and placebo interventions or between baseline and 3 weeks post-intervention levels. No side- or adverse effects were reported. CONCLUSIONS: Supplementation with two strains of the probiotic L. reuteri did not affect sIgA or cytokine levels in whole saliva in healthy young adults. The results thereby indicate that daily oral supplementation with L. reuteri do not seem to modulate the salivary oral immune response in healthy young subjects (ClinicalTrials.gov NCT02017886).

Jose, Fabrega M., Aguilera, L., Gimenez, R., Varela, E., Alexandra, Canas M., Antolin, M., Badia, J., and Baldoma, L. Activation of Immune and Defense Responses in the Intestinal Mucosa by Outer Membrane Vesicles of Commensal and Probiotic Escherichia coli Strains. Front Microbiol. 2016; 7:705

ABSTRACT: The influence of microbiota in human health is well-known. Imbalances in microbiome structure have been linked to several diseases. Modulation of microbiota composition through probiotic therapy is an attempt to harness the beneficial effects of commensal microbiota. Although, there is wide knowledge of the responses induced by gut microbiota, the microbial factors that mediate these effects are not well-known. Gram-negative bacteria release outer membrane vesicles (OMVs) as a secretion mechanism of microbial factors, which have an important role in intercellular communication. Here, we investigated whether OMVs from the probiotic Escherichia coli strain Nissle 1917 (EcN) or the commensal E. coli strain ECOR12 trigger immune responses in various cellular models: (i) peripheral blood mononuclear cells (PBMCs) as a model of intestinal barrier disruption, (ii) apical stimulation of Caco-2/PMBCs co-culture as a model of intact intestinal mucosa, and (iii) colonic mucosa explants as an ex vivo model. Stimulations with bacterial lysates were also performed. Whereas, both OMVs and lysates activated expression and secretion of several cytokines and chemokines in PBMCs, only OMVs induced basolateral secretion and mRNA upregulation of these mediators in the co-culture model. We provide evidence that OMVs are internalized in polarized Caco-2 cells. The activated epithelial cells elicit a response in the underlying immunocompetent cells. The OMVs effects were corroborated in the ex vivo model. This experimental study shows that OMVs are an effective strategy used by beneficial gut bacteria to

communicate with and modulate host responses, activating signaling events through the intestinal epithelial barrier.

Joyce, S. A. and Gahan, C. G. Bile Acid Modifications at the Microbe-Host Interface: Potential for Nutraceutical and Pharmaceutical Interventions in Host Health. Annu.Rev.Food Sci.Technol. 2016; 7:313-333.

ABSTRACT: Bile acids have emerged as important signaling molecules in the host, as they interact either locally or systemically with specific cellular receptors, in particular the farnesoid X receptor (FXR) and TGR5. These signaling functions influence systemic lipid and cholesterol metabolism, energy metabolism, immune homeostasis, and intestinal electrolyte balance. Through defined enzymatic activities, the gut microbiota can significantly modify the signaling properties of bile acids and therefore can have an impact upon host health. Alterations to the gut microbiota that influence bile acid metabolism are associated with metabolic disease, obesity, diarrhea, inflammatory bowel disease (IBD), Clostridium difficile infection, colorectal cancer, and hepatocellular carcinoma. Here, we examine the regulation of this gut-microbiota-liver axis in the context of bile acid metabolism and indicate how this pathway represents an important target for the development of new nutraceutical (diet and/or probiotics) and targeted pharmaceutical interventions.

Jurjus, A., Eid, A., Al, Kattar S., Zeenny, M. N., Gerges-Geagea, A., Haydar, H., Hilal, A., Oueidat, D., Matar, M., Tawilah, J., Hussein, I. H., Schembri-Wismayer, P., Cappello, F., Tomasello, G., Leone, A., and Jurjus, R. A. Inflammatory bowel disease, colorectal cancer and type 2 diabetes mellitus: The links. BBA.Clin. 2016; 5:16-24.

ABSTRACT: The co-occurrence of the three disease entities, inflammatory bowel disease (IBD), colorectal cancer (CRC), type 2diabetes mellitus (T2DM) along with inflammation and dismicrobism has been frequently reported. Some authors have even suggested that dysbiosis could be the link through a molecular crosstalk of multiple inflammatory loops including TGFbeta, NFKB, TNFalpha and ROS among others. This review focuses on the inflammatory process along with the role of microbiota in the pathophysiology of the three diseases. The etiology of IBD is multifactorial, and like CRC and T2DM, it is associated with a widespread and sustained GI inflammation and dismicrobism, whereby an array of pro-inflammatory mediators and other related biomolecules are up-regulated, both locally and systematically. Such a persistent or an inadequately resolved chronic inflammation may be a causative agent, in the presence other factors, leading to several pathologies such as IBD, CRC and T2DM. TGFbeta plays a crucial role in pancreatic beta cell malfunctioning as glucotoxicity stimulates its signaling cascade through smad 3, IL-6 and epithelial to mesenchymal transition. Such a cascade could lead to macrophages and other cells recruitment, inflammation, then IBD and CRC. NFkB is also another key regulator in the crosstalk among the pathways leading to the three disease entities. It plays a major role in linking inflammation to cancer development through its ability to up regulate several inflammatory and tumor promoting cytokines like: IL-6, IL-1 alpha and TNF alpha, as well as genes like BCL2 and BCLXL. It activates JAK/STAT signaling network via STAT3 transcription factors and promotes epithelial to mesenchymal transition. It also increases the risk for T2DM in obese people. In brief, NFKB is a matchmaker between inflammation, IBD, cancer and diabetes. In addition, TNFalpha plays a pivotal role in systemic inflammation. It is increased in the mucosa of IBD patients and has a central role in its pathogenesis. It also activates other signaling

pathways like NFKB and MAPK leading to CRC. It is also overexpressed in the adipose tissues of obese patients thus linking it to T2DM, chronic inflammation and consequently CRC. On the other hand, increasing evidence suggests that dysbiosis plays a role in initiating, maintaining and determining the severity of IBD. Actually, among its functions, it modulates genotoxic metabolites which are able to induce CRC, a fact proven to be sustained by stool transfer from patients with CRC. Probiotics, however, may actively prevent CRC as well as IBD and results in a significant decrease in fasting glycemia in T2DM patients. In conclusion, IBD, CRC and T2DM are commonly occurring interrelated clinical problems. They share a common basis influenced by an inflammatory process, an imbalance in intestinal microbiota, and a crosstalk between various signaling pathways. Would probiotics interrupt the crosstalk or orient it in the physiological direction?

Kalani, M., Hodjati, H., Sajedi, Khanian M., and Doroudchi, M. Lactobacillus acidophilus Increases the Anti-apoptotic Micro RNA-21 and Decreases the Pro-inflammatory Micro RNA-155 in the LPS-Treated Human Endothelial Cells. Probiotics.Antimicrob.Proteins. 2016; 8(2):61-72.

ABSTRACT: Given the anti-inflammatory and protective role of probiotics in atherosclerosis and the regulatory role of micro RNA (miRNA) in endothelial cell (dys) functions, this study aimed to investigate the effect of Lactobacillus acidophilus (La) on cellular death and the expression of miRNA-21, 92a, 155, and 663 in human umbilical vein endothelial cell (HUVEC) induced by Escherichia coli lipopolysaccharide (Ec-LPS). LPS-treated and untreated HUVECs were cultured in the presence of different La conditions such as La-conditioned media (LaCM), La water extract (LaWE), La culture-filtered (LaFS) and unfiltered supernatants (LaUFS). After 24 h, apoptosis, necrosis and the levels of the mentioned miRNAs were measured using flow cytometry and real-time PCR methods, respectively. LaCM decreased apoptosis, necrosis and inflammatory miR-155 and conversely increased anti-apoptotic miR-21 in Ec-LPS-treated HUVECs. Association analysis revealed negative correlations between necrosis and the levels of miR-21, miR-92a, and miR-155. The beneficial effects of L. acidophilus on the ECs death and expression of atherosclerosis related miRNAs in these cells imply a new aspect of its regulation in cardiovascular diseases rather than previously described ones and suggest this probiotic bacterium as a candidate in the preventative therapy of atherosclerosis.

Kalima, K., Lehtoranta, L., He, L., Pitkaniemi, J., Lundell, R., Julkunen, I., Roivainen, M., Narkio, M., Makela, M. J., Siitonen, S., Korpela, R., and Pitkaranta, A. Probiotics and respiratory and gastrointestinal tract infections in Finnish military conscripts - a randomized placebo-controlled double-blinded study. Benef.Microbes. 4-6-2016; 1-10.

ABSTRACT: Military conscripts are susceptible to respiratory and gastrointestinal tract infections. In previous studies probiotics have shown potency to reduce upper respiratory and gastrointestinal infections. The aim was to study whether probiotic intervention has an impact on seasonal occurrence of upper respiratory and gastrointestinal infections in two different conscript groups. In a randomised, double-blinded, placebo controlled study (https://clinicaltrials.gov NCT01651195), a total of 983 healthy adults were enrolled from two intakes of conscripts. Conscripts were randomised to receive either a probiotic combination of Lactobacillus rhamnosus GG (LGG) and Bifidobacterium animalis ssp. lactis BB12 (BB12) or a control chewing tablet twice daily for 150 days (recruits) or for 90 days (reserve officer candidates). Clinical examinations were carried out and daily symptom diaries were collected. Outcome measures were the number of days with

respiratory and gastrointestinal symptoms and symptom incidence, number and duration of infection episodes, number of antibiotic treatments received and number of days out of service because of the infection. Statistically no significant differences were found between the intervention groups either in the risk of symptom incidence or duration. However, probiotic intervention was associated with reduction of specific respiratory infection symptoms in military recruits, but not in reserve officer candidates. Probiotics did not significantly reduce overall respiratory and gastrointestinal infection morbidity.

Kalyuzhin, O. V., Afanasyev, S. S., and Bykov, A. S. [Probiotics as stimulators of immune response against pathogens in the respiratory tract]. Ter.Arkh. 2016; 88(5):118-124.

ABSTRACT: This review analyzes whether.it is expedient to use oral probiotics for the stimulation of immune response against pathogens in the respiratory tract. It considers a relationship between.mucosal microbial colonization in different biotopes of the body and mucosal.immunity in the respiratory tract. The principal and terminological controversial issues of colonic dysbiosis and the possibilities of using the medicines and products containing live commensals/symbionts to correct microbiota disturbances are examined. There are data on the degree of resistance and resilience of the colonic microbial community exposed to destabilizing factors, antibiotics in particular. The properties of probiotics that have been proven to enhance host response against pathogens and the phenomena that characterize these probiotics as immunomodifiers and distinguish them from other immunostimulating/immunomodulating agents are described. Criteria for choosing effective and safe oral probiotics to stimulate an immune response in the respiratory tract are formulated. Finally, we review the data on the clinical and immunomodulatory effects of dietary supplement containing a combination of three probiotic strains (Lactobacillus gasseri PA 16/8, Bifidobacterium bifidum MF 20/5 and Bifidobacterium longum SP 07/3) with vitamins and minerals as an agent to prevent and reduce the severity of acute and recurrent respiratory tract infections.

Kantor, R. and Silverberg, J. I. Environmental risk factors and their role in the management of atopic dermatitis. Expert.Rev.Clin.Immunol. 7-28-2016; 1-12.

ABSTRACT: INTRODUCTION: The etiology of atopic dermatitis (AD) is multifactorial with interaction between genetics, immune and environmental factors. AREAS COVERED: We review the role of prenatal exposures, irritants and pruritogens, pathogens, climate factors, including temperature, humidity, ultraviolet radiation, outdoor and indoor air pollutants, tobacco smoke exposure, water hardness, urban vs. rural living, diet, breastfeeding, probiotics and prebiotics on AD. Expert commentary: The increased global prevalence of AD cannot be attributed to genetics alone, suggesting that evolving environmental exposures may trigger and/or flare disease in predisposed individuals. There is a complex interplay between different environmental factors, including individual use of personal care products and exposure to climate, pollution, food and other exogenous factors. Understanding these complex risk factors is crucial to developing targeted interventions to prevent the disease in millions. Moreover, patients require counseling on optimal regimens for minimization of exposure to irritants and pruritogens and other harmful exposures.

Karamali, M., Dadkhah, F., Sadrkhanlou, M., Jamilian, M., Ahmadi, S., Tajabadi-Ebrahimi, M., Jafari, P., and Asemi, Z. Effects of probiotic supplementation on glycaemic control and

lipid profiles in gestational diabetes: A randomized, double-blind, placebo-controlled trial. Diabetes Metab. 5-18-2016;

ABSTRACT: BACKGROUND: To our knowledge, data on the effects of probiotic supplementation on glycaemic control and lipid concentrations in patients with gestational diabetes mellitus (GDM) are scarce. AIM: The aim of the present study was to determine the effects of probiotic supplementation on glycaemic control and lipid profiles in GDM patients. METHODS: Sixty pregnant women with GDM, primigravida and aged 18-40years, were divided into two groups to receive either probiotic capsules (n=30) or a matching placebo (n=30) in this randomized double-blind, placebo-controlled trial. The patients in the probiotic group took a daily capsule that contained three viable freeze-dried strains: Lactobacillus acidophilus (2x109CFU/g), L. casei (2x109CFU/g) and Bifidobacterium bifidum (2x109CFU/g) for 6weeks. The placebo group took capsules filled with cellulose for the same time period. Fasting blood samples were taken at the beginning and end of the study to quantify the relevant markers. RESULTS: After 6weeks of intervention, probiotic supplementation vs a placebo resulted in significant decreases in fasting plasma glucose (-9.2+/-9.2mg/dL vs +1.1+/-12.2mg/dL, P<0.001), serum insulin levels (-0.8+/-3.1muIU/mL vs +4.5+/-10.6muIU/mL, P=0.01), homoeostasis model assessment (HOMA) for insulin resistance (-0.4+/-0.9 vs +1.1+/-2.5, P=0.003) and HOMA for beta-cell function (+1.1+/-9.8 vs +18.0+/-42.5, P=0.03), and a significant increase in the quantitative insulin sensitivity check index (+0.007+/-0.01 vs -0.01+/-0.02, P=0.007). In addition, significant decreases in serum triglycerides (-1.6+/-59.4mg/dL vs +27.1+/-37.9mg/dL, P=0.03) and VLDL cholesterol concentrations (-0.3+/-11.9mg/dL vs +5.4+/-7.6mg/dL, P=0.03) were seen following supplementation with the probiotics compared with the placebo. However, no significant changes in other lipid profiles were seen with the intervention. CONCLUSION: Overall, the results of our study have demonstrated that taking probiotic supplements for 6weeks in patients with GDM had beneficial effects on glycaemic control, triglycerides and VLDL cholesterol concentrations, although there was no effect on other lipid profiles.

Karimi, S., Ahl, D., Vagesjo, E., Holm, L., Phillipson, M., Jonsson, H., and Roos, S. In Vivo and In Vitro Detection of Luminescent and Fluorescent Lactobacillus reuteri and Application of Red Fluorescent mCherry for Assessing Plasmid Persistence. PLoS.One. 2016; 11(3):e0151969

ABSTRACT: Lactobacillus reuteri is a symbiont that inhabits the gastrointestinal (GI) tract of mammals, and several strains are used as probiotics. After introduction of probiotic strains in a complex ecosystem like the GI tract, keeping track of them is a challenge. The main objectives of this study were to introduce reporter proteins that would enable in vivo and in vitro detection of L. reuteri and increase knowledge about its interactions with the host. We describe for the first time cloning of codon-optimized reporter genes encoding click beetle red luciferase (CBRluc) and red fluorescent protein mCherry in L. reuteri strains ATCC PTA 6475 and R2LC. The plasmid persistence of mCherry-expressing lactobacilli was evaluated by both flow cytometry (FCM) and conventional plate count (PC), and the plasmid loss rates measured by FCM were lower overall than those determined by PC. Neutralization of pH and longer induction duration significantly improved the mCherry signal. The persistency, dose-dependent signal intensity and localization of the recombinant bacteria in the GI tract of mice were studied with an in vivo imaging system (IVIS), which allowed us to detect fluorescence from 6475-CBRluc-mCherry given at a dose of 1x1010 CFU and luminescence signals at doses ranging from 1x105 to 1x1010 CFU. Both 6475-CBRluc-mCherry and R2LC-CBRluc were localized in the colon 1 and 2 h

after ingestion, but the majority of the latter were still found in the stomach, possibly reflecting niche specificity for R2LC. Finally, an in vitro experiment showed that mCherry-producing R2LC adhered efficiently to the intra cellular junctions of cultured IPEC-J2 cells. In conclusion, the two reporter genes CBRluc and mCherry were shown to be suitable markers for biophotonic imaging (BPI) of L. reuteri and may provide useful tools for future studies of in vivo and in vitro interactions between the bacteria and the host.

Kathrani, A., Larsen, J. A., Kass, P. H., and Fascetti, A. J. Effect of short-term probiotic Enterococcus faecium SF68 dietary supplementation in overweight and obese cats without comorbidities. Vet.Rec.Open. 2016; 3(1):e000164

ABSTRACT: Obesity in cats is associated with metabolic abnormalities and increased susceptibility to diseases such as diabetes mellitus. Studies in mouse models and human beings have shown that probiotics can reduce food intake, promote weight loss and improve metabolic profile. Studies assessing the effects of probiotics on these same parameters are absent in cats. Therefore, the aim of this study was to determine if probiotic Enterococcus faecium strain SF68 dietary supplementation reduces food intake, promotes weight loss and improves metabolic profile in overweight and obese cats without comorbidities. Twenty overweight and obese specific pathogen-free cats without comorbidities were acclimatised to a dry diet for four weeks. After exclusion of four cats for unrelated reasons, eight cats received a daily oral probiotic for eight weeks and eight control cats received no probiotic. All cats were fed ad libitum with food intake measured daily and bodyweight weekly. Blood was collected at three time points: after four weeks of acclimatisation to the diet, after eight weeks of intervention and after six weeks of washout for measurement of glucose, triglyceride, cholesterol, fructosamine, insulin, leptin, total adiponectin and deuterium oxide for body composition. There were no differences in food intake, metabolic parameters and body composition between the probiotic and control groups after eight weeks of intervention and six weeks of washout (P>/=0.050). Short-term use of E faecium SF68 dietary supplementation had no significant effect on food intake, bodyweight, body composition or metabolic parameters in overweight and obese specific pathogen-free cats without comorbidities.

Kato-Kataoka, A., Nishida, K., Takada, M., Kawai, M., Kikuchi-Hayakawa, H., Suda, K., Ishikawa, H., Gondo, Y., Shimizu, K., Matsuki, T., Kushiro, A., Hoshi, R., Watanabe, O., Igarashi, T., Miyazaki, K., Kuwano, Y., and Rokutan, K. Fermented Milk Containing Lactobacillus casei Strain Shirota Preserves the Diversity of the Gut Microbiota and Relieves Abdominal Dysfunction in Healthy Medical Students Exposed to Academic Stress. Appl.Environ.Microbiol. 6-15-2016; 82(12):3649-3658.

ABSTRACT: Stress-induced abdominal dysfunction is an attractive target for probiotics. To investigate the effects of the probiotic Lactobacillus casei strain Shirota on abdominal dysfunction, a double-blind, placebo-controlled trial was conducted with healthy medical students undertaking an authorized nationwide examination for academic advancement. For 8 weeks, until the day before the examination, 23 and 24 subjects consumed an L. casei strain Shirota-fermented milk and a placebo milk daily, respectively. In addition to assessments of abdominal symptoms, psychophysical state, and salivary stress markers, gene expression changes in peripheral blood leukocytes and composition of the gut microbiota were analyzed using DNA microarray analysis and 16S rRNA gene amplicon sequence analysis, respectively, before and after the intervention. Stress-induced increases in a visual analog scale measuring feelings of stress, the total

score of abdominal dysfunction, and the number of genes with changes in expression of more than 2-fold in leukocytes were significantly suppressed in the L. casei strain Shirota group compared with those in the placebo group. A significant increase in salivary cortisol levels before the examination was observed only in the placebo group. The administration of L. casei strain Shirota, but not placebo, significantly reduced gastrointestinal symptoms. Moreover, 16S rRNA gene amplicon sequencing demonstrated that the L. casei strain Shirota group had significantly higher numbers of species, a marker of the alpha-diversity index, in their gut microbiota and a significantly lower percentage of Bacteroidaceae than the placebo group. Our findings indicate that the daily consumption of probiotics, such as L. casei strain Shirota, preserves the diversity of the gut microbiota and may relieve stress-associated responses of abdominal dysfunction in healthy subjects exposed to stressful situations. IMPORTANCE: A novel clinical trial was conducted with healthy medical students under examination stress conditions. It was demonstrated that the daily consumption of lactic acid bacteria provided health benefits to prevent the onset of stress-associated abdominal symptoms and a good change of gut microbiota in healthy medical students.

Kato-Kataoka, A., Nishida, K., Takada, M., Suda, K., Kawai, M., Shimizu, K., Kushiro, A., Hoshi, R., Watanabe, O., Igarashi, T., Miyazaki, K., Kuwano, Y., and Rokutan, K. Fermented milk containing Lactobacillus casei strain Shirota prevents the onset of physical symptoms in medical students under academic examination stress. Benef.Microbes. 2016; 7(2):153-156.

ABSTRACT: This pilot study investigated the effects of the probiotic Lactobacillus casei strain Shirota (LcS) on psychological, physiological, and physical stress responses in medical students undertaking an authorised nationwide examination for promotion. In a double-blind, placebo-controlled trial, 24 and 23 healthy medical students consumed a fermented milk containing LcS and a placebo milk, respectively, once a day for 8 weeks until the day before the examination. Psychophysical state, salivary cortisol, faecal serotonin, and plasma L-tryptophan were analysed on 5 different sampling days (8 weeks before, 2 weeks before, 1 day before, immediately after, and 2 weeks after the examination). Physical symptoms were also recorded in a diary by subjects during the intervention period for 8 weeks. In association with a significant elevation of anxiety at 1 day before the examination, salivary cortisol and plasma L-tryptophan levels were significantly increased in only the placebo group ($P<0.05$). Two weeks after the examination, the LcS group had significantly higher faecal serotonin levels ($P<0.05$) than the placebo group. Moreover, the rate of subjects experiencing common abdominal and cold symptoms and total number of days experiencing these physical symptoms per subject were significantly lower in the LcS group than in the placebo group during the pre-examination period at 5-6 weeks (each $P<0.05$) and 7-8 weeks (each $P<0.01$) during the intervention period. Our results suggest that the daily consumption of fermented milk containing LcS may exert beneficial effects preventing the onset of physical symptoms in healthy subjects exposed to stressful situations.

Keelan, J. A. and Newnham, J. P. Editorial: Advances in the Prevention and Treatment of Inflammation-Associated Preterm Birth. Front Immunol. 2016; 7:264.

No abstract currently available.

Khatri, I., Sharma, S., Ramya, T. N., and Subramanian, S. Complete Genomes of Bacillus coagulans S-lac and Bacillus subtilis TO-A JPC, Two Phylogenetically Distinct Probiotics. PLoS.One. 2016; 11(6):e0156745

ABSTRACT: Several spore-forming strains of Bacillus are marketed as probiotics due to their ability to survive harsh gastrointestinal conditions and confer health benefits to the host. We report the complete genomes of two commercially available probiotics, Bacillus coagulans S-lac and Bacillus subtilis TO-A JPC, and compare them with the genomes of other Bacillus and Lactobacillus. The taxonomic position of both organisms was established with a maximum-likelihood tree based on twenty six housekeeping proteins. Analysis of all probiotic strains of Bacillus and Lactobacillus reveal that the essential sporulation proteins are conserved in all Bacillus probiotic strains while they are absent in Lactobacillus spp. We identified various antibiotic resistance, stress-related, and adhesion-related domains in these organisms, which likely provide support in exerting probiotic action by enabling adhesion to host epithelial cells and survival during antibiotic treatment and harsh conditions.

Khoder, G., Al-Menhali, A. A., Al-Yassir, F., and Karam, S. M. Potential role of probiotics in the management of gastric ulcer. Exp.Ther.Med. 2016; 12(1):3-17.

ABSTRACT: Gastric ulcer is one of the most common chronic gastrointestinal diseases characterized by a significant defect in the mucosal barrier. Helicobacter pylori (H. pylori) infection and the frequent long-term use of non-steroidal anti-inflammatory drugs are major factors involved in gastric ulcer development. Acid inhibitors and antibiotics are commonly used to treat gastric ulcer. However, in the last few decades, the accumulating evidence for resistance to antibiotics and the side effects of antibiotics and acid inhibitors have drawn attention to the possible use of probiotics in the prevention and treatment of gastric ulcer. Probiotics are live microorganisms that when administered in adequate amounts confer health benefits on the host. Currently, the available experimental and clinical studies indicate that probiotics are promising for future applications in the management of gastric ulcers. This review aims to provide an overview of the general health benefits of probiotics on various systemic and gastrointestinal disorders with a special focus on gastric ulcer and the involved cellular and molecular mechanisms: i) Protection of gastric mucosal barrier; ii) upregulation of prostaglandins, mucus, growth factors and anti-inflammatory cytokines; iii) increased cell proliferation to apoptosis ratio; and iv) induction of angiogenesis. Finally, some of the available data on the possible use of probiotics in H. pylori eradication are discussed.

Kiess, A. S., Hirai, J. H., Triplett, M. D., Parker, H. M., and McDaniel, C. D. Impact of oral Lactobacillus acidophilus gavage on rooster seminal and cloacal Lactobacilli concentrations. Poult.Sci. 8-1-2016; 95(8):1934-1938.

ABSTRACT: The use of antibiotics in poultry is being heavily scrutinized, therefore alternatives such as probiotics are being investigated. Lactobacilli spp. are a commonly used bacteria in formulating probiotics, and the addition of Lactobacilli to broiler diets has demonstrated increased growth rates, stimulated immune systems, and reduced pathogen loads in the gastro-intestinal tract (GI:) tract. However, previous research has shown that when rooster semen is directly exposed to Lactobacillus acidophilus (L. acidophilus) sperm quality is reduced. Therefore, the objective of the current study was to determine if oral administration of L. acidophilus increases the concentration of

Lactobacilli in semen as well as the cloaca. A total of 30 roosters were used: 15 roosters were gavaged with 1X PBS (Control) and 15 roosters were gavaged with 10(7) cfu/mL of L. acidophilus (Treated). All roosters were gavaged for 14 consecutive days. Semen was collected on a 3 d interval, and cloacal swabs were collected on a 2 d interval, beginning on the first day prior to oral administration. Semen and cloacal swabs were serial diluted, and 100 muL of each dilution was then plated on Man, Rogosa, Sharpe (MRS:) agar plates. All plates were incubated for 48 h at 37 degrees C under anaerobic conditions and counted. All Lactobacilli counts were first log transformed, then log transformed (day 0) pre-counts were subtracted from the log transformed day counts providing log differences for the analysis. Seminal Lactobacilli counts were not altered by treatments. However, the main effect of treatment (P = 0.026) for cloacal counts indicated that roosters gavaged with Lactobacilli yielded higher counts than the controls. Additionally, cloaca samples also demonstrated a treatment by day interaction trend (P = 0.082), where Lactobacilli was higher in the L. acidophilus gavaged roosters than the controls only on days 3, 5, 13, and 15. In conclusion, the addition of L. acidophilus to the male breeder diet over extended periods may increase concentrations of Lactobacilli in the cloaca even higher than the concentrations observed in this study. If Lactobacilli reaches high enough concentrations in the cloaca, then sperm quality may be impacted which could lead to poor fertility within the breeder flock.

Kim, B., Park, K. Y., Ji, Y., Park, S., Holzapfel, W., and Hyun, C. K. Protective effects of Lactobacillus rhamnosus GG against dyslipidemia in high-fat diet-induced obese mice. Biochem.Biophys.Res.Commun. 4-29-2016; 473(2):530-536.

ABSTRACT: Recent reports suggest that gut microbiota can be a major determinant of dyslipidemia and non-alcoholic fatty liver disease (NAFLD) and its modulation by treating probiotics is a valid strategy to exert a protective effect. In this study, high-fat diet (HFD)-fed mice were orally administrated with Lactobacillus rhamnosus GG (LGG) for 13 weeks. Significant reductions in the weights of the liver, mesenteric and subcutaneous adipose tissues were observed in LGG-treated HFD-fed mice compared to LGG-non-treated controls. The serum levels of triglyceride and cholesterol were also significantly reduced in LGG-treated mice. Gut microbial composition analysis showed that shifts in the diversity of dominant gut bacteria were caused by HFD and restored by LGG treatment. A remarkable decrease of hepatic fat content was also observed in LGG-treated mice, accompanied by downregulated expressions of lipogenic and pro-inflammatory genes in the liver. LGG-treated mice had lower expression levels of genes involved in cholesterol synthesis, but conversely, higher expression levels of cholesterol efflux-related genes compared to LGG-non-treated controls. The cholesterol-lowering effect of LGG was also found to be mediated by suppression of FXR and FGF15 signaling, resulting in the upregulation of hepatic CYP7A1. Our findings confirm a therapeutic potential of probiotics for ameliorating dyslipidemia and NAFLD.

Kim, C. J., Walmsley, S. L., Raboud, J. M., Kovacs, C., Coburn, B., Rousseau, R., Reinhard, R., Rosenes, R., and Kaul, R. Can Probiotics Reduce Inflammation and Enhance Gut Immune Health in People Living with HIV: Study Designs for the Probiotic Visbiome for Inflammation and Translocation (PROOV IT) Pilot Trials. HIV.Clin.Trials. 2016; 17(4):147-157.

ABSTRACT: OBJECTIVES: Despite substantial improvements in HIV outcomes with combination antiretroviral therapy (cART), morbidity and mortality remain above

population norms. The gut mucosal immune system is not completely restored by cART, and the resultant microbial translocation may contribute to chronic inflammation, inadequate CD4 T-cell recovery, and increased rates of serious non-AIDS events. Since the microbial environment surrounding a CD4 T cell may influence its development and function, we hypothesize that probiotics provided during cART might reduce inflammation and improve gut immune health in HIV-positive treatment-naive individuals (PROOV IT I) and individuals with suboptimal CD4 recovery on cART (PROOV IT II). METHODS: These prospective, double-blinded, randomized, placebo-controlled, multicenter pilot studies will assess the impact of the probiotic Visbiome at 900 billion bacteria daily. Forty HIV positive cART-naive men will be randomized in the PROOV IT I study, coincident with antiretroviral initiation, and be followed for 24 weeks. In PROOV IT II, 36 men on cART, but with a CD4 T-cell count below 350 cells/mm(3) will be followed for 48 weeks. The primary outcome for both studies is the comparison of blood CD8 T-cell immune activation. Secondary analyses will include comparison of blood inflammatory biomarkers, microbial translocation, blood and gut immunology and HIV levels, the bacterial community composition, diet, intestinal permeability, and the safety, adherence and tolerability of the study product. DISCUSSION: These studies will evaluate the ability of probiotics as a safe and tolerable therapeutic intervention to reduce systemic immune activation and to accelerate gut immune restoration in people living with HIV.

Kim, H. W., Yan, F. F., Hu, J. Y., Cheng, H. W., and Kim, Y. H. Effects of probiotics feeding on meat quality of chicken breast during postmortem storage. Poult.Sci. 6-1-2016; 95(6):1457-1464.

ABSTRACT: This study evaluated the effects of dietary probiotic supplement and postmortem storage on meat quality of chicken breast during retail display. A total of 35 birds were randomly obtained from 3 feeding groups (control without probiotic supplement, 250 ppm Sporulin, and 500 ppm PoultryStar). The probiotic supplement had no influence on feed conversion ratio and body weight gain, as well as body weight at 29 and 44 d ($P > 0.05$). After slaughter, each side of the breast muscles (M. Pectoralis major) was assigned to either one d or 5 d of postmortem storage. Probiotic supplement had no influence on the rate of pH decline of chicken breast muscles during the initial 6 h postmortem ($P > 0.05$). No interactions between probiotic supplement and postmortem storage on meat quality were found ($P > 0.05$). Postmortem storage decreased drip loss from 25.30 to 18.05% ($P < 0.05$). Probiotics-fed chicken groups, particularly PoultryStar treatment, had a higher myofibrillar fragmentation index than the control group ($P < 0.05$). However, shear force values were not affected by the probiotic treatments. Decreases in color and lipid stabilities of breast muscles were found during display ($P < 0.05$), but were not affected by the probiotic supplement ($P > 0.05$). Our result suggests that probiotic supplement had no adverse impacts on proteolysis and oxidative changes during 5 d postmortem display storage.

Kim, J. S., Hosseindoust, A., Lee, S. H., Choi, Y. H., Kim, M. J., Lee, J. H., Kwon, I. K., and Chae, B. J. Bacteriophage cocktail and multi-strain probiotics in the feed for weanling pigs: effects on intestine morphology and targeted intestinal coliforms and Clostridium. Animal. 6-29-2016; 1-9.

ABSTRACT: Two experiments were conducted to investigate the effects of dietary supplementation of bacteriophage cocktail, probiotics and a combination of these two supplements on performance and gut health of weanling pigs. In Experiment 1, 150

weaned piglets were randomly allotted to three treatments on the basis of BW. The dietary treatments included a basal diet supplemented with 0 (control), 1.0 and 1.5 g/kg bacteriophage cocktail. Pigs fed 1.0 and 1.5 g/kg bacteriophage product had greater (P<0.05) average daily gain (ADG), apparent total tract digestibility of dry matter from day 22 to 35, ileal Lactobacillus spp., villus height (duodenum and jejunum), and fewer coliforms (ileum) and Clostridium spp. (ileum). In Experiment 2, 200 weaned piglets were randomly allotted to four treatments. Dietary treatments included basal diet, basal diet supplemented with 3.0 g/kg fermented probiotic product (P), 1.0 g/kg bacteriophage cocktail (B) and combination of 1.0 g/kg bacteriophage cocktail and 3.0 g/kg fermented probiotic product. Pigs fed bacteriophage cocktail diets had greater (P<0.05) overall ADG, gain to feed ratio (G : F), fecal score from day 8 to day 21, and pigs fed bacteriophage cocktail diets had fewer coliforms (ileum) Clostridium spp. (ileum and cecum). Probiotics significantly increased G : F, colonization of Lactobacillus spp. in ileum. At day 35, bacteriophage treatment group showed greater (P<0.05) villus height of the duodenum, but a deeper crypt in duodenum. The present results indicate that the bacteriophage cocktail had a potential to enhance the performance and gut health of weanling pigs, however their combination with probiotics did not show an interaction.

Kim, J. Y., Awji, E. G., Park, N. H., Park, J. Y., Kim, J. C., Lee, S. P., Suh, J. W., and Park, S. C. Probiotic Properties and Adsorption of Enterococcus faecalis PSCT3-7 to Vermiculite. J.Vet.Sci. 7-25-2016;

ABSTRACT: The probiotic properties of Enterococcus (E) faecalis PSCT3-7, a new strain isolated from the intestines of a pig fed dietary fiber containing 50% sawdust, was investigated. E. faecalis PSCT3-7 tolerated a pH range of 3 to 8 and 0.3% bile salts and inhibited the growth of Salmonella Typhimurium in a concentration-dependent manner. It showed resistance to several antibacterial agents. Vermiculite, a nutrient and microbial carrier, increased the bile tolerance of the strain. SEM images revealed good adsorption of E.faecalis PSCT3-7 onto vermiculite. E. faecalis PSCT3-7 represents a potential probiotic candidate to administer with vermiculite to swine.

Kim, Y. J. and Lee, S. H. Inhibitory effect of Lactococcus lactis HY 449 on cariogenic biofilm. J.Microbiol.Biotechnol. 7-19-2016;

ABSTRACT: Dental caries is caused by cariogenic biofilm, an oral biofilm including Streptococcus mutans. Recently, the prevention of dental caries using various probiotics has been attempted. Lactococcus lactis HY 449 is a probiotic bacterium. The aim of this study was to investigate the effect of L. lactis HY 449 on cariogenic biofilm and to analyze inhibitory mechanisms. Cariogenic biofilm was formed in the presence or absence of L. lactis HY 449 and L. lactis ATCC 19435, and analyzed by confocal laser microscope. The formation of cariogenic biofilm was reduced in cultures spiked with both L. lactis, and L. lactis HY 449 exhibited more inhibitory effects than L. lactis ATCC 19435. In order to analyze and to compare inhibitory mechanisms, the antibacterial activity of the spent culture medium (SCM) from both L. lactis against S. mutans was investigated, and the expression of glucosyltransferases (gtfs) of S. mutans was then analyzed by real-time RT-PCR. Also, the sucrose ferment ability of both L. lactis was examined. Both L. lactis showed the antibacterial activity and inhibited the expression of gtfs, and the difference between both L. lactis did not show. In case of sucrose-ferment ability, L. lactis HY 449 fermented sucrose but L. lactis ATCC 19435 did not. L. lactis HY 449 inhibits the uptake sucrose and gtfs expression of S. mutans, whereby the development

of cariogenic biofilm may be inhibited. In conclusion, L. lactis HY 449 may be a useful probiotic for prevention of dental caries.

Kimoto-Nira, H., Moriya, N., Yamasaki, S., Takenaka, A., and Suzuki, C. Effect of sodium acetate on the adhesion to porcine gastric mucin in a Lactococcus lactis strain grown on fructose. Anim Sci.J. 2016; 87(6):802-808.

ABSTRACT: The association of lactic acid bacteria with mucosal surfaces plays important roles in the beneficial effects of these bacteria on human health, such as colonization of the gastrointestinal tract for pathogen antagonism. Previously, we found that the adhesion of Lactococcus lactis 7-1 to porcine gastric mucin was higher with fructose than with lactose, galactose or xylose as the carbon source. In this study, we examined the effect of growth conditions on the adhesion of strain 7-1 grown on fructose. Medium components affect the adhesion: the adhesion of strain 7-1 grown with sodium acetate was higher than that without it. The enhancement of adhesion by sodium acetate was not observed under aerobic conditions. Cellular properties grown with or without sodium acetate were characterized: strain 7-1 grown with sodium acetate had similar sugar contents, and different fatty acid composition to those grown without it. Strain 7-1 grown with sodium acetate showed significantly lower cell yield and significantly higher hydrophobicity than those grown without it, which is associated with higher adhesion. Fructose and sodium acetate are frequently used in the food industry; this study may reveal a simple way to enhance the adhesion of lactic acid bacteria by growing them with these substances.

Klu, Y. A. and Chen, J. Influence of probiotics, included in peanut butter, on the fate of selected Salmonella and Listeria strains under simulated gastrointestinal conditions. J.Appl.Microbiol. 2016; 120(4):1052-1060.

ABSTRACT: AIMS: This study observed the behaviour of probiotics and selected bacterial pathogens co-inoculated into peanut butter during gastrointestinal simulation. METHODS AND RESULTS: Peanut butter homogenates co-inoculated with Salmonella/Listeria strains (5 log CFU ml(-1)) and lyophilized or cultured probiotics (9 log CFU ml(-1)) were exposed to simulated gastrointestinal conditions for 24 h at 37 degrees C. Sample pH, titratable acidity and pathogen populations were determined. Agar diffusion assay was performed to assess the inhibitory effect of probiotic culture supernatants with either natural (3.80 (Lactobacillus), 3.78 (Bifidobacteirum) and 5.17 (Streptococcus/Lactococcus)) or neutralized (6.0) pH. Antibacterial effect of crude bacteriocin extracts were also evaluated against the pathogens. After 24 h, samples with probiotics had lower pH and higher titratable acidity than those without probiotics. The presence of probiotics caused a significant reduction ($P < 0.05$) in pathogen populations. Supernatants of Bifidobacterium and Lactobacillus cultures inhibited pathogen growth; however, the elevation of pH diminished their antibacterial activities. Crude bacteriocin extracts had a strain-specific inhibitory effect only towards Listeria monocytogenes. CONCLUSION: Probiotics in 'peanut butter' survived simulated gastrointestinal conditions and inhibited the growth of Salmonella/Listeria. SIGNIFICANCE AND IMPACT OF THE STUDY: Peanut butter is a plausible carrier to deliver probiotics to improve the gastrointestinal health of children in developing countries.

Kobyliak, N., Virchenko, O., and Falalyeyeva, T. Pathophysiological role of host microbiota in the development of obesity. Nutr.J. 2016; 15:43

ABSTRACT: Overweight and obesity increase the risk for a number of diseases, namely, cardiovascular diseases, type 2 diabetes, dyslipidemia, premature death, non-alcoholic fatty liver disease as well as different types of cancer. Approximately 1.7 billion people in the world suffer from being overweight, most notably in developed countries. Current research efforts have focused on host and environmental factors that may affect energy balance. It was hypothesized that a microbiota profile specific to an obese host with increased energy-yielding behavior may exist. Consequently, the gut microbiota is becoming of significant research interest in relation to obesity in an attempt to better understand the aetiology of obesity and to develop new methods of its prevention and treatment. Alteration of microbiota composition may stimulate development of obesity and other metabolic diseases via several mechanisms: increasing gut permeability with subsequent metabolic inflammation; increasing energy harvest from the diet; impairing short-chain fatty acids synthesis; and altering bile acids metabolism and FXR/TGR5 signaling. Prebiotics and probiotics have physiologic functions that contribute to the health of gut microbiota, maintenance of a healthy body weight and control of factors associated with obesity through their effects on mechanisms that control food intake, body weight, gut microbiota and inflammatory processes.

Kobyliak, N., Conte, C., Cammarota, G., Haley, A. P., Styriak, I., Gaspar, L., Fusek, J., Rodrigo, L., and Kruzliak, P. Probiotics in prevention and treatment of obesity: a critical view. Nutr.Metab (Lond). 2016; 13:14

ABSTRACT: The worldwide prevalence of obesity more than doubled between 1980 and 2014. The obesity pandemic is tightly linked to an increase in energy availability, sedentariness and greater control of ambient temperature that have paralleled the socioeconomic development of the past decades. The most frequent cause which leads to the obesity development is a dysbalance between energy intake and energy expenditure. The gut microbiota as an environmental factor which influence whole-body metabolism by affecting energy balance but also inflammation and gut barrier function, integrate peripheral and central food intake regulatory signals and thereby increase body weight. Probiotics have physiologic functions that contribute to the health of gut microbiota, can affect food intake and appetite, body weight and composition and metabolic functions through gastrointestinal pathways and modulation of the gut bacterial community.

Kobyliak, N., Falalyeyeva, T., Virchenko, O., Mykhalchyshyn, G., Bodnar, P., Spivak, M., Yankovsky, D., Beregova, T., and Ostapchenko, L. Comparative experimental investigation on the efficacy of mono- and multiprobiotic strains in non-alcoholic fatty liver disease prevention. BMC.Gastroenterol. 2016; 16:34

ABSTRACT: BACKGROUND: To investigate the efficacy of different probiotic strains, their combinations and forms (alive or lyophilized) in nonalcoholic fatty liver disease (NAFLD) prevention. METHODS: In this study, 70 rats have been used divided into 7 groups of 10 animals in each: I - intact rats, II-.

Koch, M., Festa, V., Chiesara, F., Moretti, A., Bianchi, M., and Dezi, A. [Diverticular disease: towards 2020. An evidence-based approach]. Recenti Prog.Med. 2016; 107(6):309-319.

ABSTRACT: Diverticular disease (DD) of the colon has an increasing burden on health service resources, in terms of hospital admissions, mortality and surgery rate. We present an overview of the clinical history of DD, and of the ways that gastroenterologists have to modify it. Prevalence of the disease increases with aging. Most of diverticulosis are occasionally identified on colonscopy, and most of them remain asymptomatic for all life. Only 4% of these subjects develop diverticulitis. However, 4-25% of these patients are expected to present a second episode of diverticulitis, and 15% of them develop complications. Hospitalizations for diverticulitis and relapses of diverticulitis show strong growth (+21% 2013 vs 2003 in USA). The total annual costs for hospitalization for DD in USA are over 2,2 billion of dollars, and in Italy exceed 63 million of euros. In-hospital mortality can reach 0,5%. Diagnosis of diverticulitis is based on clinical history, lab tests and imaging (ultrasonography, CAT). Clinical diagnosis has a sensitivity of 68% and specificity around 98%. According to a meta-analysis, the performance of ultrasonograhy and CAT results very high ("pooled" sensitivity 92-94%, and specificity 90-99%; "pooled" Likelihood Ratio positive 9.6 for ultrasonography and 78.4 for CAT. Likelihood Rato negative 0.09 and 0.06 respectively). Evidences for preventing relapse are poor. Anyway, a very recent meta-analysis on 6 RCTs suggests no role for mesalazine (GRADE SCALE for evidence 3). Non absorbable antibiotics (rifaximin) have been used in two studies (one RCT, one retrospective observational). Data from the two studies suggest some evidence in favour of its use (GRADE SCALE 1). The number of admitted patients is 291. Considering a base-line risk of 19 relapses every 100 patients (5-year observation period), the absolute risk difference is minus 9 patients with relapse (CI 95% -14 a + 3) in the RCT and minus 14 patients (CI 95% -17 a -5) in the observational study. A 2020 preview suggests an exploding interest in assessing the risk factors for relapse (including aspirin and NSAIDs) and identifying the better strategy to reduce it. Further trials are requested, including the use of probiotics alone.

Kocijancic, D., Felgner, S., Frahm, M., Komoll, R. M., Iljazovic, A., Pawar, V., Rohde, M., Heise, U., Zimmermann, K., Gunzer, F., Hammer, J., Crull, K., Leschner, S., and Weiss, S. Therapy of solid tumors using probiotic Symbioflor-2: restraints and potential. Oncotarget. 4-19-2016; 7(16):22605-22622.

ABSTRACT: To date, virulent bacteria remain the basis of most bacteria mediated cancer therapies. For clinical application attenuation is required. However, this might result in a drastically lowered therapeutic capacity. Herein we argue that the E. coli probiotic Symbioflor-2, with a history of safe application may constitute a viable tumor therapeutic candidate. We demonstrate that Symbioflor-2 displays a highly specific tumor targeting ability as determined in murine CT26 and RenCa tumor models. The excellent specificity was ascribed to reduced levels of adverse colonization. A high safety standard was demonstrated in WT and Rag1-/- mice. Thus, Symbioflor-2 may represent an ideal tumor targeting delivery system for therapeutic molecules. Moreover, Symbioflor-2 was capable of inducing CT26 tumor clearance as result of an adjuvant effect on tumor specific CD8+ T cells analogous to the Salmonella variant SL7207. However, lower therapeutic efficacy against RenCa tumors suggested a generally reduced therapeutic potency for probiotics. Interestingly, concurrent depletion of Gr-1+ or Ly6G+ cells installed therapeutic efficacy equal to SL7207, thus highlighting the role of innate effector cells in restraining the anti-tumor effects of Symbioflor-2. Collectively, our findings argue for a strategy of

safe strain application and a more sustainable use of bacteria as a delivery system for therapeutic molecules.

Koletzko, B. Childhood Obesity: Current Situation and Future Opportunities. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S18-S21.

ABSTRACT: PURPOSE OF REVIEW: The early origins of overweight and obesity and the opportunities for early prevention are explored. RECENT FINDINGS: Overweight and obesity prevalence globally has increased at an alarming rate. No single intervention can halt the rise of the obesity epidemic. Particular attention is given to exploring causative factors and preventive measures in early life, when biological determinants of risk trajectories, feeding behaviour and dietary preferences are shaped. Some lifestyle and nutrition modifications in pregnancy and infancy can reduce subsequent obesity risk. Also postnatal infant gut colonisation may modify later obesity risk, but currently available evidence does not allow firm conclusions. Surprisingly, about 3.2 times more systematic reviews (SR) than randomized clinical trials (RCTs) were published on "probiotics" and health, and even 7.9 times more SR than RCTs on "probiotics" and obesity, which is not helpful. SUMMARY: Multiple research opportunities exist for exploring the early origins of obesity to contribute towards halting the rise in obesity prevalence. Exploring the early development of the microbiome in its complexity, its dependence on dietary and other exogenous factors, and its metabolic and regulatory functions is promising. Meaningful progress for obesity prevention can most likely be achieved by combining several strategies.

Koletzko, S. Probiotics and Prebiotics for Prevention of Food Allergy: Indications and Recommendations by Societies and Institutions. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S9-S10.

ABSTRACT: Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". Unfortunately, misuse of the term probiotic is very common. According to the regulation of the European food safety authority (EFSA) health claims on pre- and probiotics are not judged as favorable. Scientific societies should give guidance to the consumers and health care professionals on the use of probiotics and prebiotics for prevention and disease management. There is currently no positive recommendation from international scientific medical societies to use prebiotics or probiotics for treatment of food allergy or other allergic manifestations and for prevention of food allergy, allergic rhinitis, and asthma. Discrepant recommendations exist for probiotics for prevention of eczema in high risk infants.

Komatsu, S., Sakamoto, E., Norimizu, S., Shingu, Y., Asahara, T., Nomoto, K., and Nagino, M. Efficacy of perioperative synbiotics treatment for the prevention of surgical site infection after laparoscopic colorectal surgery: a randomized controlled trial. Surg.Today. 2016; 46(4):479-490.

ABSTRACT: PURPOSE: The aim of this study was to assess the effect of perioperative oral administration of synbiotics on the surgical outcome in patients undergoing laparoscopic colorectal resection. METHODS: In this single-center randomized, controlled trial, patients scheduled to undergo elective laparoscopic colorectal surgery were eligible to participate and randomly assigned to a synbiotics group or a control group. The primary

study outcome was the development of infectious complications, particularly surgical site infection (SSI), within 30 days of surgery. RESULTS: In this study, 379 patients were enrolled and randomly assigned (173 to the synbiotics group and 206 to the control group), of whom 362 patients (168 to the synbiotics group and 194 to the control group) were eligible for this study. SSI occurred in 29 (17.3%) patients in the synbiotics group and 44 (22.7%) patients in the control group (OR: 0.761, 95% CI 0.50-1.16; p = 0.20). Overall, the rate of postoperative complications, including anastomotic leakage, did not differ significantly between the two groups. Synbiotics treatment reversed the changes in fecal bacteria and organic acids after surgery and suppressed the increases in potentially pathogenic species, such as Clostridium difficile. CONCLUSION: The efficacy of perioperative administration of synbiotics was not validated as a treatment for reducing the incidence of infectious complications after laparoscopic colorectal resection. However, the microbial imbalance, in addition to the reduction in organic acids, could be improved by perioperative synbiotics treatment.

Kong, Q., Dong, S., Gao, J., and Jiang, C. In vitro fermentation of sulfated polysaccharides from E. prolifera and L. japonica by human fecal microbiota. Int.J.Biol.Macromol. 6-15-2016; 91:867-871.

ABSTRACT: In vitro fermentation of the sulfated polysaccharides from seaweeds Enteromorpha prolifera and Laminaria japonica and their prebiotic effects on human fecal microbiota were investigated in this study. The sulfated polysaccharides were fermented in vitro for 48h by human fecal cultures. When 0.8g MWCOL (polysaccharides MWCO<30kD) from L. japonica was fermented, the pH in fecal cultures decreased from 6.5 to 5.1 and the levels of short chain fatty acids, such as acetic, butyric and lactic acids all significantly increased. After 48h fermentation, 0.8g MWCOL showed good effect on modulating the gut microflora balance, because the beneficial strains (Lactobacillus and Bifidobacterium) were both significantly higher than those in control group ($p<0.05$). As far as we know, this is the first report that consumption of sulfated polysaccharides from E. prolifera and L. japonica is beneficial to the ecosystem of the intestinal tract by increasing the populations of probiotics and short chain fatty acids. Furthermore, our reports indicated that molecular weight of sulfated polysaccharide from marine algae is related to its prebiotic effects.

Koppen, I. J., Benninga, M. A., and Tabbers, M. M. Is There A Role for Pre-, Pro- and Synbiotics in the Treatment of Functional Constipation in Children? A Systematic Review. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S27-S35.

ABSTRACT: PURPOSE OF REVIEW: To investigate the efficacy and safety of pre-, pro- and synbiotics in the treatment of pediatric functional constipation (FC). RECENT FINDINGS: A recent study reported that the gut microbiota in obese children with FC differs from that of obese children without FC. The gut microbiota may be involved in the pathophysiology of FC. Pre- and probiotics have been suggested as potential treatment modalities for FC in children. SUMMARY: PubMed and Cochrane databases were searched from inception to February 2016. We found 6 RCTs on prebiotics, 6 RCTs on probiotics and 1 RCT concerning synbiotics. Overall, most studies were at high risk of bias. The majority of studies were unable to demonstrate a significant effect of pre-, pro- or synbiotics on predefined outcome measures such as defecation frequency, fecal incontinence and painful or difficult defecation. Pre-, pro- and synbiotics were not associated with significant adverse effects. In conclusion, there is insufficient evidence to

recommend pre-, pro- or synbiotics in the treatment of children with functional constipation. High-quality randomized controlled trials are warranted to further explore these treatment modalities.

Korada, S. K., Yarla, N. S., Bishayee, A., Aliev, G., Aruna, Lakshmi K., Arunasree, M. K., Dananajaya, B. L., and Mishra, V. Can Probiotics Cure Inflammatory Bowel Diseases? Curr.Pharm.Des. 2016; 22(7):904-917.

ABSTRACT: Gastrointestinal (GI) disorders, especially microbial dysbiosis play role in several GI ailments such as irritable bowel syndrome, colorectal cancer, inflammatory bowel diseases, and antibiotic-associated diarrhoea. Role of inflammatory bowel disease (IBD) is multifactorial as it involves loss of maintaining intestinal epithelial barrier integrity, increased release of pro-inflammatory molecules, and microbial dysbiosis in gut microflora. Some specific pathogens also play a key role in the IBD development. The origin and causation are still in unfathomable condition and the exact root cause is unknown. Recently probiotic studies have been gaining importance because of their positive responses in their IBD experimental results. According to joint Food and Agricultural Organisation/World Health Organisation working group, probiotics are defined as live microorganisms which when administered in adequate amount confer health benefit on the host. These live beneficial microorganisms are considered helpful in improving gut colonization and perseverance thereby improves prophylactic effect. In the direction of IBD research, a number of studies are needed to standardize its methodology and its applicability on human usage. The particular review presents an overview of gut microflora and its impact on host health, types of IBD and existing therapies to treat this disorder, mechanism of several probiotic actions, role of probiotics in IBD prevention with their supporting evidences.

Korpela, K., Salonen, A., Virta, L. J., Kumpu, M., Kekkonen, R. A., and de Vos, W. M. Lactobacillus rhamnosus GG Intake Modifies Preschool Children's Intestinal Microbiota, Alleviates Penicillin-Associated Changes, and Reduces Antibiotic Use. PLoS.One. 2016; 11(4):e0154012

ABSTRACT: Antibiotic use is considered among the most severe causes of disturbance to children's developing intestinal microbiota, and frequently causes adverse gastrointestinal effects ranging from mild and transient diarrhoea to life-threatening infections. Probiotics are commonly advocated to help in preventing antibiotic-associated gastrointestinal symptoms. However, it is currently unknown whether probiotics alleviate the antibiotic-associated changes in children's microbiota. Furthermore, it is not known how long-term probiotic consumption influences the developing microbiota of children. We analysed the influence of long-term Lactobacillus rhamnosus GG intake on preschool children's antibiotic use, and antibiotic-associated gastrointestinal complaints in a double blind, randomized placebo-controlled trial with 231 children aged 2-7. In addition, we analysed the effect of L. rhanmosus GG on the intestinal microbiota in a subset of 88 children. The results show that long-term L. rhamnosus GG supplementation has an influence on the composition of the intestinal microbiota in children, causing an increase in the abundance of Prevotella, Lactococcus, and Ruminococcus, and a decrease in Escherichia. The treatment appeared to prevent some of the changes in the microbiota associated with penicillin use, but not those associated with macrolide use. The treatment, however, did reduce the frequency of gastrointestinal complaints after a macrolide course. Finally, the

treatment appeared to prevent certain bacterial infections for up to 3 years after the trial, as indicated by reduced antibiotic use. TRIAL REGISTRATION: ClinicalTrials.gov NCT01014676.

Kreuzer-Redmer, S., Bekurtz, J. C., Arends, D., Bortfeldt, R., Kutz-Lohroff, B., Sharbati, S., Einspanier, R., and Brockmann, G. A. Feeding of Enterococcus faecium NCIMB 10415 Leads to Intestinal miRNA-423-5p-Induced Regulation of Immune-Relevant Genes. Appl.Environ.Microbiol. 2016; 82(8):2263-2269.

ABSTRACT: Probiotics are widely used in human and animal health, but little is known about the mode of action of probiotics. One possible mechanism at the molecular level could be an influence on microRNAs (miRNAs) and the related immune-relevant target genes. Here, we analyzed differential expression of miRNA and potential target genes of ileal and jejunal lymphatic tissues from Enterococcus faeciumNCIMB 10415-fed piglets versus untreated controls by using next-generation sequencing. We identified miR-423-5p as being greatly affected by the treatment group (2.32-fold;P= 0.014). Validation by reverse transcription-quantitative PCR (RT-qPCR) confirmed a significant upregulation of miR-423-5p (2.11-fold;P= 0.03) and, additionally, downregulation of the important immune-relevant immunoglobulin lambda light C region (IGLC) (0.61-fold;P= 0.03) and immunoglobulin kappa constant (IGKC) (0.69-fold;P= 0.04) target genes. Expression analysis of miR-423-5p and IGLC at different age points shows a clear anti correlated relationship. Luciferase reporter assays with a HeLa cell line verified IGLC as a target of miR-423-5p. The results provided evidence for an effect of feeding of E. faeciumon the expression of miR-423-5p and on the regulation of the IGLC gene through miR-423-5p. This might be a possible mode of action of E. faeciumon immune cell regulation in the small intestine.

Kristensen, N. B., Bryrup, T., Allin, K. H., Nielsen, T., Hansen, T. H., and Pedersen, O. Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials. Genome Med. 2016; 8(1):52

ABSTRACT: BACKGROUND: The effects of probiotic supplementation on fecal microbiota composition in healthy adults have not been well established. We aimed to provide a systematic review of the potential evidence for an effect of probiotic supplementation on the composition of human fecal microbiota as assessed by high-throughput molecular approaches in randomized controlled trials (RCTs) of healthy adults. METHODS: The survey of peer-reviewed papers was performed on 17 August 2015 by a literature search through PubMed, SCOPUS, and ISI Web of Science. Additional papers were identified by checking references of relevant papers. Search terms included healthy adult, probiotic, bifidobacterium, lactobacillus, gut microbiota, fecal microbiota, intestinal microbiota, intervention, and (clinical) trial. RCTs of solely probiotic supplementation and placebo in healthy adults that examined alteration in composition of overall fecal microbiota structure assessed by shotgun metagenomic sequencing, 16S ribosomal RNA sequencing, or phylogenetic microarray methods were included. Independent collection and quality assessment of studies were performed by two authors using predefined criteria including methodological quality assessment of reports of the clinical trials based on revised tools from PRISMA/Cochrane and by the Jadad score. RESULTS: Seven RCTs investigating the effect of probiotic supplementation on fecal microbiota in healthy adults were identified and included in the present systematic review. The quality of the studies was assessed as medium to high. Still, no effects were

observed on the fecal microbiota composition in terms of alpha-diversity, richness, or evenness in any of the included studies when compared to placebo. Only one study found that probiotic supplementation significantly modified the overall structure of the fecal bacterial community in terms of beta-diversity when compared to placebo. CONCLUSIONS: This systematic review of the pertinent literature demonstrates a lack of evidence for an impact of probiotics on fecal microbiota composition in healthy adults. Future studies would benefit from pre-specifying the primary outcome and transparently reporting the results including effect sizes, confidence intervals, and P values as well as providing a clear distinction of between-group and within-group comparisons.

Ku, S. Finding and Producing Probiotic Glycosylases for the Biocatalysis of Ginsenosides: A Mini Review. Molecules. 2016; 21(5)

ABSTRACT: Various microorganisms have been widely applied in nutraceutical industries for the processing of phytochemical conversion. Specifically, in the Asian food industry and academia, notable attention is paid to the biocatalytic process of ginsenosides (ginseng saponins) using probiotic bacteria that produce high levels of glycosyl-hydrolases. Multiple groups have conducted experiments in order to determine the best conditions to produce more active and stable enzymes, which can be applicable to produce diverse types of ginsenosides for commercial applications. In this sense, there are various reviews that cover the biofunctional effects of multiple types of ginsenosides and the pathways of ginsenoside deglycosylation. However, little work has been published on the production methods of probiotic enzymes, which is a critical component of ginsenoside processing. This review aims to investigate current preparation methods, results on the discovery of new glycosylases, the application potential of probiotic enzymes and their use for biocatalysis of ginsenosides in the nutraceutical industry.

Kumar, M., Dhaka, P., Vijay, D., Vergis, J., Mohan, V., Kumar, A., Kurkure, N. V., Barbuddhe, S. B., Malik, S. V., and Rawool, D. B. Antimicrobial effects of Lactobacillus plantarum and Lactobacillus acidophilus against multidrug-resistant enteroaggregative Escherichia coli. Int.J.Antimicrob.Agents. 7-5-2016;

ABSTRACT: The in vitro and in vivo antimicrobial effects of Lactobacillus plantarum and Lactobacillus acidophilus were evaluated individually and synergistically against multidrug-resistant enteroaggregative Escherichia coli (MDR-EAEC). In vitro evaluation of each probiotic strain when co-cultured with MDR-EAEC isolates revealed a reduction in MDR-EAEC counts (eosin-methylene blue agar) in a dose- and time-dependent manner: probiotics at a dose rate of 1010 CFU inhibited MDR-EAEC isolates at 72 h post-inoculation (PI), whereas at lower concentrations (108 and 109 CFU) MDR-EAEC isolates were inhibited at 96 h PI. The synergistic antimicrobial effect of both probiotic strains (each at 1010 CFU) was highly significant ($P < 0.01$) and inhibited the growth of MDR-EAEC isolates at 24 h PI. For in vivo evaluation, weaned mice were fed orally with 107 CFU of MDR-EAEC. At Day 3 post-infection, treated mice were fed orally with the probiotic strains (each at 1010 CFU). Compared with the control, post-treatment a significant ($P < 0.01$) reduction in MDR-EAEC counts was observed in faeces by Day 2 and in intestinal tissues of treated mice by Days 3 and 4 as evidenced by plate count (mean 2.71 log and 2.27 log, respectively) and real-time PCR (mean 1.62 log and 1.57 log, respectively) methods. Histopathologically, comparatively mild changes were observed in the ileum and colon from Days 3 to 5 post-treatment with probiotics; however, from Day 6 the

changes were regenerative or normal. These observations suggest that these probiotic strains can serve as alternative therapeutics against MDR-EAEC-associated infections in humans and animals.

Kumar, M., Yadav, A. K., Verma, V., Singh, B., Mal, G., Nagpal, R., and Hemalatha, R. Bioengineered probiotics as a new hope for health and diseases: an overview of potential and prospects. Future.Microbiol. 2016; 11:585-600.

ABSTRACT: Despite the use of microorganisms as therapeutics for over a century, the scientific and clinical admiration of their potential is a recent phenomenon. Genome sequencing and genetic engineering has enabled researchers to develop novel strategies, such as bioengineered probiotics or pharmabiotics, which may become a therapeutic strategy. Bioengineered probiotics with multiple immunogenic or antagonistic properties could be a viable option to improve human health. The bacteria are tailored to deliver drugs, therapeutic proteins or gene therapy vectors with precision and a higher degree of site specificity than conventional drug administration regimes. This article provides an overview of methodological concepts, thereby encouraging research and interest in this topic, with the ultimate goal of using designer probiotics as therapeutics in clinical practice.

Kumari, A., Angmo, K., Monika, and Bhalla, T. C. Probiotic attributes of indigenous Lactobacillus spp. isolated from traditional fermented foods and beverages of north-western Himalayas using in vitro screening and principal component analysis. J.Food Sci.Technol. 2016; 53(5):2463-2475.

ABSTRACT: The present research was designed to explore indigenous probiotic Lactic acid bacteria from traditional fermented foods and beverages of North-western Himalayas for their probiotic potential. It was achieved through a step-by step approach focused on the technological characterization, evaluation of the probiotic traits and adherence ability. Fifty one LAB isolates from traditional fermented foods and beverages were initially screened for their technological properties and among them twenty isolates were selected. These isolates were further characterized and identified using 16S rRNA gene sequencing as Lactobacillus brevis (7 isolates), Lactobacillus casei (5), Lactobacillus paracasei (2), Lactobacillus buchneri (1), Lactobacillus plantarum (1) and Lactobacillus sp. (3). Identified isolates were evaluated by in vitro methods including survival in gastrointestinal tract, antibiotic susceptibility, antimicrobial activity, cell surface characteristics, exopolysacharride production and haemolytic activity. The results of these experiments were used as input data for Principal Component Analysis; thus, to select the most promising probiotic isolates. Three isolates (L. brevis PLA2, L. paracasei PLA8 and L. brevis PLA16) were found to be most technological relevant and promising probiotic candidates in comparison to commercial probiotic strains. L. brevis PLA2 was selected as best isolate with probiotic potential by in vitro adherence to the human intestinal HT-29 cell line.

Kunugi, H. [Depressive Disorder and Gut-brain Interaction]. Brain Nerve. 2016; 68(6):641-646.

ABSTRACT: Depressive disorder is a stress-induced condition, which has been suggested to have bidirectional interactions with the gut microbiota. Probiotics such as Bifidobacterium and Lactobacillus have been suggested to mitigate stress response.

Irritable bowel syndrome (IBS) is a typical phenotype of psychological distress manifested in the gastrointestinal system, and often develops in patients with depressive disorder. The altered gut microbiota and resultant inflammation in the gut play an important role in at least a portion of IBS. Animal models of depression have shown abnormalities in the gut such as increased gut permeability, and the probiotics ameliorate their chronic depression-like behaviors and altered stress responses. There have been only a few studies that have directly investigated the gut microbiota in patients with depression. We reported results suggesting that individuals with lower bacterial counts for Bifidobacterium and/or Lactobacillus are more common in patients with major depressive disorder than in healthy controls. the collectively use of gut microbiota in the diagnosis and treatment of depressive disorder seems to be a promising approach.

Kuperman, A. A. and Koren, O. Antibiotic use during pregnancy: how bad is it? BMC.Med. 2016; 14(1):91

ABSTRACT: BACKGROUND: Our microbial companions (the "microbiota") are extremely important for the preservation of human health. Although changes in bacterial communities (dysbiosis) are commonly associated with disease, such changes have also been described in healthy pregnancies, where the microbiome plays an essential role in maternal and child health outcomes, including normal immune and metabolic function in later life. Nevertheless, this new understanding of the importance of the microbiome has not yet influenced contemporary clinical practice regarding antibiotic use during pregnancy. DISCUSSION: Antibiotic treatment during pregnancy is widespread in Western countries, and accounts for 80 % of prescribed medications in pregnancy. However, antibiotic treatment, while at times lifesaving, can also have detrimental consequences. A single course of antibiotics perturbs bacterial communities, with evidence that the microbial ecosystem does not return completely to baseline following treatment. Antibiotics in pregnancy should be used only when indicated, choosing those with the narrowest range possible. Bacteria are essential for normal human development and, while antibiotic treatment during pregnancy has an important role in controlling and preventing infections, it may have undesired effects regarding the maternal and fetoplacental microbiomes. We expect that microbiota manipulation in pregnancy, through the use of probiotics and fecal microbiota transplantation, will be the subject of increasing clinical interest.

Kuugbee, E. D., Shang, X., Gamallat, Y., Bamba, D., Awadasseid, A., Suliman, M. A., Zang, S., Ma, Y., Chiwala, G., Xin, Y., and Shang, D. Structural Change in Microbiota by a Probiotic Cocktail Enhances the Gut Barrier and Reduces Cancer via TLR2 Signaling in a Rat Model of Colon Cancer. Dig.Dis.Sci. 7-6-2016;

ABSTRACT: BACKGROUND: Structural change in the gut microbiota is implicated in cancer. The beneficial modulation of the microbiota composition with probiotics and prebiotics prevents diseases. AIM: We investigated the effect of oligofructose-maltodextrin-enriched Lactobacillus acidophilus, Bifidobacteria bifidum, and Bifidobacteria infantum (LBB), on the gut microbiota composition and progression of colorectal cancer. METHODS: Sprague Dawley rats were acclimatized, given ampicillin (75 mg/kg), and treated as follows; GCO: normal control; GPR: LBB only; GPC: LBB+ 1,2-dimethylhydrazine dihydrochloride (DMH); and GCA: DMH only (cancer control). 16S V4 Pyrosequencing for gut microbiota analysis, tumor studies, and the expression of MUC2, ZO-1, occludin, TLR2, TLR4, caspase 3, COX-2, and beta-catenin were conducted at the

end of experiment. RESULTS: Probiotic LBB treatment altered the gut microbiota. The relative abundance of genera Pseudomonas, Congregibacter, Clostridium, Candidactus spp., Phaeobacter, Escherichia, Helicobacter, and HTCC was decreased ($P < 0.05$), but the genus Lactobacillus increased ($P < 0.05$), in LBB treatment than in cancer control. The altered gut microbiota was associated with decreased tumor incidence (80 % in GPC vs. 100 % in GCA, $P = 0.0001$), tumor volume (GPC 84.23 (42.75-188.4) mm3 vs. GCA 243 (175.5-344.5) mm3, $P < 0.0001$) and tumor multiplicity/count (GPC 2.92 +/- 0.26 vs. GCA 6.27 +/- 0.41; $P < 0.0001$). The expression of MUC2, ZO-1, occludin, and TLR2 was increased, but expression of TLR4, caspase 3, Cox-2, and beta-catenin was decreased by LBB treatment than in cancer control GCA ($P < 0.05$). CONCLUSION: Administration of LBB modulates the gut microbiota and reduces colon cancer development by decreasing tumor incidence, multiplicity/count, and volume via enhanced TLR2-improved gut mucosa epithelial barrier integrity and suppression of apoptosis and inflammation.

Kwak, W., Kim, K., Lee, C., Lee, C., Kang, J., Cho, K., Yoon, S. H., Kang, D. K., Kim, H., Heo, J., and Cho, S. Comparative Analysis of the Complete Genome of Lactobacillus plantarum GB-LP2 and Potential Candidate Genes for Host Immune System Enhancement. J.Microbiol.Biotechnol. 4-28-2016; 26(4):684-692.

ABSTRACT: Acute respiratory virus infectious diseases are a growing health problem, particularly among children and the elderly. Much effort has been made to develop probiotics that prevent influenza virus infections by enhancing innate immunity in the respiratory tract until vaccines are available. Lactobacillus plantarum GB-LP2, isolated from a traditional Korean fermented vegetable, has exhibited preventive effects on influenza virus infection in mice. To identify the molecular basis of this strain, we conducted a whole-genome assembly study. The single circular DNA chromosome of 3,284,304 bp was completely assembled and 3,250 proteinencoding genes were predicted. Evolutionarily accelerated genes related to the phenotypic trait of anti-infective activities for influenza virus were identified. These genes encode three integral membrane proteins, a teichoic acid export ATP-binding protein and a glucosamine - fructose-6-phosphate aminotransferase involved in host innate immunity, the nonspecific DNA-binding protein Dps, which protects bacteria from oxidative damage, and the response regulator of the three-component quorum-sensing regulatory system, which is related to the capacity of adhesion to the surface of the respiratory tract and competition with pathogens. This is the first study to identify the genetic backgrounds of the antiviral activity in L. plantarum strains. These findings provide insight into the anti-infective activities of L. plantarum and the development of preventive probiotics.

Lacy, B. E. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. Int.J.Gen.Med. 2016; 9:7-17.

ABSTRACT: Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders worldwide. The economic impact of IBS on the health care system is substantial, as is the personal impact on patients. Patients with diarrhea-predominant IBS (IBS-D) comprise a substantial proportion of the overall IBS population. Primary care providers are often the first point of contact for patients with IBS-D and can accurately diagnose IBS after a careful history and examination without extensive diagnostic tests. Several pharmacologic treatments (eg, loperamide, alosetron, and antidepressants) and non-pharmacologic treatments (eg, dietary modification and probiotics) are available for

IBS-D, but restrictions on use (eg, alosetron) or the lack of controlled trial data showing reductions in both global and individual IBS-D symptoms (eg, bloating, pain and stool frequency) emphasize the need for alternative treatment options. Two newer medications (eluxadoline and rifaximin) were approved in May 2015 for the treatment of IBS-D, and represent new treatment options for this common gastrointestinal condition.

Lai, C. H., Tsai, C. C., Kuo, W. W., Ho, T. J., Day, C. H., Pai, P. Y., Chung, L. C., Huang, C. C., Wang, H. F., Liao, P. H., and Huang, C. Y. Multi-Strain Probiotics Inhibit Cardiac Myopathies and Autophagy to Prevent Heart Injury in High-Fat Diet-Fed Rats. Int.J.Med.Sci. 2016; 13(4):277-285.

ABSTRACT: High-fat diets induce obesity, leading to cardiomyocyte fibrosis and autophagy imbalance. In addition, no previous studies have indicated that probiotics have potential health effects associated with cardiac fibrosis and autophagy in obese rats. This study investigates the effects of probiotics on high-fat (HF) diet-induced obesity and cardiac fibrosis and autophagy in rat hearts. Eight-week-old male Wistar rats were separated randomly into five equally sized experimental groups: Normal diet (control) and high-fat (HF) diet groups and groups fed a high-fat diet supplemented with low (HL), medium (HM) or high (HH) doses of multi-strain probiotic powders. These experiments were designed for an 8-week trial period. The myocardial architecture of the left ventricle was evaluated using Masson's trichrome staining and immunohistochemistry staining. Key probiotics-related pathway molecules were analyzed using western blotting. Abnormal myocardial architecture and enlarged interstitial spaces were observed in HF hearts. These interstitial spaces were significantly decreased in groups provided with multi-strain probiotics compared with HF hearts. Western blot analysis demonstrated that key components of the TGF/MMP2/MMP9 fibrosis pathways and ERK5/uPA/ANP cardiac hypertrophy pathways were significantly suppressed in probiotic groups compared to the HF group. Autophagy balance is very important in cardiomyocytes. In this study, we observed that the beclin-1/LC3B/Atg7 autophagy pathway in HF was increased after probiotic supplementation was significantly decreased. Together, these results suggest that oral administration of probiotics may attenuate cardiomyocyte fibrosis and cardiac hypertrophy and the autophagy-signaling pathway in obese rats.

Lamari, F., Mahdhi, A., Chakroun, I., Esteban, M. A., Mazurais, D., Amina, B., and Gatesoupe, F. J. Interactions between candidate probiotics and the immune and antioxidative responses of European sea bass (Dicentrarchus labrax) larvae. J.Fish.Dis. 5-2-2016;

ABSTRACT: The use of lactic acid bacteria (LAB) as probiotics in aquaculture may improve the quality of seed production and limit the use of antibiotics in fish hatcheries. This study attempted to further characterize the candidate probiotic Lactobacillus casei X2, and the immune and physiological responses of the sea bass larvae. L. casei X2 was confirmed as a good candidate, due to its wide antibacterial spectrum against both Gram-positive and Gram-negative bacteria, and its free radical scavenging activity. In addition, if the strain did not seem able to form biofilm on abiotic surfaces, it adhered strongly to Hep-2 cells. However, these characteristics did not seem efficient in vivo. At 20 days post-hatch (dph), the expression level of CAT gene was significantly different between group fed without probiotic and the two groups treated with either Pediococcus acidilactici or L. casei. This gene was upregulated in the group treated with strain X2 and downregulated in the group with a commercial probiotic strain P.

acidilactici, suggesting a better antioxidant activity with the later strain. At the same sampling date, the IL-1beta gene was upregulated in the group treated with P. acidilactici, and the HSP70 gene was overexpressed at 41 dph. As the stimulation of these two last genes, such transcriptomic indicators must be cautiously interpreted.

Lan, R., Koo, J., and Kim, I. Effects of Lactobacillus acidophilus supplementation on growth performance, nutrient digestibility, fecal microbial and noxious gas emission in weaning pigs. J.Sci.Food Agric. 6-25-2016;

ABSTRACT: BACKGROUND: Antibiotics used as growth promoters in livestock have been banned in the European Union since 2006. Antibiotics alternatives have focused on probiotics, such as Lactobacillus acidophilus. The concentration of L. acidophilus is considered crucial for obtaining the desired effects. However, limited studies have been conducted to test the dose-dependent effects of L. acidophilus. Therefore, the present study aimed to test the dose-dependent effects of L. acidophilus on growth performance, nutrient digestibility, fecal microbial flora and fecal noxious gas emission in weaning pigs. RESULTS: Lactobacillus acidophilus supplementation increased ($P < 0.05$) average daily gain, average daily feed intake, apparent nutrient digestibility of dry matter, nitrogen and gross energy, and Lactobacillus counts compared to the basal diet treatment, and a linear effect ($P < 0.05$) was observed on those criteria. Escherichia coli counts and NH3 emission were decreased ($P < 0.05$) by L. acidophilus supplementation, and a linear effect ($P < 0.05$) was observed on E. coli counts. CONCLUSION: These results suggest that L. acidophilus could be used as an antibiotic alternative by improving growth performance, nutrient digestibility and gut balance (i.e. increased Lactobacillus counts and decreased E. coli counts), and decreasing NH3 emission, of weaning pigs. (c) 2016 Society of Chemical Industry.

Lan, R., Tran, H., and Kim, I. Effects of probiotic supplementation in different nutrient density diets on growth performance, nutrient digestibility, blood profiles, fecal microflora and noxious gas emission in weaning pig. J.Sci.Food Agric. 6-25-2016;

ABSTRACT: BACKGROUND: Probiotics can serve as alternatives to antibiotics to increase the performance of weaning pigs, and the intake of probiotics is affected by dietary nutrient density. The objective of this study was to evaluate the effects of a probiotic complex in different nutrient density diets on growth performance, digestibility, blood profiles, fecal microflora and noxious gas emission in weaning pigs. RESULTS: From day 22 to day 42, both high-nutrient-density and probiotic complex supplementation diets increased ($P < 0.05$) the average daily gain. On day 42, the apparent total tract digestibility (ATTD) of dry matter, nitrogen and gross energy (GE), blood urea nitrogen concentration and NH3 and H2 S emissions were increased ($P < 0.05$) in pigs fed high-nutrient-density diets. Pigs fed probiotic complex supplementation diets had higher ($P < 0.05$) ATTD of GE than pigs fed non-supplemented diets. Fecal Lactobacillus counts were increased whereas Escherichia coli counts and NH3 and H2 S emissions were decreased ($P < 0.05$) in pigs fed probiotic complex supplementation diets. Interactive effects on average daily feed intake (ADFI) were observed from day 22 to day 42 and overall, where probiotic complex improved ADFI more dramatically in low-nutrient-density diets. CONCLUSION: The beneficial effects of probiotic complex (Bacillus coagulans, Bacillus licheniformis, Bacillus subtilis and Clostridium butyricum) supplementation on ADFI is more dramatic with low-nutrient-density diets. (c) 2016 Society of Chemical Industry.

Landete, J. M., Medina, M., and Arques, J. L. Fluorescent reporter systems for tracking probiotic lactic acid bacteria and bifidobacteria. World J.Microbiol.Biotechnol. 2016; 32(7):119

ABSTRACT: In the last two decades, there has been increasing evidence supporting the role of the intestinal microbiota in health and disease, as well as the use of probiotics to modulate its activity and composition. Probiotic bacteria selected for commercial use in foods, mostly lactic acid bacteria and bifidobacteria, must survive in sufficient numbers during the manufacturing process, storage, and passage through the gastro-intestinal tract. They have several modes of action and it is crucial to unravel the mechanisms underlying their postulated beneficial effects. To track their survival and persistence, and to analyse their interaction with the gastro-intestinal epithelia it is essential to discriminate probiotic strains from endogenous microbiota. Fluorescent reporter proteins are relevant tools that can be exploited as a non-invasive marker system for in vivo real-time imaging in complex ecosystems as well as in vitro fluorescence labelling. Oxygen is required for many of these reporter proteins to fluoresce, which is a major drawback in anoxic environments. However, some new fluorescent proteins are able to overcome the potential problems caused by oxygen limitations. The current available approaches and the benefits/disadvantages of using reporter vectors containing fluorescent proteins for labelling of bacterial probiotic species commonly used in food are addressed.

Landman, C. and Quevrain, E. [Gut microbiota: Description, role and pathophysiologic implications]. Rev.Med.Interne. 2016; 37(6):418-423.

ABSTRACT: The human gut contains 10(14) bacteria and many other micro-organisms such as Archaea, viruses and fungi. Studying the gut microbiota showed how this entity participates to gut physiology and beyond this to human health, as a real "hidden organ". In this review, we aimed to bring information about gut microbiota, its structure, its roles and its implication in human pathology. After bacterial colonization in infant, intestinal microbial composition is unique for each individual although more than 95% can be assigned to four major phyla. The use of culture independent methods and more recently the development of high throughput sequencing allowed to depict precisely gut microbiota structure and diversity as well as its alteration in diseases. Gut microbiota is implicated in the maturation of the host immune system and in many fundamental metabolic pathways including sugars and proteins fermentation and metabolism of bile acids and xenobiotics. Imbalance of gut microbial populations or dysbiosis has important functional consequences and is implicated in many digestive diseases (inflammatory bowel diseases, colorectal cancer, etc.) but also in obesity and autism. These observations have led to a surge of studies exploring therapeutics which aims to restore gut microbiota equilibrium such as probiotics or fecal microbiota transplantation. But recent research also investigates biological activity of microbial products which could lead to interesting therapeutics leads.

Langdon, A., Crook, N., and Dantas, G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med. 2016; 8(1):39

ABSTRACT: The widespread use of antibiotics in the past 80 years has saved millions of human lives, facilitated technological progress and killed incalculable numbers of microbes, both pathogenic and commensal. Human-associated microbes perform an

array of important functions, and we are now just beginning to understand the ways in which antibiotics have reshaped their ecology and the functional consequences of these changes. Mounting evidence shows that antibiotics influence the function of the immune system, our ability to resist infection, and our capacity for processing food. Therefore, it is now more important than ever to revisit how we use antibiotics. This review summarizes current research on the short-term and long-term consequences of antibiotic use on the human microbiome, from early life to adulthood, and its effect on diseases such as malnutrition, obesity, diabetes, and Clostridium difficile infection. Motivated by the consequences of inappropriate antibiotic use, we explore recent progress in the development of antivirulence approaches for resisting infection while minimizing resistance to therapy. We close the article by discussing probiotics and fecal microbiota transplants, which promise to restore the microbiota after damage of the microbiome. Together, the results of studies in this field emphasize the importance of developing a mechanistic understanding of gut ecology to enable the development of new therapeutic strategies and to rationally limit the use of antibiotic compounds.

Lau, C. S. and Chamberlain, R. S. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Int.J.Gen.Med. 2016; 9:27-37.

ABSTRACT: INTRODUCTION: Clostridium difficile infection (CDI) is the leading cause of antibiotic-associated diarrhea. CDI has increased in incidence and severity over the past decade, and is a growing worldwide health problem associated with substantial health care costs and significant morbidity and mortality. This meta-analysis examines the impact of probiotics on the incidence of Clostridium difficile-associated diarrhea (CDAD) among children and adults, in both hospital and outpatient settings. METHODS: A comprehensive literature search of all published randomized control trials (RCTs) assessing the use of probiotics in the prevention of CDAD in patients receiving antibiotic therapy was conducted, and the incidence of CDAD was analyzed. RESULTS: Twenty-six RCTs involving 7,957 patients were analyzed. Probiotic use significantly reduced the risk of developing CDAD by 60.5% (relative risk [RR] =0.395; 95% confidence interval [CI], 0.294-0.531; P<0.001). Probiotics proved beneficial in both adults and children (59.5% and 65.9% reduction), especially among hospitalized patients. Lactobacillus, Saccharomyces, and a mixture of probiotics were all beneficial in reducing the risk of developing CDAD (63.7%, 58.5%, and 58.2% reduction). CONCLUSION: Probiotic supplementation is associated with a significant reduction in the risk of developing CDAD in patients receiving antibiotics. Additional studies are required to determine the optimal dose and strain of probiotic.

Leal, J. R., Heitman, S. J., Conly, J. M., Henderson, E. A., and Manns, B. J. Cost-Effectiveness Analysis of the Use of Probiotics for the Prevention of Clostridium difficile-Associated Diarrhea in a Provincial Healthcare System. Infect.Control Hosp.Epidemiol. 7-5-2016; 1-8.

ABSTRACT: OBJECTIVE To conduct a full economic evaluation assessing the costs and consequences related to probiotic use for the primary prevention of Clostridium difficile-associated diarrhea (CDAD). DESIGN Cost-effectiveness analysis using decision analytic modeling. METHODS A cost-effectiveness analysis was used to evaluate the risk of CDAD and the costs of receiving oral probiotics versus not over a time horizon of 30 days. The target population modeled was all adult inpatients receiving any therapeutic course of antibiotics from a publicly funded healthcare system perspective. Effectiveness estimates

were based on a recent systematic review of probiotics for the primary prevention of CDAD. Additional estimates came from local data and the literature. Sensitivity analyses were conducted to assess how plausible changes in variables impacted the results. RESULTS Treatment with oral probiotics led to direct costs of CDN $24 per course of treatment per patient. On average, patients treated with oral probiotics had a lower overall cost compared with usual care (CDN $327 vs $845). The risk of CDAD was reduced from 5.5% in those not receiving oral probiotics to 2% in those receiving oral probiotics. These results were robust to plausible variation in all estimates. CONCLUSIONS Oral probiotics as a preventive strategy for CDAD resulted in a lower risk of CDAD as well as cost-savings. The cost-savings may be greater in other healthcare systems that experience a higher incidence and cost associated with CDAD. Infect Control Hosp Epidemiol 2016;1-8.

Leccese Terraf, M. C., Juarez Tomas, M. S., Rault, L., Le, Loir Y., Even, S., and Nader-Macias, M. E. Biofilms of vaginal Lactobacillus reuteri CRL 1324 and Lactobacillus rhamnosus CRL 1332: kinetics of formation and matrix characterization. Arch.Microbiol. 2016; 198(7):689-700.

ABSTRACT: Adhesion and biofilm formation are strain properties that reportedly contribute to the permanence of lactobacilli in the human vagina. The kinetics of biofilm formation and the chemical nature of the biofilm matrix formed by Lactobacillus reuteri CRL (Centro de Referencia para Lactobacilos Culture Collection) 1324 and Lactobacillus rhamnosus CRL 1332, vaginal beneficial strains, were evaluated in this work. Crystal violet-stained microplate assay and techniques of epifluorescence, electron and confocal microscopy were applied. The highest density and complexity of biofilms of both vaginal lactobacilli were observed at 72 h of incubation. Protease, proteinase K, alpha-chymotrypsin and trypsin treatments efficiently detached L. reuteri CRL 1324 biofilm that was also partially affected by alpha-amylase. However, L. rhamnosus CRL 1332 biofilm was slightly affected by protease, proteinase K and alpha-amylase. Confocal microscopy revealed greater amount of polysaccharides in L. rhamnosus CRL 1332 biofilm matrix than in L. reuteri CRL 1324 biofilm matrix. The results indicate that proteins are one of the main components of the L. reuteri CRL 1324 biofilm, while the biofilm matrix of L. rhamnosus CRL 1332 is composed of carbohydrates and proteins. The results obtained support the knowledge, understanding and characterization of two biofilm-forming vaginal Lactobacillus strains.

Lee, B. B., Toh, S. L., Ryan, S., Simpson, J. M., Clezy, K., Bossa, L., Rice, S. A., Marial, O., Weber, G., Kaur, J., Boswell-Ruys, C., Goodall, S., Middleton, J., Tudehope, M., and Kotsiou, G. Probiotics [LGG-BB12 or RC14-GR1] versus placebo as prophylaxis for urinary tract infection in persons with spinal cord injury [ProSCIUTTU]: a study protocol for a randomised controlled trial. BMC.Urol. 2016; 16:18

ABSTRACT: BACKGROUND: Urinary tract infections [UTIs] are very common in people with Spinal Cord Injury [SCI]. UTIs are increasingly difficult and expensive to treat as the organisms that cause them become more antibiotic resistant. Among the SCI population, there is a high rate of multi-resistant organism [MRO] colonisation. Non-antibiotic prevention strategies are needed to prevent UTI without increasing resistance. Probiotics have been reported to be beneficial in preventing UTIs in post-menopausal women in several in vivo and in vitro studies. The main aim of this study is to determine whether probiotic therapy with combinations of Lactobacillus reuteri RC-14 + Lactobacillus rhamnosus GR-1 [RC14-GR1] and/or Lactobacillus rhamnosus GG +

Bifidobacterium BB-12 [LGG-BB12] are effective in preventing UTI in people with SCI compared to placebo. METHOD: This is a multi-site randomised double-blind double-dummy placebo-controlled factorial design study conducted in New South Wales, Australia. All participants have a neurogenic bladder as a result of spinal injury. Recruitment started in April 2011. Participants are randomised to one of four arms, designed for factorial analysis of LGG-BB12 and/or RC14-GR1 v Placebo. This involves 24 weeks of daily oral treatment with RC14-GR1 + LGG-BB12, RC14-GR1 + placebo, LGG-BB12 + placebo or two placebo capsules. Randomisation is stratified by bladder management type and inpatient status. Participants are assessed at baseline, three months and six months for Short Form Health Survey [SF-36], microbiological swabs of rectum, nose and groin; urine culture and urinary catheters for subjects with indwelling catheters. A bowel questionnaire is administered at baseline and three months to assess effect of probiotics on bowel function. The primary outcome is time from randomisation to occurrence of symptomatic UTI. The secondary outcomes are change of MRO status and bowel function, quality of life and cost-effectiveness of probiotics in persons with SCI. The primary outcome will be analysed using survival analysis of factorial groups, with Cox regression modelling to test the effect of each treatment while allowing for the other, assuming no interaction effect. Hazard ratios and Kaplan-Meier survival curves will be used to summarise results. DISCUSSION: If these probiotics are shown to be effective in preventing UTI and MRO colonisation, they would be a very attractive alternative for UTI prophylaxis and for combating the increasing rate of antibiotic resistance after SCI. TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registry [ACTRN 12610000512022]. Date of registration: 21 June 2010.

Lee, J., Yang, W., Hostetler, A., Schultz, N., Suckow, M. A., Stewart, K. L., Kim, D. D., and Kim, H. S. Characterization of the anti-inflammatory Lactobacillus reuteri BM36301 and its probiotic benefits on aged mice. BMC.Microbiol. 2016; 16:69

ABSTRACT: BACKGROUND: The gut microbiota is playing more important roles in host immune regulation than was initially expected. Since many benefits of microbes are highly strain-specific and their mechanistic details remain largely elusive, further identification of new probiotic bacteria with immunoregulatory potentials is of great interest. RESULTS: We have screened our collection of probiotic lactic acid bacteria (LAB) for their efficacy in modulating host immune response. Some LAB are characterized by suppression of TNF-alpha induction when LAB culture supernatants are added to THP-1 cells, demonstrating the LAB's anti-inflammatory potential. These suppressive materials were not inactivated by heat or trypsin. On the other hand, treatment of THP-1 directly with live bacterial cells identified a group of pro-inflammatory LAB, which stimulated significant production of TNF-alpha. Among those, we chose the Lactobacillus reuteri BM36301 as an anti-inflammatory strain and the L. reuteri BM36304 as a pro-inflammatory strain, and further studied their in vivo effects. We supplied C57BL/6 mice with these bacteria in drinking water while feeding them a standard diet for 20 weeks. Interestingly, these L. reuteri strains evoked different consequences depending on the gender of the mice. That is, males treated with anti-inflammatory BM36301 experienced less weight gain and higher testosterone level; females treated with BM36301 maintained lower serum TNF-alpha as well as healthy skin with active folliculogenesis and hair growth. Furthermore, while males treated with pro-inflammatory BM36304 developed higher serum levels of TNF-alpha and insulin, in contrast females did not experience such effects from this bacteria strain. CONCLUSION: The L. reuteri BM36301 was selected as an anti-inflammatory strain in vitro. It helped mice maintain healthy conditions as they aged.

These findings propose the L. reuteri BM36301 as a potential probiotic strain to improve various aspects of aging issues.

Lee, M. H., Kim, M., Kim, M., Kwak, J. H., Chang, D. H., Yu, W. K., Lee, S. H., and Lee, J. H. Consumption of dairy yogurt with the polysaccharide rhamnogalacturonan from the peel of the Korean citrus hallabong enhances immune function and attenuates the inflammatory response. Food Funct. 6-15-2016; 7(6):2833-2839.

ABSTRACT: The aim of this study was to investigate the impact of consuming dairy yogurt supplemented with rhamnogalacturonan (RG), a polysaccharide from the peel of the Korean citrus hallabong, on natural killer (NK) cell activity and circulating cytokine levels. A randomized, double-blind, placebo-controlled study was conducted on 120 nondiabetic and nonobese subjects. Over an eight-week period, the test group consumed one pack (150 mL) of dairy yogurt containing 50 mg of probiotics and 100 mg of hallabong peel polysaccharide (60% RG) each day, whereas the placebo group consumed the same product without the hallabong peel supplement. NK cell activity (%) was measured based on the ratios of the effector cells (E; peripheral blood mononuclear cells, PBMCs) from each participant relative to the target cells (T; K562 cells) at E : T ratios of 10 : 1, 5 : 1, 2.5 : 1, or 1.25 : 1. NK cell activities under all assay conditions and interleukin (IL)-12 and interferon (IFN)-gamma levels were significantly increased in the test group at eight weeks compared to the baseline values, whereas the placebo group showed a significant increase only in NK cell activity at E : T = 1.25 : 1. The test group had significantly greater increases in the changes in serum NK cell activity at the E : T ratios of 10 : 1, 5 : 1, and 2.5 : 1 and in the increases in IL-12 and IFN-gamma levels than were observed in the placebo group, after adjusting for baseline values. After eight weeks of treatment, significant reductions were found in IL-6 and IL-1beta levels in both the placebo and test groups. The daily consumption of dairy yogurt supplemented with RG, a polysaccharide from the peel of the Korean citrus hallabong, enhanced NK cell function and attenuated pro-inflammatory cytokine levels (ClinicalTrials.gov: NCT02535663).

Lee, S. J., Cha, J., and Lee, J. W. Probiotics prophylaxis in pyelonephritis infants with normal urinary tracts. World J.Pediatr. 4-8-2016;

ABSTRACT: BACKGROUND: Pyelonephritis in infants is considered as a major factor for the formation of renal scar. To prevent recurrent pyelonephritis and renal damage, prophylaxis is extremely important. The aim of this study was to compare the effectiveness of probiotic and antibiotic prophylaxis or no-prophylaxis in infants with pyelonephritis and normal urinary tract. METHODS: Altogether 191 infants, who were diagnosed with acute pyelonephritis, proven to have normal urinary tracts and followed up for 6 months on prophylaxis, were retrospectively evaluated. According to the types of prophylaxis, the infants were divided into three groups [probiotics (Lactobacillus species), antibiotics (trimethoprim/sulfamethoxazole, TMP/SMX), and noprophylaxis]. The incidence of recurrent urinary tract infection (UTI) during 6 months after the development of pyelonephritis, main causative uropathogens, and its antimicrobial sensitivities were compared. RESULTS: The incidence of recurrent UTI in the probiotic group was 8.2%, which was significantly lower than 20.6% in the no-prophylaxis group (P=0.035) and was not significantly different from 10.0% of the antibiotic group (P=0.532). The significant difference between the probiotic and no-prophylaxis groups was seen only in male infants (P=0.032). The main causative organism of recurrent UTI was Escherichia coli

(E.coli), which was not different among the three groups (P=0.305). The resistance rate of E. coli to TMP/SMX was 100% in the antibiotic group, which was significantly higher than 25.0% in the probiotic group and 41.7% in the no-prophylaxis group (P=0.008). CONCLUSIONS: Probiotic prophylaxis was more effective in infants with pyelonephritis and normal urinary tract than in those with no-prophylaxis. It could be used as a natural alternative to antibiotic prophylaxis.

Lee, Y., Yoshitsugu, R., Kikuchi, K., Joe, G. H., Tsuji, M., Nose, T., Shimizu, H., Hara, H., Minamida, K., Miwa, K., and Ishizuka, S. Combination of soya pulp and Bacillus coagulans lilac-01 improves intestinal bile acid metabolism without impairing the effects of prebiotics in rats fed a cholic acid-supplemented diet. Br.J.Nutr. 2016; 116(4):603-610.

ABSTRACT: Intestinal bacteria are involved in bile acid (BA) deconjugation and/or dehydroxylation and are responsible for the production of secondary BA. However, an increase in the production of secondary BA modulates the intestinal microbiota due to the bactericidal effects and promotes cancer risk in the liver and colon. The ingestion of Bacillus coagulans improves constipation via the activation of bowel movement to promote defaecation in humans, which may alter BA metabolism in the intestinal contents. BA secretion is promoted with high-fat diet consumption, and the ratio of cholic acid (CA):chenodeoxycholic acid in primary BA increases with ageing. The dietary supplementation of CA mimics the BA environment in diet-induced obesity and ageing. We investigated whether B. coagulans lilac-01 and soya pulp influence both BA metabolism and the maintenance of host health in CA-supplemented diet-fed rats. In CA-fed rats, soya pulp significantly increased the production of secondary BA such as deoxycholic acid and omega-muricholic acids, and soya pulp ingestion alleviated problems related to plasma adiponectin and gut permeability in rats fed the CA diet. The combination of B. coagulans and soya pulp successfully suppressed the increased production of secondary BA in CA-fed rats compared with soya pulp itself, without impairing the beneficial effects of soya pulp ingestion. In conclusion, it is possible that a combination of prebiotics and probiotics can be used to avoid an unnecessary increase in the production of secondary BA in the large intestine without impairing the beneficial functions of prebiotics.

Lepargneur, J. P. Lactobacillus crispatus as biomarker of the healthy vaginal tract. Ann.Biol.Clin.(Paris). 8-1-2016; 74(4):421-427.

ABSTRACT: Decades of research have shown that the lactobacilli inhabiting the human vagina are the first line of defense in the female urogenital and reproductive tracts. In healthy cervicovaginal microbiota, Lactobacillus crispatus is prevalent and beneficial with production of copious amounts of lactic acid potent broad spectrum bactericide virucide and immunomodulator. Future and preventic approaches may need to include probiotics, prebiotics also have the potential to optimize and restore the vaginal ecosystem.

Li, C., Li, X., Han, H., Cui, H., Peng, M., Wang, G., and Wang, Z. Effect of probiotics on metabolic profiles in type 2 diabetes mellitus: A meta-analysis of randomized, controlled trials. Medicine (Baltimore). 2016; 95(26):e4088

ABSTRACT: Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disease which is imposing heavy burden on global health and economy. Recent studies indicate gut microbiota play important role on the pathogenesis and metabolic disturbance of T2DM. As an effective mean of regulating gut microbiota, probiotics are live micro-organisms that are believed to provide a specific health benefit on the host. Whether probiotic supplementation could improve metabolic profiles by modifying gut microbiota in T2DM or not is still in controversy.The aim of the study is to assess the effect of probiotic supplementation on metabolic profiles in T2DM.We searched PubMed, EMBASE, and Cochrane Library up to 12 April 2016. Two review authors independently assessed study eligibility, extracted data, and evaluated risk of bias of included studies. Data were pooled by using the random-effect model and expressed as standardized mean difference (SMD) with 95% confidence interval (CI). Heterogeneity was assessed and quantified (I).A total of 12 randomized controlled trials (RCTs) were included. Lipid profiles (n = 508) and fasting blood glucose (FBG) (n = 520) were reported in 9 trials; the homeostasis model of assessment for insulin resistance index (HOMA-IR) (n = 368) and glycosylated hemoglobin (HbA1c) (n = 380) were reported in 6 trials. Probiotics could alleviate FBG (SMD -0.61 mmol/L, 95% CI [-0.92, -0.30], P = 0.0001). Probiotics could increase high-density lipoprotein-cholesterol (HDL-C) (SMD 0.42 mmol/L, 95% CI [0.08, 0.76], P = 0.01). There were no significant differences in low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), HbA1c and HOMA-IR between the treatment group and the control group.Probiotics may improve glycemic control and lipid metabolism in T2DM. Application of probiotic agents might become a new method for glucose management in T2DM.

Li, C., Wang, C. L., Sun, Y., Li, A. L., Liu, F., and Meng, X. C. Microencapsulation of Lactobacillus rhamnosus GG by Transglutaminase Cross-Linked Soy Protein Isolate to Improve Survival in Simulated Gastrointestinal Conditions and Yoghurt. J.Food Sci. 2016; 81(7):M1726-M1734.

ABSTRACT: Microencapsulation is an effective way to improve the survival of probiotics in simulated gastrointestinal (GI) conditions and yoghurt. In this study, microencapsulation of Lactobacillus rhamnosus GG (LGG) was prepared by first cross-linking of soy protein isolate (SPI) using transglutaminase (TGase), followed by embedding the bacteria in cross-linked SPI, and then freeze-drying. The survival of microencapsulated LGG was evaluated in simulated GI conditions and yoghurt. The results showed that a high microencapsulation yield of 67.4% was obtained. The diameter of the microencapsulated LGG was in the range of 52.83 to 275.16 mum. Water activity did not differ between free and microencapsulated LGG after freeze-drying. The survival of microencapsulated LGG under simulated gastric juice (pH 2.5 and 3.6), intestinal juice (0.3% and 2% bile salt) and storage at 4 degrees C were significantly higher than that of free cells. The survival of LGG in TGase cross-linked SPI microcapsules was also improved to 14.5 +/- 0.5% during storage in yoghurt. The microencapsulation of probiotics by TGase-treated SPI can be a suitable alternative to polysaccharide gelation technologies.

Li, D., Breiman, A., le, Pendu J., and Uyttendaele, M. Anti-viral Effect of Bifidobacterium adolescentis against Noroviruses. Front Microbiol. 2016; 7:864

ABSTRACT: This study aims to investigate the effect of Bifidobacterium adolescentis against noroviruses (NoVs). Murine norovirus-1 (MNV-1) used as a surrogate was detected by plaque assay and RT-qPCR. Human NoV virus like particles (VLPs) were detected by

cell-binding assay. It was shown that the presence of B. adolescentis could inhibit the multiplication of MNV-1 on RAW 264.7 cells within 48 h of co-incubation period at 37 degrees C. This inhibition did not occur at the viral binding stage, as no difference was observed in MNV-1 genomic copies collected from washed RAW 264.7 cells without and with B. adolescentis after co-incubation for 1 h at room temperature. Meanwhile, the presence of B. adolescentis decreased the binding of human NoV GI.1 VLPs to both Caco-2 cells and HT-29 cells, while no reduction was induced for the binding of human NoV GII.4 VLPs to Caco-2 cells.

Li, F., Duan, K., Wang, C., McClain, C., and Feng, W. Probiotics and Alcoholic Liver Disease: Treatment and Potential Mechanisms. Gastroenterol.Res.Pract. 2016; 2016:5491465

ABSTRACT: Despite extensive research, alcohol remains one of the most common causes of liver disease in the United States. Alcoholic liver disease (ALD) encompasses a broad spectrum of disorders, including steatosis, steatohepatitis, and cirrhosis. Although many agents and approaches have been tested in patients with ALD and in animals with experimental ALD in the past, there is still no FDA (Food and Drug Administration) approved therapy for any stage of ALD. With the increasing recognition of the importance of gut microbiota in the onset and development of a variety of diseases, the potential use of probiotics in ALD is receiving increasing investigative and clinical attention. In this review, we summarize recent studies on probiotic intervention in the prevention and treatment of ALD in experimental animal models and patients. Potential mechanisms underlying the probiotic function are also discussed.

Li, J. Y., Chassaing, B., Tyagi, A. M., Vaccaro, C., Luo, T., Adams, J., Darby, T. M., Weitzmann, M. N., Mulle, J. G., Gewirtz, A. T., Jones, R. M., and Pacifici, R. Sex steroid deficiency-associated bone loss is microbiota dependent and prevented by probiotics. J.Clin.Invest. 6-1-2016; 126(6):2049-2063.

ABSTRACT: A eubiotic microbiota influences many physiological processes in the metazoan host, including development and intestinal homeostasis. Here, we have shown that the intestinal microbiota modulates inflammatory responses caused by sex steroid deficiency, leading to trabecular bone loss. In murine models, sex steroid deficiency increased gut permeability, expanded Th17 cells, and upregulated the osteoclastogenic cytokines TNFalpha (TNF), RANKL, and IL-17 in the small intestine and the BM. In germ-free (GF) mice, sex steroid deficiency failed to increase osteoclastogenic cytokine production, stimulate bone resorption, and cause trabecular bone loss, demonstrating that the gut microbiota is central in sex steroid deficiency-induced trabecular bone loss. Furthermore, we demonstrated that twice-weekly treatment of sex steroid-deficient mice with the probiotics Lactobacillus rhamnosus GG (LGG) or the commercially available probiotic supplement VSL#3 reduces gut permeability, dampens intestinal and BM inflammation, and completely protects against bone loss. In contrast, supplementation with a nonprobiotic strain of E. coli or a mutant LGG was not protective. Together, these data highlight the role that the gut luminal microbiota and increased gut permeability play in triggering inflammatory pathways that are critical for inducing bone loss in sex steroid-deficient mice. Our data further suggest that probiotics that decrease gut permeability have potential as a therapeutic strategy for postmenopausal osteoporosis.

Li, P., Li, X., Gu, Q., Lou, X. Y., Zhang, X. M., Song, D. F., and Zhang, C. Comparative genomic analysis of Lactobacillus plantarum ZJ316 reveals its genetic adaptation and potential probiotic profiles. J.Zhejiang.Univ Sci.B. 2016; 17(8):569-579.

ABSTRACT: OBJECTIVE: In previous studies, Lactobacillus plantarum ZJ316 showed probiotic properties, such as antimicrobial activity against various pathogens and the capacity to significantly improve pig growth and pork quality. The purpose of this study was to reveal the genes potentially related to its genetic adaptation and probiotic profiles based on comparative genomic analysis. METHODS: The genome sequence of L. plantarum ZJ316 was compared with those of eight L. plantarum strains deposited in GenBank. BLASTN, Mauve, and MUMmer programs were used for genome alignment and comparison. CRISPRFinder was applied for searching the clustered regularly interspaced short palindromic repeats (CRISPRs). RESULTS: We identified genes that encode proteins related to genetic adaptation and probiotic profiles, including carbohydrate transport and metabolism, proteolytic enzyme systems and amino acid biosynthesis, CRISPR adaptive immunity, stress responses, bile salt resistance, ability to adhere to the host intestinal wall, exopolysaccharide (EPS) biosynthesis, and bacteriocin biosynthesis. CONCLUSIONS: Comparative characterization of the L. plantarum ZJ316 genome provided the genetic basis for further elucidating the functional mechanisms of its probiotic properties. ZJ316 could be considered a potential probiotic candidate.

Li, Q. and Zhou, J. M. The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder. Neuroscience. 6-2-2016; 324:131-139.

ABSTRACT: Autism spectrum disorder (ASD) is a series of neurodevelopmental disorders that are characterized by deficits in both social and cognitive functions. Although the exact etiology and pathology of ASD remain unclear, a disorder of the microbiota-gut-brain axis is emerging as a prominent factor in the generation of autistic behaviors. Clinical studies have shown that gastrointestinal symptoms and compositional changes in the gut microbiota frequently accompany cerebral disorders in patients with ASD. A disturbance in the gut microbiota, which is usually induced by a bacterial infection or chronic antibiotic exposure, has been implicated as a potential contributor to ASD. The bidirectional microbiota-gut-brain axis acts mainly through neuroendocrine, neuroimmune, and autonomic nervous mechanisms. Application of modulators of the microbiota-gut-brain axis, such as probiotics, helminthes and certain special diets, may be a promising strategy for the treatment of ASD. This review mainly discusses the salient observations of the disruptions of the microbiota-gut-brain axis in the pathogenesis of ASD and reveals its potential therapeutic role in autistic deficits.

Li, R., Zhang, Y., Polk, D. B., Tomasula, P. M., Yan, F., and Liu, L. Preserving viability of Lactobacillus rhamnosus GG in vitro and in vivo by a new encapsulation system. J.Control Release. 5-28-2016; 230:79-87.

ABSTRACT: Probiotics have shown beneficial effects on health and prevention of diseases in humans. However, a concern for application of probiotics is the loss of viability during storage and gastrointestinal transit. The aim of this study was to develop an encapsulation system to preserve viability of probiotics when they are administrated orally and apply Lactobacillus rhamnosus GG (LGG) as a probiotic model to evaluate the effectiveness of this approach using in vitro and in vivo experiments. LGG was encapsulated in hydrogel beads prepared using pectin, a food grade polysaccharide,

glucose, and calcium chloride, and lyophilized by freeze-drying. Encapsulated LGG was cultured in vitro under the condition that mimicked the physiological environment of the human gastrointestinal tract. Compared to non-encapsulated LGG, encapsulation increased tolerance of LGG in the acid condition, protected LGG from protease digestion, and improved shelf time when stored at the ambient condition, in regard of survivability and production of p40, a known LGG-derived protein involved in LGG's beneficial effects on intestinal homeostasis. To evaluate the effects of encapsulation on p40 production in vivo and prevention of intestinal inflammation by LGG, mice were gavaged with LGG containing beads and treated with dextran sulphate sodium (DSS) to induce intestinal injury and colitis. Compared to non-encapsulated LGG, encapsulated LGG enhanced more p40 production in mice, and exerted higher levels of effects on prevention of DSS-induced colonic injury and colitis and suppression of pro-inflammatory cytokine production. These data indicated that the encapsulation system developed in this study preserves viability of LGG in vitro and in vivo, leading to longer shelf time and enhancing the functions of LGG in the gastrointestinal tract. Thus, this encapsulation approach may have the potential application for improving efficacy of probiotics.

Li, S., Gong, G., Ma, C., Liu, Z., and Cai, J. Study on the Influence of Tea Extract on Probiotics in Skim Milk: From Probiotics Propagation to Metabolite. J.Food Sci. 2016; 81(8):M1981-M1986.

ABSTRACT: In this study, the influence of tea extract (TE) on the growth of probiotics in skim milk was examined. Lactobacillus plantarum ST-III, Bifidobacterium bifidum Bb02, Lactobacillus acidophilus NCFM, and Lactobacillus rhamnosus GG were used in this study. The introduction of TE in milk significantly stimulated the propagation and acidification of L. rhamnosus GG and L. acidophilus NCFM. The antioxidant capacities and the total free amino acid contents of all fermented milk products were enhanced by the addition of TE; however, there were different antioxidant properties and free amino acid contents of fermented milk samples fermented by different bacteria. With a 9% (w/w) level, the fermentation with L. rhamnosus GG and L. acidophilus NCFM showed larger numbers of viable cells and faster acidifying rates, as well as excellent antioxidant capacity and abundant free amino acids. The stimulative effects of TE on probiotics can be considered for industrial purposes and has practical implications for commercial applications.

Li, W., Luo, X., Song, R., Zhu, Y., Li, B., and Liu, S. Porous Cellulose Microgel Particle: A Fascinating Host for the Encapsulation, Protection, and Delivery of Lactobacillus plantarum. J.Agric.Food Chem. 5-4-2016; 64(17):3430-3436.

ABSTRACT: Advances in probiotic markets are always restrained by a low viable loading capacity and poor viability. Herein, cellulose microgels (CMs) with high porosity of 95.83 +/- 0.38%, prepared by the sol-gel transition method, turned out to be a hospitable host that accommodated a large number of viable Lactobacillus plantarum higher than 10(9) colony-forming units (cfu)/g. The unique porous structure fascinated probiotics to penetrate into the core of microgels. The conjugation with alginate helped for better acid resistance and bacterial survival of the probiotics. In comparison to Ca-alginate gels, core-shell gels showed sustainable release of L. plantarum cells without damage of viability, lasting for 360 min in simulated intestine fluid. The cellulose host helped to sustain the viable cell release for a longer duration and afford better shelter for L. plantarum

cells as a result of the porous structure and rigid supporting property. The core-shell gels are promising for constructing targeted delivery vehicles of bioactive nutrients.

Liang, S., Xu, L., Zhang, D., and Wu, Z. Effect of probiotics on small intestinal bacterial overgrowth in patients with gastric and colorectal cancer. Turk.J.Gastroenterol. 2016; 27(3):227-232.

ABSTRACT: BACKGROUND/AIMS: Small intestinal bacterial overgrowth (SIBO) may be related to the presence of gastrointestinal cancer. The exact link, however, between SIBO and cancer prevalence as well as cancer symptoms remains unclear, especially in Asian populations. In addition, there is a paucity of data documenting the influence of probiotic treatment of SIBO on cancer symptoms. Here, the aims were to correlate the presence of SIBO with cancer prevalence and cancer symptoms, as well as to investigate the effect of probiotic intervention on SIBO and cancer symptoms. MATERIALS AND METHODS: Employing a case-control design, 112 gastric and 88 colorectal cancer patients were evaluated. Questionnaires were used to assess gastrointestinal symptoms and a glucose-H2-breath test (GHBT) was used to determine SIBO status. Patients with SIBO were administered Bifidobacterium triple viable capsule therapy or placebo. Subsequently, SIBO status and gastrointestinal symptom scores were reanalyzed. RESULTS: In our study group, 63.0% of patients versus 16.3% of controls was tested positive for SIBO. In patients with cancer, SIBO was associated with proton pump inhibitor (PPI) use. Bifidobacterium triple viable capsule was effective in combating SIBO and was associated with a significant improvement in gastrointestinal cancer-related symptoms. CONCLUSION: In a Chinese cohort, SIBO is associated with gastrointestinal cancer. Based on the preliminary intervention study, we conclude that probiotic intervention combats SIBO in patients with gastrointestinal cancer and alleviates its symptoms.

Liao, H. Y., Tao, L., Zhao, J., Qin, J., Zeng, G. C., Cai, S. W., Li, Y., Zhang, J., and Chen, H. G. Clostridium butyricum in combination with specific immunotherapy converts antigen-specific B cells to regulatory B cells in asthmatic patients. Sci.Rep. 2016; 6:20481

ABSTRACT: The effect of antigen specific immunotherapy (SIT) on asthma is supposed to be improved. Published data indicate that administration of probiotics alleviates allergic diseases. B cells play important roles in the pathogenesis of allergic diseases. This study aims to modulate antigen specific B cell property by the administration of Clostridium butyrate (CB) in combination with SIT. The results showed that after a 3-month treatment, the total asthma clinical score and serum specific IgE were improved in the patients treated with SIT, which was further improved in those treated with both SIT and CB, but not in those treated with CB alone. Treatment with SIT and CB increased p300 and STAT3 activation, up regulated the IL-10 gene transcription and increased the frequency of peripheral antigen specific B cells. In conclusion, administration with SIT in combination with CB converts Der p 1 specific B cells to regulatory B cells in asthma patients allergic to Der p 1. The data suggest a potential therapeutic remedy in the treatment of allergic diseases.

Lim, S. M., Jeong, J. J., Woo, K. H., Han, M. J., and Kim, D. H. Lactobacillus sakei OK67 ameliorates high-fat diet-induced blood glucose intolerance and obesity in mice by inhibiting gut microbiota lipopolysaccharide production and inducing colon tight junction protein expression. Nutr.Res. 2016; 36(4):337-348.

ABSTRACT: A high-fat diet (HFD) induces obesity and the associated increases in blood glucose and inflammation through changes in gut microbiota, endotoxemia, and increased gut permeability. To counteract this, researchers have suggested that the use of probiotics that suppress production of proinflammatory lipopolysaccharide (LPS). Here, we tested whether Lactobacillus sakei OK67, which inhibits gut microbiota LPS production selected from among the lactic acid bacteria isolated from kimchi, exerted antihypoglycemic or anti-inflammatory effects in HFD-fed mice. Mice were randomly divided into 2 groups and fed an HFD or a low-fat diet for 4 weeks. These groups were further subdivided; 1 subgroup was treated with L sakei OK67 and fed the experimental diet for 4.5 weeks, whereas the other subgroup was fed the experimental diet alone. L sakei OK67 treatment lowered HFD-elevated LPS levels in blood and colonic fluid and significantly decreased HFD-elevated fasting blood glucose levels and the area under the curve in an oral glucose tolerance test. L sakei OK67 treatment inhibited HFD-induced body and epididymal fat weight gains, suppressed HFD-induced tumor necrosis factor-alpha and interleukin-1beta expression and nuclear factor-kappaB activation in the colon, and significantly increased HFD-suppressed interleukin-10 and tight junction protein expression in the colon. Oral administration of L sakei OK67 significantly downregulated HFD-induced expression of peroxisome proliferator-activated receptor gamma, fatty acid synthase, and tumor necrosis factor-alpha in adipose tissue. In addition, L sakei OK67 treatment strongly inhibited nuclear factor-kappaB activation in LPS-stimulated peritoneal macrophages. We report that L sakei OK67 ameliorates HFD-induced hyperglycemia and obesity by reducing inflammation and increasing the expression of colon tight junction proteins in mice.

Linares, D. M., Ross, P., and Stanton, C. Beneficial Microbes: The pharmacy in the gut. Bioengineered. 2016; 7(1):11-20.

ABSTRACT: The scientific evidence supporting the gut microbiome in relation to health maintenance and links with various disease states afflicting humans, from metabolic to mental health, has grown dramatically in the last few years. Strategies addressing the positive modulation of microbiome functionality associated with these disorders offer huge potential to the food and pharmaceutical industries to innovate and provide therapeutic solutions to many of the health issues affecting modern society. Such strategies may involve the use of probiotics and prebiotics as nutritional adjunct therapies. Probiotics are generally recognized to be a good form of therapy to keep harmful, intestinal microorganisms in check, aid digestion and nutrient absorption, and contribute to immune function. Probiotics are reported to improve microbial balance in the intestinal tract and promote the return to a baseline microbial community following a perturbing event (dysbiosis) such as antibiotic therapy. Prebiotics are selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora, which confers benefits upon host well-being and health.

Liu, D., Jiang, X. Y., Zhou, L. S., Song, J. H., and Zhang, X. Effects of Probiotics on Intestinal Mucosa Barrier in Patients With Colorectal Cancer after Operation: Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016; 95(15):e3342

ABSTRACT: Many studies have found that probiotics or synbiotics can be used in patients with diarrhea or inflammatory bowel disease for the prevention and treatment of some pathologies by improving gastrointestinal barrier function. However, there are few studies

availing the use of probiotics in patients with colorectal cancer. To lay the foundation for the study of nutritional support in colorectal cancer patients, a meta-analysis has been carried out to assess the efficacy of probiotics on the intestinal mucosa barrier in patients with colorectal cancer after operation.To estimate the efficacy of probiotics on the intestinal mucosa barrier in patients with colorectal cancer after operation, a meta-analysis of randomized controlled trials has been conducted.Databases including PubMed, Ovid, Embase, the Cochrane Central Register of Controlled Trials, and the China National Knowledge Infrastructure have been searched to identify suitable studies. Stata 12.0 was used for statistical analysis, and sensitivity analysis was also conducted. Six indicators were chosen to evaluate probiotics in protecting the intestinal mucosa barrier in patients with colorectal cancer. Ratios of lactulose to mannitol (L/M) and Bifidobacterium to Escherichia (B/E), occludin, bacterial translocation, and levels of secretory immunoglobulin A (SIgA), interleukin-6 (IL-6), and C-reactive protein (CRP) were chosen to evaluate probiotics in protecting the intestinal mucosa barrier in patients with colorectal cancer.Seventeen studies including 1242 patients were selected for meta-analysis, including 5 English studies and 12 Chinese studies. Significant effects were found in ratios of L/M (standardized mean difference = 3.83, P = 0.001) and B/E (standardized mean difference = 3.91, P = 0.000), occludin (standardized mean difference = 4.74, P = 0.000), bacterial translocation (standardized mean difference = 3.12, P = 0.002), and levels of SIgA (standardized mean difference = 2.91, P = 0.004) and CRP (standardized mean difference = 4.21, P = 0.000), but no significant effects were found for levels of IL-6 (standardized mean difference = 1.33, P = 0.184).Probiotics can effectively protect the intestinal mucosa physical and biological barrier in patients with colorectal cancer after operation. However, to evaluate the protective effect on intestinal mucosal barrier, further studies on the type and concentration of the probiotics, duration of therapy, and the therapeutic route are required.

Liu, M., Wu, Q., Wang, M., Fu, Y., and Wang, J. Lactobacillus rhamnosus GR-1 Limits Escherichia coli-Induced Inflammatory Responses via Attenuating MyD88-Dependent and MyD88-Independent Pathway Activation in Bovine Endometrial Epithelial Cells. Inflammation. 2016; 39(4):1483-1494.

ABSTRACT: Intrauterine Escherichia coli infection after calving reduces fertility and causes major economic losses in the dairy industry. We investigated the protective effect of the probiotic Lactobacillus rhamnosus GR-1 on E. coli-induced cell damage and inflammation in primary bovine endometrial epithelial cells (BEECs). L. rhamnosus GR-1 reduced ultrastructure alterations and the percentage of BEECs apoptosis after E. coli challenge. Increased messenger RNA (mRNA) expression of immune response indicators, including pattern recognition receptors (toll-like receptor [TLR]2, TLR4, nucleotide-binding oligomerization domain [NOD]1, and NOD2), inflammasome proteins (NOD-like receptor family member pyrin domain-containing protein 3, apoptosis-associated speck-like protein, and caspase-1), TLR4 downstream adaptor molecules (myeloid differentiation antigen 88 [MyD88], toll-like receptor adaptor molecule 2 [TICAM2]), nuclear transcription factor kB (NF-kB), and the inflammatory cytokines tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, IL-8, IL-10, IL-18, and interferon (IFN)-beta, was observed following E. coli challenge. However, these increases were attenuated by L. rhamnosus GR-1 pretreatment. Our data indicate that L. rhamnosus GR-1 ameliorates the E. coli-induced disruption of cellular ultrastructure, subsequently reducing the percentage of BEECs apoptosis and limiting inflammatory responses, partly via attenuation of MyD88-dependent and MyD88-independent pathway activation. Certain

probiotics could potentially prevent postpartum uterine diseases in dairy cows, ultimately reducing the use of antibiotics.

Liu, Z., Liu, W., Ran, C., Hu, J., and Zhou, Z. Abrupt suspension of probiotics administration may increase host pathogen susceptibility by inducing gut dysbiosis. Sci.Rep. 2016; 6:23214

ABSTRACT: In this study, we investigated the risk associated with suspension of probiotics administration in tilapia, an animal model that may mimic immune-compromised conditions in humans. Tilapias were fed for 14 days using a probiotics-supplemented diet, followed by a three-day suspension of probiotics treatment and a subsequent challenge by Aeromonas hydrophila. Unexpectedly, the suspension of a probiotic strain Lactobacillus plantarum JCM1149 significantly triggered susceptibility of the host to A. hydrophila. We further observed that suspension of JCM1149 resulted in host gut microbiota dysbiosis and the subsequent disorder in the intestinal metabolites (bile acids, amino acids, and glucose) and damage in the intestinal epithelium, giving rise to a condition similar to antibiotics-induced gut dysbiosis, which collectively impaired tilapia's gut health and resistance to pathogenic challenges. Additionally, we determined that JCM1149 adhered relatively poorly to tilapia intestinal mucosa and was rapidly released from the gastrointestinal tract (GIT) after suspension, with the rapid loss of probiotic strain probably being the direct cause of gut dysbiosis. Finally, three other probiotic Lactobacillus strains with low intestinal mucosa binding activity showed similar rapid loss phenotype following administration suspension, and induced higher host susceptibility to infection, indicating that the risk is a generic phenomenon in Lactobacillus.

Lo, Vecchio A., Dias, J. A., Berkley, J. A., Boey, C., Cohen, M. B., Cruchet, S., Liguoro, I., Salazar, Lindo E., Sandhu, B., Sherman, P., Shimizu, T., and Guarino, A. Comparison of Recommendations in Clinical Practice Guidelines for Acute Gastroenteritis in Children. J.Pediatr.Gastroenterol.Nutr. 2016; 63(2):226-235.

ABSTRACT: OBJECTIVE: Acute gastroenteritis (AGE) is a major cause of child mortality and morbidity. This study aimed at systematically reviewing clinical practice guidelines (CPGs) on AGE to compare recommendations and provide the basis for developing single universal guidelines. METHODS: CPGs were identified by searching MEDLINE, Cochrane-Library, National Guideline Clearinghouse and Web sites of relevant societies/organizations producing and/or endorsing CPGs. RESULTS: The definition of AGE varies among the 15 CPGs identified. The parameters most frequently recommended to assess dehydration are skin turgor and sunken eyes (11/15, 73.3%), general appearance (11/15, 66.6%), capillary refill time, and mucous membranes appearance (9/15, 60%). Oral rehydration solution is universally recognized as first-line treatment. The majority of CPGs recommend hypo-osmolar (Na 45-60 mmol/L, 11/15, 66.6 %) or low-osmolality (Na 75 mmol/L, 9/15, 60%) solutions. In children who fail oral rehydration, most CPGs suggest intravenous rehydration (66.6%). However, nasogastric tube insertion for fluid administration is preferred according by 5/15 CPGs (33.3%). Changes in diet and withdrawal of food are discouraged by all CPGs, and early refeeding is strongly recommended in 13 of 15 (86.7%). Zinc is recommended as an adjunct to ORS by 10 of 15 (66.6%) CPGs, most of them from low-income countries. Probiotics are considered by 9 of 15 (60%) CPGs, 5 from high-income countries. Antiemetics are not recommended in 9 of 15 (60%) CPGs. Routine use of antibiotics is discouraged. CONCLUSIONS: Key recommendations for the management of AGE in children are similar in CPGs. Together

with accurate review of evidence-base this may represent a starting point for developing universal recommendations for the management of children with AGE worldwide.

Lopetuso, L. R., Scaldaferri, F., Franceschi, F., and Gasbarrini, A. Bacillus clausii and gut homeostasis: state of the art and future perspectives. Expert.Rev.Gastroenterol.Hepatol. 2016; 10(8):943-948.

ABSTRACT: INTRODUCTION: The intestinal barrier is a complex system responsible for the host health. Many gastrointestinal and extra-intestinal diseases are associated to gut barrier disruption. An increasing interest on nutritional supplements and functional foods focused on the hypothesis that specific prebiotics and probiotics may modulate and interact with gut barrier, re-establishing gut homeostasis. AREAS COVERED: The application of preparations containing B. clausii in the treatment or prevention of gut phisiology impairment has been largely supported in the last years and has driven its clinical applications. This review focuses on B. clausii clinical applications and speculates on the possible interactions among B. clausii, gut barrier and immune system and on the consequences of this interplay in modulating human health. Expert commentary: Its favorable effects have been linked to several properties, such as antimicrobial and immunomodulatory activity, regulation of cell growth and differentiation, cell-cell signaling, cell adhesion, signal transcription and transduction, production of vitamins and gut protection from genotoxic agents. In this scenario, future studies will need to better clarify its mechanisms of action and focus on the possible role of B. clausii in modulating gut immune system.

Lopez, P., de, Paz B., Rodriguez-Carrio, J., Hevia, A., Sanchez, B., Margolles, A., and Suarez, A. Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients. Sci.Rep. 2016; 6:24072

ABSTRACT: Intestinal dysbiosis, characterized by a reduced Firmicutes/Bacteroidetes ratio, has been reported in systemic lupus erythematosus (SLE) patients. In this study, in vitro cultures revealed that microbiota isolated from SLE patient stool samples (SLE-M) promoted lymphocyte activation and Th17 differentiation from naive CD4(+) lymphocytes to a greater extent than healthy control-microbiota. Enrichment of SLE-M with Treg-inducing bacteria showed that a mixture of two Clostridia strains significantly reduced the Th17/Th1 balance, whereas Bifidobacterium bifidum supplementation prevented CD4(+) lymphocyte over-activation, thus supporting a possible therapeutic benefit of probiotics containing Treg-inducer strains in order to restore the Treg/Th17/Th1 imbalance present in SLE. In fact, ex vivo analyses of patient samples showed enlarged Th17 and Foxp3(+) IL-17(+) populations, suggesting a possible Treg-Th17 trans-differentiation. Moreover, analyses of fecal microbiota revealed a negative correlation between IL-17(+) populations and Firmicutes in healthy controls, whereas in SLE this phylum correlated directly with serum levels of IFNgamma, a Th1 cytokine slightly reduced in patients. Finally, the frequency of Synergistetes, positively correlated with the Firmicutes/Bacteroidetes ratio in healthy controls, tended to be reduced in patients when anti-dsDNA titers were increased and showed a strong negative correlation with IL-6 serum levels and correlated positively with protective natural IgM antibodies against phosphorylcholine.

Lu, C., Sang, J., He, H., Wan, X., Lin, Y., Li, L., Li, Y., and Yu, C. Probiotic supplementation does not improve eradication rate of Helicobacter pylori infection compared to placebo based on standard therapy: a meta-analysis. Sci.Rep. 2016; 6:23522

ABSTRACT: This meta-analysis included eligible randomized controlled trials (RCTs) with the aim of determining whether probiotic supplementation can improve H. pylori eradication rates. PUBMED, EBSCO, Web of Science, and Ovid databases were searched. We included RCTs that investigated the effect of combining probiotics, with or without a placebo, with standard therapy. A total of 21 RCTs that reported standard therapy plus probiotics were included. Compared to the placebo group, the probiotics group was 1.21(OR 1.21, 95% CI: 0.86, 1.69) and 1.28 (OR 1.28, 95% CI: 0.88, 1.86) times more likely to achieve eradication of H. pylori infection in intent-to-treat (ITT) analysis and per protocol (PP) analysis, respectively. Probiotics with triple therapy plus a 14-day course of treatment did not improve the eradication of H. pylori infection (OR 1.44, 95% CI: 0.87, 2.39) compared to the placebo. Moreover, the placebo plus standard therapy did not improve eradication rates compared to standard therapy alone (P = 0.816). However, probiotics did improve the adverse effects of diarrhea and nausea. These pooled data suggest that the use of probiotics plus standard therapy does not improve the eradication rate of H. pylori infection compared to the placebo.

Luo, L., Reedy, A. R., and Jones, R. M. Detecting Reactive Oxygen Species Generation and Stem Cell Proliferation in the Drosophila Intestine. Methods Mol.Biol. 2016; 1422:103-113.

ABSTRACT: The conservation of intestinal stem cell crypt dynamics between Drosophila melanogaster and mammals allows for the genetically tractable fly model to be used for analyses of intestinal development, homeostasis, and renewal in relation to microbiota. The invertebrate fly model is advantageous for genetic research due to its anatomical and genetic simplicity and short lifespan. Accordingly, experimental resources such as large numbers of mutant and genetically modified flies have been developed. We have developed techniques to generate germ-free Drosophila, monoassociate them with candidate bacteria, and assess ensuing physiological responses within the gut tissue that include the generation of reactive oxygen species and cell proliferation.

Lyte, M. Microbial Endocrinology: An Ongoing Personal Journey. Adv.Exp.Med.Biol. 2016; 874:1-24.

ABSTRACT: The development of microbial endocrinology is covered from a decidedly personal perspective. Specific focus is given to the role of microbial endocrinology in the evolutionary symbiosis between man and microbe as it relates to both health and disease. Since the first edition of this book series 5 years ago, the role of microbial endocrinology in the microbiota-gut-brain axis is additionally discussed. Future avenues of research are suggested.

Machado, M. V. and Cortez-Pinto, H. Diet, Microbiota, Obesity, and NAFLD: A Dangerous Quartet. Int.J.Mol.Sci. 2016; 17(4):481

ABSTRACT: Recently, the importance of the gut-liver-adipose tissue axis has become evident. Nonalcoholic fatty liver disease (NAFLD) is the hepatic disease of a systemic metabolic disorder that radiates from energy-surplus induced adiposopathy. The gut

microbiota has tremendous influences in our whole-body metabolism, and is crucial for our well-being and health. Microorganisms precede humans in more than 400 million years and our guest flora evolved with us in order to help us face aggressor microorganisms, to help us maximize the energy that can be extracted from nutrients, and to produce essential nutrients/vitamins that we are not equipped to produce. However, our gut microbiota can be disturbed, dysbiota, and become itself a source of stress and injury. Dysbiota may adversely impact metabolism and immune responses favoring obesity and obesity-related disorders such as insulin resistance/diabetes mellitus and NAFLD. In this review, we will summarize the latest evidence of the role of microbiota/dysbiota in diet-induced obesity and NAFLD, as well as the potential therapeutic role of targeting the microbiota in this set.

Madan, J. C. Neonatal Gastrointestinal and Respiratory Microbiome in Cystic Fibrosis: Potential Interactions and Implications for Systemic Health. Clin.Ther. 2016; 38(4):740-746.

ABSTRACT: PURPOSE: The gastrointestinal microbiome plays a critical role in nutrition and metabolic and immune functions in infants and young children and has implications for lifelong health. Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) mutations in CF result in viscous mucous production, frequent exposure to antibiotics, and atypical colonization patterns, resulting in an evolving dysbiosis of the gastrointestinal and respiratory microsystems; dysbiosis in CF results in systemic inflammation, chronic infection, and dysregulation of immune function. Dysbiosis in both the respiratory system and gut contributes to undernutrition, growth failure, and long-term respiratory and systemic morbidity in infants and children with CF. Understanding the role that the gut and respiratory microbiome plays in health or disease progression in CF will afford opportunities to better identify interventions to affect clinical changes. METHODS: Summary was done of the pertinent literature in CF and the study of the microbiome and probiotics. FINDINGS: New studies have identified bacteria in the respiratory tract in CF that are typically members of the intestinal microbiota, and enteral exposures to breast milk and probiotics are associated with prolonged periods of respiratory stability in CF. IMPLICATIONS: Understanding the complex interactions between the CFTR mutations, microbial colonization, and mucosal and systemic immunity is of major importance to inform new treatment strategies (such as restoring a healthier microbiome with probiotics or dietary interventions) to improve nutritional status and immune competence and to decrease morbidity and mortality in CF.

Majeed, M., Nagabhushanam, K., Natarajan, S., Sivakumar, A., Eshuis-de, Ruiter T., Booij-Veurink, J., de Vries, Y. P., and Ali, F. Evaluation of genetic and phenotypic consistency of Bacillus coagulans MTCC 5856: a commercial probiotic strain. World J.Microbiol.Biotechnol. 2016; 32(4):60

ABSTRACT: Commercial probiotics preparation containing Bacillus coagulans have been sold in the market for several decades. Due to its high intra-species genomic diversity, it is very likely that B. coagulans strain may alter in different ways over multiple years of production. Therefore, the present study focuses to evaluate the genetic consistency and probiotic potential of B. coagulans MTCC 5856. Phenotypic and genotypic techniques including biochemical profiling, 16S rRNA sequencing, GTG 5'', BOX PCR fingerprinting, and Multi-Locus-Sequence typing (MLST) were carried out to evaluate the identity and consistency of the B. coagulans MTCC 5856. Further, in vitro probiotic potential, safety and stability at ambient temperature conditions of B. coagulans MTCC

5856 were evaluated. All the samples were identified as B. coagulans by biochemical profiling and 16S rRNA sequencing. GTG 5", BOX PCR fingerprints and MLST studies revealed that the same strain was present over 3 years of commercial production. B. coagulans MTCC 5856 showed resistance to gastric acid, bile salt and exhibited antimicrobial activity in in-vitro studies. Additionally, B. coagulans MTCC 5856 was found to be non-mutagenic, non-cytotoxic, negative for enterotoxin genes and stable at ambient temperature (25 +/- 2 degrees C) for 36 months. The data of the study verified that the same strain of B. coagulans MTCC 5856 was present in commercial preparation over multiple years of production.

Maldonado-Barragan, A., Caballero-Guerrero, B., Martin, V., Ruiz-Barba, J. L., and Rodriguez, J. M. Purification and genetic characterization of gassericin E, a novel co-culture inducible bacteriocin from Lactobacillus gasseri EV1461 isolated from the vagina of a healthy woman. BMC.Microbiol. 2016; 16:37

ABSTRACT: BACKGROUND: Lactobacillus gasseri is one of the dominant Lactobacillus species in the vaginal ecosystem. Some strains of this species have a high potential for being used as probiotics in order to maintain vaginal homeostasis, since they may confer colonization resistance against pathogens in the vagina by direct inhibition through production of antimicrobial compounds, as bacteriocins. In this work we have studied bacteriocin production of gassericin E (GasE), a novel bacteriocin produced by L. gasseri EV1461, a strain isolated from the vagina of a healthy woman, and whose production was shown to be promoted by the presence of certain specific bacteria in co-culture. Biochemical and genetic characterization of this novel bacteriocin are addressed. RESULTS: We found that the inhibitory spectrum of L. gasseri EV1461 was broad, being directed to species both related and non-related to the producing strain. Interestingly, L. gasseri EV1461 inhibited the grown of pathogens usually associated with bacterial vaginosis (BV). The antimicrobial activity was due to the production of a novel bacteriocin, gassericin E (GasE). Production of this bacteriocin in broth medium only was achieved at high cell densities. At low cell densities, bacteriocin production ceased and only was restored after the addition of a supernatant from a previous bacteriocin-producing EV1461 culture (autoinduction), or through co-cultivation with several other Gram-positive strains (inducing bacteria). DNA sequence of the GasE locus revealed the presence of two putative operons which could be involved in biosynthesis and immunity of this bacteriocin (gaeAXI), and in regulation, transport and processing (gaePKRTC). The gaePKR encodes a putative three-component regulatory system, involving an autoinducer peptide (GaeP), a histidine protein kinase (GaeK) and a response regulator (GaeR), while the gaeTC encodes for an ABC transporter (GaeT) and their accessory protein (GaeC), involved in transport and processing of the bacteriocin. The gaeAXI, encodes for the bacteriocin gassericin E (GasE), a putative peptide bacteriocin (GaeX), and their immunity protein (GaeI). CONCLUSIONS: The origin of the strain (vagina of healthy woman) and its ability to produce bacteriocins with inhibitory activity against vaginal pathogens may be an advantage for using L. gasseri EV1461 as a probiotic strain to fight and/or prevent bacterial infections as bacterial vaginosis (BV), since it could be better adapted to live and compete into the vaginal environment.

Malik, A., Sumayyah, S., Yeh, C. W., and Heng, N. C. Identification and sequence analysis of pWcMBF8-1, a bacteriocin-encoding plasmid from the lactic acid bacterium Weissella confusa. FEMS Microbiol.Lett. 2016; 363(8)

ABSTRACT: Members of the Gram-positive lactic acid bacteria (LAB) are well-known for their beneficial properties as starter cultures and probiotics. Many LAB species produce ribosomally synthesized proteinaceous antibiotics (bacteriocins). Weissella confusa MBF8-1 is a strain isolated from a fermented soybean product that not only produces useful exopolysaccharides but also exhibits bacteriocin activity, which we call weissellicin MBF. Here, we show that bacteriocin production by W. confusa MBF8-1 is specified by a large plasmid, pWcMBF8-1. Plasmid pWcMBF8-1 (GenBank accession number KR350502), which was identified from the W. confusa MBF8-1 draft genome sequence, is 17 643 bp in length with a G + C content of 34.8% and contains 25 open reading frames (ORFs). Six ORFs constitute the weissellicin MBF locus, encoding three putative double-glycine-motif peptides (Bac1, Bac2, Bac3), an ABC transporter complex (BacTE) and a putative immunity protein (BacI). Two ORFs encode plasmid partitioning and mobilization proteins, suggesting that pWcMBF8-1 is transferable to other hosts. To the best of our knowledge, plasmid pWcMBF8-1 not only represents the first large Weissella plasmid to be sequenced but also the first to be associated with bacteriocin production in W. confusa.

Mamo, G. Anaerobes as Sources of Bioactive Compounds and Health Promoting Tools. Adv.Biochem.Eng Biotechnol. 7-19-2016;

ABSTRACT: Aerobic microorganisms have been sources of medicinal agents for several decades and an impressive variety of drugs have been isolated from their cultures, studied and formulated to treat or prevent diseases. On the other hand, anaerobes, which are believed to be the oldest life forms on earth and evolved remarkably diverse physiological functions, have largely been neglected as sources of bioactive compounds. However, results obtained from the limited research done so far show that anaerobes are capable of producing a range of interesting bioactive compounds that can promote human health. In fact, some of these bioactive compounds are found to be novel in their structure and/or mode of action.Anaerobes play health-promoting roles through their bioactive products as well as application of whole cells. The bioactive compounds produced by these microorganisms include antimicrobial agents and substances such as immunomodulators and vitamins. Bacteriocins produced by anaerobes have been in use as preservatives for about 40 years. Because these substances are effective at low concentrations, encounter relatively less resistance from bacteria and are safe to use, there is a growing interest in these antimicrobial agents. Moreover, several antibiotics have been reported from the cultures of anaerobes. Closthioamide and andrimid produced by Clostridium cellulolyticum and Pantoea agglomerans, respectively, are examples of novel antibiotics of anaerobe origin. The discovery of such novel bioactive compounds is expected to encourage further studies which can potentially lead to tapping of the antibiotic production potential of this fascinating group of microorganisms.Anaerobes are widely used in preparation of fermented foods and beverages. During the fermentation processes, these organisms produce a number of bioactive compounds including anticancer, antihypertensive and antioxidant substances. The well-known health promoting effect of fermented food is mostly due to these bioactive compounds. In addition to their products, whole cell anaerobes have very interesting applications for enhancing the quality of life. Probiotic anaerobes have been on the market for many years and are receiving growing acceptance as health promoters. Gut anaerobes have been used to treat patients suffering from severe Clostridium difficile infection syndromes including diarrhoea and colitis which cannot be treated by other means. Whole cell anaerobes are also studied to detect and cure cancer. In recent years, evidence is emerging that anaerobes constituting the microbiome are linked to our overall health. A dysfunctional microbiome

is believed to be the cause of many diseases including cancer, allergy, infection, obesity, diabetes and several other disorders. Maintaining normal microflora is believed to alleviate some of these serious health problems. Indeed, the use of probiotics and prebiotics which favourably change the number and composition of the gut microflora is known to render a health promoting effect. Our interaction with the microbiome anaerobes is complex. In fact, not only our lives but also our identities are more closely linked to the anaerobic microbial world than we may possibly imagine. We are just at the beginning of unravelling the secret of association between the microbiome and human body, and a clear understanding of the association may bring a paradigm shift in the way we diagnose and treat diseases and disorders. This chapter highlights some of the work done on bioactive compounds and whole cell applications of the anaerobes that foster human health and improve the quality of life.

Mandal, H., Jariwala, R., and Bagchi, T. Isolation and characterization of lactobacilli from human faeces and indigenous fermented foods for their potential application as probiotics. Can.J.Microbiol. 2016; 62(4):349-359.

ABSTRACT: This study was conducted to select Lactobacillus strains from various sources on the basis of their probiotic attributes, such as acid and bile tolerance, binding to intestinal cells, and antimicrobial activity. Twelve isolates were obtained from human and food sources and were evaluated against standard probiotic Lactobacillus rhamnosus GG (LGG). Isolates were also studied for their antibiotic susceptibility. Isolate Lactobacillus fermentum GPI-6 showed the best survival profile at 0.3% and 1% bile salt, as compared with LGG. Isolates Lactobacillus plantarum GRI-2 and Lactobacillus salivarius GPI-4 showed no reduction in survival rate at pH 2.5. As expected, isolates showed strain-specific differences when comparing various attributes. Isolates GPI-4, GPI-7, and FA-5 showed better adhesion to HT-29, while isolate GPI-4 adhered better to Caco-2 cells than did LGG. However, when studying their ability to compete with Escherichia coli O26:H11, isolates GPI-6 and GPI-7 significantly inhibited E. coli adhesion to both HT-29 and Caco-2 cells compared with LGG. In conclusion, isolates GPI-4, GPI-7, and FA-5 showed excellent binding ability and antagonistic activity and better tolerance to acidic pH (pH 2.5) and to different bile salt concentrations in comparison with LGG, and hence, they could be considered as potential probiotic candidates.

Mandal, S. M., Pati, B. R., Chakraborty, R., and Franco, O. L. New insights into the bioactivity of peptides from probiotics. Front Biosci.(Elite.Ed). 2016; 8:450-459.

ABSTRACT: Probiotics are unique bacteria that offer several therapeutic benefits to human beings when administered in optimum amounts. Probiotics are able to produce antimicrobial substances, which stimulate the body's immune responses. Here, we review in detail the anti-infective peptides derived from probiotics and their potential immunomodulatory and anti-inflammatory activities, including a major role in cross-talk between probiotics and gut microbiota under adverse conditions. Insights from the engineered cell surface of probiotics may provide novel anti-infective therapy by heterologous expression of receptor peptides of bacterial toxins. It may be possible to use antigenic peptides from viral pathogens as live vaccines. Another possibility is to generate antiviral peptides that bind directly to virus particles, while some peptides exert anti-inflammatory and anticancer effects. Some extracellular polymeric substances might serve as anti-infective peptides. These avenues of treatment have remained

largely unexplored to date, despite their potential in generating powerful anti-inflammatory and anti-infective products.

Manhar, A. K., Bashir, Y., Saikia, D., Nath, D., Gupta, K., Konwar, B. K., Kumar, R., Namsa, N. D., and Mandal, M. Cellulolytic potential of probiotic Bacillus Subtilis AMS6 isolated from traditional fermented soybean (Churpi): An in-vitro study with regards to application as an animal feed additive. Microbiol.Res. 2016; 186-187:62-70.

ABSTRACT: The aim of the present study is to evaluate the probiotic attributes of Bacillus subtilis AMS6 isolated from fermented soybean (Churpi). This isolate exhibited tolerance to low pH (pH 2.0) and bile salt (0.3%), capability to autoaggregate and coaggregate. AMS6 also showed highest antibacterial activity against the pathogenic indicator strain Salmonella enterica typhimurium (MTCC 1252) and susceptibility towards different antibiotics tested. The isolate was effective in inhibiting the adherence of food borne pathogens to Caco-2 epithelial cell lines, and was also found to be non-hemolytic which further strengthen the candidature of the isolate as a potential probiotic. Further studies revealed B. subtilis AMS6 showed cellulolytic activity (0.54+/-0.05 filter paper units mL(-1)) at 37 degrees C. The isolate was found to hydrolyze carboxymethyl cellulose, filter paper and maize (Zea mays) straw. The maize straw digestion was confirmed by scanning electron microscopy studies. The isolate was able to degrade filter paper within 96h of incubation. A full length cellulase gene of AMS6 was amplified using degenerate primers consisting of 1499 nucleotides. The ORF encoded for a protein of 499 amino acids residues with a predicted molecular mass of 55.04kDa. The amino acids sequence consisted of a glycosyl hydrolase family 5 domain at N-terminal; Glycosyl hydrolase catalytic core and a CBM-3 cellulose binding domain at its C terminal. The study suggests potential probiotic B. subtilis AMS6 as a promising candidate envisaging its application as an animal feed additive for enhanced fiber digestion and gut health of animal.

Mansour, N. M. and Abdelaziz, S. A. "Oral Immunization of Mice with Engineered Lactobacillus gasseri NM713 Strain Expressing Streptococcus pyogenes M6 Antigen". Microbiol.Immunol. 6-15-2016;

ABSTRACT: The aim of this work is in vivo evaluating our recombinant probiotic strain Lactobacillus gasseri NM713 that express the conserved region of streptococcal M6 protein (CRR6) as effective oral vaccine against streptococcus pyogenes. A dose of 109 cells of the recombinant strain in a 150 microl PBS buffer was administrated orally to a group of mice, and two control groups received either the equivalent dose of Lb. gasseri NM613 (containing the empty plasmid without insert) or PBS buffer. Each group contained 30 mice and the immunization protocol was carried on three following days and repeated two times more as booster dose based on two weeks interval protocol. Faecal and sera samples of mice were collected on days 18, 32, 46, 58 after the first immunization in addition to 0 day before immunization. The anti-CRR6 IgA and IgG levels were measured by ELISA respectively in faecal and sera samples to confirm the immune response. The vaccination with the recombinant Lb. gasseri NM713 strain showed significant protection after the nasal challenge with S. pyogenes. Where this group presented very low percentage of streptococcal infection (10%) and mortality (3.3%) compared to the two control groups which showed high streptococcal infection ranging from 43.3% to 46.7% and high mortality ranging from 46.7% to 53%. The results indicate that the recombinant Lb. gasseri NM713 has potential as an oral delivery vaccine against streptococcus group A.

Marasco, G., Di Biase, A. R., Schiumerini, R., Eusebi, L. H., Iughetti, L., Ravaioli, F., Scaioli, E., Colecchia, A., and Festi, D. Gut Microbiota and Celiac Disease. Dig.Dis.Sci. 2016; 61(6):1461-1472.

ABSTRACT: Recent evidence regarding celiac disease has increasingly shown the role of innate immunity in triggering the immune response by stimulating the adaptive immune response and by mucosal damage. The interaction between the gut microbiota and the mucosal wall is mediated by the same receptors which can activate innate immunity. Thus, changes in gut microbiota may lead to activation of this inflammatory pathway. This paper is a review of the current knowledge regarding the relationship between celiac disease and gut microbiota. In fact, patients with celiac disease have a reduction in beneficial species and an increase in those potentially pathogenic as compared to healthy subjects. This dysbiosis is reduced, but might still remain, after a gluten-free diet. Thus, gut microbiota could play a significant role in the pathogenesis of celiac disease, as described by studies which link dysbiosis with the inflammatory milieu in celiac patients. The use of probiotics seems to reduce the inflammatory response and restore a normal proportion of beneficial bacteria in the gastrointestinal tract. Additional evidence is needed in order to better understand the role of gut microbiota in the pathogenesis of celiac disease, and the clinical impact and therapeutic use of probiotics in this setting.

Mariman, R., Reefman, E., Tielen, F., Persoon-Deen, C., van de, Mark K., Worms, N., Koning, F., and Nagelkerken, L. Lactobacillus plantarum NCIMB8826 ameliorates inflammation of colon and skin in human APOC1 transgenic mice. Benef.Microbes. 2016; 7(2):215-225.

ABSTRACT: Genetic predisposition and environmental factors, including the gut microbiota, have been suggested as major factors in the development and progression of atopic dermatitis. Hyperlipidemic human APOC1(+/+) transgenic mice display many features of human atopic dermatitis, such as scaling, lichenification, excoriations, and pruritus, along with a disturbed skin barrier function. Cytokine analysis of serum shows an increase of various pro-inflammatory cytokines, including interleukin (IL)-12p40, IL-6, and IL-1alpha, but lower levels of interferon-gamma. These mice also display aspects of colitis evident from macroscopic and histological abnormalities. Genome-wide transcriptome analysis of the intestine shows up-regulation of several genes associated with mast cells and eosinophils and this observation was confirmed by demonstrating increased numbers of IgE(+) and FcRepsilon(+) mast cells in the colon and in the skin. Oral treatment with Lactobacillus plantarum NCIMB8826 resulted in decreased numbers of mast cells in the colon. Moreover, this L. plantarum strain ameliorated skin pathology, evident from improved skin barrier integrity, absence of skin thickening, and less excoriations. These results suggest that modulation of intestinal immune homeostasis contributes to the suppression of atopic dermatitis.

Martensson, A., Greiff, L., Lamei, S. S., Lindstedt, M., Olofsson, T. C., Vasquez, A., and Cervin, A. Effects of a honeybee lactic acid bacterial microbiome on human nasal symptoms, commensals, and biomarkers. Int.Forum Allergy Rhinol. 4-15-2016;

ABSTRACT: BACKGROUND: Lactic acid bacteria (LAB) can restore commensal microbiomes and prevent infections. Arguably, nasal administrations of LAB may therefore be beneficial in chronic rhinosinusitis (CRS). Previous studies have examined

effects of topical/nasal LAB in children with secretory otitis media, but little is as yet known about their effects on the human nasal airway. The aim of this pilot study was to examine effects on nasal symptoms and commensal bacteria in healthy subjects of nasal administration of a honeybee LAB microbiome; ie, a mixture of 9 Lactobacillus spp. and 4 Bifidobacterium spp. obtained from the honeybee Apis mellifera. Furthermore, we aimed to assess whether or not the honeybee LAB produced a local inflammatory response. METHODS: Twenty-two healthy subjects received a single administration of honeybee LAB in a sham-controlled, double-blinded, and crossover design. Using questionnaires, microbiological methods, and nasal lavages, they were assessed regarding symptoms, changes to commensal bacteria, and inflammatory products in nasal lavage fluids. RESULTS: The honeybee LAB did not produce any symptoms or other untoward effects. No changes were observed of commensal bacteria by the honeybee LAB, and no inflammatory response was detected (compared to sham); ie, unaffected nasal lavage fluid levels of monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), monokine induced by interferon-gamma (MIG), interleukin-15 (IL-15), epidermal growth factor (EGF), eotaxin, interferon gamma-induced protein-10 (IP-10), and interleukin-1 receptor antagonist (IL-1RA). CONCLUSION: A single human nasal administration of a honeybee LAB microbiome is well tolerated. Specifically, it does not affect commensal bacteria and does not produce an inflammatory response.

Martin-Cabezas, R., Davideau, J. L., Tenenbaum, H., and Huck, O. Clinical efficacy of probiotics as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis: a systematic review and meta-analysis. J.Clin.Periodontol. 2016; 43(6):520-530.

ABSTRACT: FOCUSED QUESTION: What is the clinical influence of probiotics as an adjunctive therapy of scaling and root planing (SRP) when compared with SRP alone or in combination with placebo in the treatment of chronic periodontitis (CP). METHODS: Electronic databases were searched up to July 2015. Randomized controlled trials (RCTs) comparing SRP + probiotic versusSRP were included. PPD reduction and CAL gain were selected as primary outcome variables. RESULTS: Independent screening resulted in four eligible publications for the systematic review and three were included in the meta-analysis. Meta-analysis showed a statistically significant CAL gain (-0.42 mm, p = 0.002) and bleeding on probing (BOP) reduction (-14.66, p = 0.003) for SRP + probiotic treatment versusSRP at short-term. Only a tendency (p = 0.06) has been observed in terms of overall PPD reduction, whereas results were significant when stratified for moderate (-0.18, p = 0.001) and deep pockets (-0.67, p < 0.001). CONCLUSION: Within the limitations of this study, the findings of this meta-analysis seem to support the adjunctive use of L. reuteri to SRP in CP treatment at short-term, especially in deep pockets. Heterogeneity and limited available data may reduce the impact of these conclusions. Future long-term RCTs evaluating the clinical efficacy of adjunctive probiotics to SRP are needed.

Matias, N. S., Padilha, M., Bedani, R., and Saad, S. M. In vitro gastrointestinal resistance of Lactobacillus acidophilus La-5 and Bifidobacterium animalis Bb-12 in soy and/or milk-based synbiotic apple ice creams. Int.J.Food Microbiol. 6-28-2016; 234:83-93.

ABSTRACT: The viability and resistance to simulated gastrointestinal (GI) conditions of Lactobacillus acidophilus La-5 and Bifidobacterium animalis Bb-12 in synbiotic ice creams, in which milk was replaced by soy extract and/or whey protein isolate (WPI) with inulin, were investigated. The ice creams were showed to be satisfactory vehicles for La-5 and Bb-12 (populations around 7.5logCFU/g), even after the whole storage period

(84days/-18 degrees C). In all formulations, the propidium monoazide qPCR (PMA-qPCR) analysis demonstrated that probiotics could resist the in vitro GI assay, with significant survival levels, achieving survival rates exceeding 50%. Additionally, scanning electron microscopy images evidenced cells with morphological differences, suggesting physiological changes in response to the induced stress during the in vitro assay. Although all formulations provided resistance to the probiotic strains under GI stress, the variation found in probiotic survival suggests that GI tolerance is indeed affected by the choice of the food matrix.

Matijasic, M., Mestrovic, T., Peric, M., Cipcic, Paljetak H., Panek, M., Vranesic, Bender D., Ljubas, Kelecic D., Krznaric, Z., and Verbanac, D. Modulating Composition and Metabolic Activity of the Gut Microbiota in IBD Patients. Int.J.Mol.Sci. 2016; 17(4)

ABSTRACT: The healthy intestine represents a remarkable interface where sterile host tissues come in contact with gut microbiota, in a balanced state of homeostasis. The imbalance of gut homeostasis is associated with the onset of many severe pathological conditions, such as inflammatory bowel disease (IBD), a chronic gastrointestinal disorder increasing in incidence and severely influencing affected individuals. Despite the recent development of next generation sequencing and bioinformatics, the current scientific knowledge of specific triggers and diagnostic markers to improve interventional approaches in IBD is still scarce. In this review we present and discuss currently available and emerging therapeutic options in modulating composition and metabolic activity of gut microbiota in patients affected by IBD. Therapeutic approaches at the microbiota level, such as dietary interventions alone or with probiotics, prebiotics and synbiotics, administration of antibiotics, performing fecal microbiota transplantation (FMT) and the use of nematodes, all represent a promising opportunities towards establishing and maintaining of well-being as well as improving underlying IBD symptoms.

Matsubara, V. H., Bandara, H. M., Mayer, M. P., and Samaranayake, L. P. Probiotics as Antifungals in Mucosal Candidiasis. Clin.Infect.Dis. 5-1-2016; 62(9):1143-1153.

ABSTRACT: Candidais an opportunistic pathogen that causes mucosal and deep systemic candidiasis. The emergence of drug resistance and the side effects of currently available antifungals have restricted their use as long-term prophylactic agents for candidal infections. Given this scenario, probiotics have been suggested as a useful alternative for the management of candidiasis. We analyzed the available data on the efficacy of probiotics in candidal colonization of host surfaces. A number of well-controlled studies indicate that probiotics, particularly lactobacilli, suppressCandidagrowth and biofilm development in vitro.A few clinical trials have also shown the beneficial effects of probiotics in reducing oral, vaginal, and enteric colonization byCandida; alleviation of clinical signs and symptoms; and, in some cases, reducing the incidence of invasive fungal infection in critically ill patients. Probiotics may serve in the future as a worthy ally in the battle against chronic mucosal candidal infections.

Matsubara, V. H., Wang, Y., Bandara, H. M., Mayer, M. P., and Samaranayake, L. P. Probiotic lactobacilli inhibit early stages of Candida albicans biofilm development by reducing their growth, cell adhesion, and filamentation. Appl.Microbiol.Biotechnol. 2016; 100(14):6415-6426.

ABSTRACT: We evaluated the inhibitory effects of the probiotic Lactobacillus species on different phases of Candida albicans biofilm development. Quantification of biofilm growth and ultrastructural analyses were performed on C. albicans biofilms treated with Lactobacillus rhamnosus, Lactobacillus casei, and Lactobacillus acidophilus planktonic cell suspensions as well as their supernatants. Planktonic lactobacilli induced a significant reduction ($p < 0.05$) in the number of biofilm cells (25.5-61.8 %) depending on the probiotic strain and the biofilm phase. L. rhamnosus supernatants had no significant effect on the mature biofilm ($p > 0.05$), but significantly reduced the early stages of Candida biofilm formation ($p < 0.01$). Microscopic analyses revealed that L. rhamnosus suspensions reduced Candida hyphal differentiation, leading to a predominance of budding growth. All lactobacilli negatively impacted C. albicans yeast-to-hyphae differentiation and biofilm formation. The inhibitory effects of the probiotic Lactobacillus on C. albicans entailed both cell-cell interactions and secretion of exometabolites that may impact on pathogenic attributes associated with C. albicans colonization on host surfaces and yeast filamentation. This study clarifies, for the first time, the mechanics of how Lactobacillus species may antagonize C. albicans host colonization. Our data elucidate the inhibitory mechanisms that define the probiotic candicidal activity of lactobacilli, thus supporting their utility as an adjunctive therapeutic mode against mucosal candidal infections.

Matsubara, V. H., Bandara, H. M., Ishikawa, K. H., Mayer, M. P., and Samaranayake, L. P. The role of probiotic bacteria in managing periodontal disease: a systematic review. Expert.Rev.Anti.Infect.Ther. 2016; 14(7):643-655.

ABSTRACT: INTRODUCTION: The frequent recolonization of treated sites by periodontopathogens and the emergence of antibiotic resistance have led to a call for new therapeutic approaches for managing periodontal diseases. As probiotics are considered a new tool for combating infectious diseases, we systematically reviewed the evidences for their effectiveness in the management of periodontitis. AREAS COVERED: An electronic search was performed in the MEDLINE, SCOPUS and Cochrane Library databases up to March 2016 using the terms 'periodontitis', 'chronic periodontitis', 'probiotic(s)', 'prebiotic(s)', 'symbiotic(s)', 'Bifidobacterium and 'Lactobacillus'. Only randomized controlled trials (RCTs) were included in the present study. Analysis of 12 RCTs revealed that in general, oral administration of probiotics improved the recognized clinical signs of chronic and aggressive periodontitis such as probing pocket depth, bleeding on probing, and attachment loss, with a concomitant reduction in the levels of major periodontal pathogens. Continuous probiotic administration, laced mainly with Lactobacillus species, was necessary to maintain these benefits. Expert commentary: Oral administration of probiotics is a safe and effective adjunct to conventional mechanical treatment (scaling) in the management of periodontitis, specially the chronic disease entity. Their adjunctive use is likely to improve disease indices and reduce the need for antibiotics.

Mayor, S. Probiotics have no effect on gut microbiota in healthy people, review suggests. BMJ. 2016; 353:i2617.

No abstract currently available.

McCarville, J. L., Caminero, A., and Verdu, E. F. Novel perspectives on therapeutic modulation of the gut microbiota. Therap.Adv.Gastroenterol. 2016; 9(4):580-593.

ABSTRACT: The gut microbiota contributes to the maintenance of health and, when disrupted, may drive gastrointestinal and extragastrointestinal disease. This can occur through direct pathways such as interaction with the epithelial barrier and mucosal immune system or indirectly via production of metabolites. There is no current curative therapy for chronic inflammatory conditions such as inflammatory bowel disease, which are complex multifactorial disorders involving genetic predisposition, and environmental triggers. Therapies are directed to suppress inflammation rather than the driver, and these approaches are not devoid of adverse effects. Therefore, there is great interest in modulation of the gut microbiota to provide protection from disease. Interventions that modulate the microbiota include diet, probiotics and more recently the emergence of experimental therapies such as fecal microbiota transplant or phage therapy. Emerging data indicate that certain bacteria can induce protective immune responses and enhance intestinal barrier function, which could be potential therapeutic targets. However, mechanistic links and specific therapeutic recommendations are still lacking. Here we provide a pathophysiological overview of potential therapeutic applications of the gut microbiota.

McFarland, L. V. Therapies on the horizon for Clostridium difficile infections. Expert.Opin.Investig.Drugs. 2016; 25(5):541-555.

ABSTRACT: INTRODUCTION: Clostridium difficile infections are a leading cause of healthcare facility outbreaks of gastrointestinal illness that may have serious complications and a high rate of recurrent disease. Despite the availability of standard antibiotic treatments, data from national surveillance programs indicate that the incidence of this disease continues to increase, placing a heavy burden on healthcare systems. New emerging strategies are being tested to replace or augment these standard antibiotics. AREAS COVERED: Thirty-two current investigational agents focusing on different strategies for both prevention and treatment of C. difficile infections are reviewed. Data was gathered from a literature search of public databases for published trials from 1999-November 13, 2015 and from the author's compendium of knowledge. Agents reviewed included 13 antibiotics, two antibiotic inactivators, seven bacteria or yeasts acting to enhance the normal microbiome, seven immunizing agents and three toxin binders. Of the 32 investigational treatments reviewed, 8 (25%) showed significant efficacy in phase II or III clinical trials and are actively being developed as new therapies for C. difficile infections. EXPERT OPINION: A number of potential treatments have floundered during their development process, while others have shown promising results. The strongest efficacy has been in the areas of newer antibiotics, probiotics, monoclonal antibodies and vaccines. By targeting the pathogenic pathway of C. difficile infections, multiple strategies for prevention and treatment have been developed.

McKenney, K. M. and Alfonzo, J. D. From Prebiotics to Probiotics: The Evolution and Functions of tRNA Modifications. Life (Basel). 2016; 6(1)

ABSTRACT: All nucleic acids in cells are subject to post-transcriptional chemical modifications. These are catalyzed by a myriad of enzymes with exquisite specificity and that utilize an often-exotic array of chemical substrates. In no molecule are modifications more prevalent than in transfer RNAs. In the present document, we will attempt to take a

chemical rollercoaster ride from prebiotic times to the present, with nucleoside modifications as key players and tRNA as the centerpiece that drove the evolution of biological systems to where we are today. These ideas will be put forth while touching on several examples of tRNA modification enzymes and their modus operandi in cells. In passing, we submit that the choice of tRNA is not a whimsical one but rather highlights its critical function as an essential invention for the evolution of protein enzymes.

McKenzie, Y. A., Thompson, J., Gulia, P., and Lomer, M. C. British Dietetic Association systematic review of systematic reviews and evidence-based practice guidelines for the use of probiotics in the management of irritable bowel syndrome in adults (2016 update). J.Hum.Nutr.Diet. 6-6-2016;

ABSTRACT: BACKGROUND: Probiotics are often taken by individuals with irritable bowel syndrome (IBS). Which products are effective is unclear, despite an increasing research base. This project will systematically review which strain- and dose- specific probiotics can be recommended to adults with IBS to improve symptoms and quality of life (QoL). It is part of a broader systematic review to update British Dietetic Association guidelines for the dietary management of IBS in adults. METHODS: CINAHL, Cochrane, Embase, Medline, Scopus and Web of Science were searched for systematic reviews (SRs) of randomised controlled trial (RCT)s recruiting adults with IBS comparing probiotic intervention with placebo. AMSTAR, risk of bias and diet bias tools were used to appraise methodological quality. Symptom and QoL data were appraised to develop probiotic-specific evidence statements on clinically meaningful and marginal outcomes in various settings, graded clinical practice recommendations and practical considerations. RESULTS: Nine systematic reviews and 35 RCTs were included (3406 participants) using 29 dose-specific probiotic formulations. None of the RCTs were at low risk of bias. Twelve out of 29 probiotics (41%) showed no symptom or QoL benefits. Evidence indicated that no strain or dose specific probiotic was consistently effective to improve any IBS symptoms or QoL. Two general clinical practice recommendations were made. CONCLUSIONS: Symptom outcomes for dose-specific probiotics were heterogeneous. Specific probiotic recommendations for IBS management in adults were not possible at this time. More data from high-quality RCTs treating specific symptom profiles are needed to support probiotic therapy in the management of IBS.

McKenzie, Y. A., Bowyer, R. K., Leach, H., Gulia, P., Horobin, J., O'Sullivan, N. A., Pettitt, C., Reeves, L. B., Seamark, L., Williams, M., Thompson, J., and Lomer, M. C. British Dietetic Association systematic review and evidence-based practice guidelines for the dietary management of irritable bowel syndrome in adults (2016 update). J.Hum.Nutr.Diet. 6-8-2016;

ABSTRACT: BACKGROUND: The first British Dietetic Association (BDA) guidelines for the dietary management of irritable bowel syndrome (IBS) in adults were published in 2012. Subsequently, there has been a wealth of new research. The aim of this work was to systematically review the evidence for the role of diet in the management of IBS and to update the guidelines. METHODS: Twelve questions relating to diet and IBS were defined based on review of the previous guideline questions, current evidence and clinical practice. Chosen topics were on healthy eating and lifestyle (alcohol, caffeine, spicy food, elimination diets, fat and fluid intakes and dietary habits), milk and dairy, dietary fibre, fermentable carbohydrates, gluten, probiotics and elimination diets/food hypersensitivity. Data sources were CINAHL, Cochrane Register of Controlled Trials, Embase, Medline, Scopus and Web of Science up to October 2015. Studies were

assessed independently in duplicate using risk of bias tools specific to each included study based on inclusion and exclusion criteria for each question. National Health and Medical Research Council grading evidence levels were used to develop evidence statements and recommendations, in accordance with Practice-based Evidence in Nutrition Global protocol used by the BDA. RESULTS: Eighty-six studies were critically appraised to generate 46 evidence statements, 15 clinical recommendations and four research recommendations. The IBS dietary algorithm was simplified to first-line (healthy eating, provided by any healthcare professional) and second-line [low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) to be provided by dietitian] dietary advice. CONCLUSIONS: These guidelines provide updated comprehensive evidence-based details to achieve the successful dietary management of IBS in adults.

Mearin, F., Ciriza, C., Minguez, M., Rey, E., Mascort, J. J., Pena, E., Canones, P., and Judez, J. Clinical Practice Guideline: Irritable bowel syndrome with constipation and functional constipation in the adult. Rev.Esp.Enferm.Dig. 2016; 108(6):332-363.

ABSTRACT: In this Clinical Practice Guideline we discuss the diagnostic and therapeutic approach of adult patients with constipation and abdominal complaints at the confluence of the irritable bowel syndrome spectrum and functional constipation. Both conditions are included among the functional bowel disorders, and have a significant personal, healthcare, and social impact, affecting the quality of life of the patients who suffer from them. The first one is the irritable bowel syndrome subtype, where constipation represents the predominant complaint, in association with recurrent abdominal pain, bloating, and abdominal distension. Constipation is characterized by difficulties with or low frequency of bowel movements, often accompanied by straining during defecation or a feeling of incomplete evacuation. Most cases have no underlying medical cause, and are therefore considered as a functional bowel disorder. There are many clinical and pathophysiological similarities between both disorders, and both respond similarly to commonly used drugs, their primary difference being the presence or absence of pain, albeit not in an "all or nothing" manner. Severity depends not only upon bowel symptom intensity but also upon other biopsychosocial factors (association of gastrointestinal and extraintestinal symptoms, grade of involvement, and perception and behavior variants). Functional bowel disorders are diagnosed using the Rome criteria. This Clinical Practice Guideline has been made consistent with the Rome IV criteria, which were published late in May 2016, and discuss alarm criteria, diagnostic tests, and referral criteria between Primary Care and gastroenterology settings. Furthermore, all the available treatment options (exercise, fluid ingestion, diet with soluble fiber-rich foods, fiber supplementation, other dietary components, osmotic or stimulating laxatives, probiotics, antibiotics, spasmolytics, peppermint essence, prucalopride, linaclotide, lubiprostone, biofeedback, antidepressants, psychological therapy, acupuncture, enemas, sacral root neurostimulation, surgery) are discussed, and practical recommendations are made regarding each of them.

Mello, A. M., Paroni, G., Daragjati, J., and Pilotto, A. Gastrointestinal Microbiota and Their Contribution to Healthy Aging. Dig.Dis. 2016; 34(3):194-201.

ABSTRACT: Studies on populations at different ages have shown that after birth, the gastrointestinal (GI) microbiota composition keeps evolving, and this seems to occur especially in old age. Significant changes in GI microbiota composition in older subjects

have been reported in relation to diet, drug use and the settings where the older subjects are living, that is, in community nursing homes or in a hospital. Moreover, changes in microbiota composition in the old age have been related to immunosenescence and inflammatory processes that are pathophysiological mechanisms involved in the pathways of frailty. Frailty is an age-related condition of increased vulnerability to stresses due to the impairment in multiple inter-related physiologic systems that are associated with an increased risk of adverse outcomes, such as falls, delirium, institutionalization, hospitalization and death. Preliminary data suggest that changes in microbiota composition may contribute to the variations in the biological, clinical, functional and psycho-social domains that occur in the frail older subjects. Multidimensional evaluation tools based on a Comprehensive Geriatric Assessment (CGA) have demonstrated to be useful in identifying and measuring the severity of frailty in older subjects. Thus, a CGA approach should be used more widely in clinical practice to evaluate the multidimensional effects potentially related to GI microbiota composition of the older subjects. Probiotics have been shown to be effective in restoring the microbiota changes of older subjects, promoting different aspects of health in elderly people as improving immune function and reducing inflammation. Whether modulation of GI microbiota composition, with multi-targeted interventions, could have an effect on the prevention of frailty remains to be further investigated in the perspective of improving the health status of frail 'high risk' older individuals.

Melnik, B. C., John, S. M., Carrera-Bastos, P., and Schmitz, G. Milk: a postnatal imprinting system stabilizing FoxP3 expression and regulatory T cell differentiation. Clin.Transl.Allergy. 2016; 6:18

ABSTRACT: BACKGROUND: Breastfeeding has protective effects for the development of allergies and atopy. Recent evidence underlines that consumption of unboiled farm milk in early life is a key factor preventing the development of atopic diseases. Farm milk intake has been associated with increased demethylation of FOXP3 and increased numbers of regulatory T cells (Tregs). Thus, the questions arose which components of farm milk control the differentiation and function of Tregs, critical T cell subsets that promote tolerance induction and inhibit the development of allergy and autoimmunity. FINDINGS: Based on translational research we identified at least six major signalling pathways that could explain milk's biological role controlling stable FoxP3 expression and Treg differentiation: (1) via maintaining appropriate magnitudes of Akt-mTORC1 signalling, (2) via transfer of milk fat-derived long-chain omega-3 fatty acids, (3) via transfer of milk-derived exosomal microRNAs that apparently decrease FOXP3 promoter methylation, (4) via transfer of exosomal transforming growth factor-beta, which induces SMAD2/SMAD3-dependent FoxP3 expression, (5) via milk-derived Bifidobacterium and Lactobacillus species that induce interleukin-10 (IL-10)-mediated differentiation of Tregs, and (6) via milk-derived oligosaccharides that serve as selected nutrients for the growth of bifidobacteria in the intestine of the new born infant. CONCLUSION: Accumulating evidence underlines that milk is a complex signalling and epigenetic imprinting network that promotes stable FoxP3 expression and long-lasting Treg differentiation, crucial postnatal events preventing atopic and autoimmune diseases.

Mendling, W. Vaginal Microbiota. Adv.Exp.Med.Biol. 2016; 902:83-93.

ABSTRACT: The knowledge about the normal and abnormal vaginal microbiome has changed over the last years. Culturing techniques are not suitable any more for determination of a normal or abnormal vaginal microbiota. Non culture-based modern technologies revealed a complex and dynamic system mainly dominated by lactobacilli.The normal and the abnormal vaginal microbiota are complex ecosystems of more than 200 bacterial species influenced by genes, ethnic background and environmental and behavioral factors. Several species of lactobacilli per individuum dominate the healthy vagina. They support a defense system together with antibacterial substances, cytokines, defensins and others against dysbiosis, infections and care for an normal pregnancy without preterm birth.The numbers of Lactobacillus (L.) iners increase in the case of dysbiosis.Bacterial vaginosis (BV) - associated bacteria (BVAB), Atopobium vaginae and Clostridiales and one or two of four Gardnerella vaginalis - strains develop in different mixtures and numbers polymicrobial biofilms on the vaginal epithelium, which are not dissolved by antibiotic therapies according to guidelines and, thus, provoke recurrences.Aerobic vaginitis seems to be an immunological disorder of the vagina with influence on the microbiota, which is here dominated by aerobic bacteria (Streptococcus agalactiae, Escherichia coli). Their role in AV is unknown.Vaginal or oral application of lactobacilli is obviously able to improve therapeutic results of BV and dysbiosis.

Meng, H., Lee, Y., Ba, Z., Peng, J., Lin, J., Boyer, A. S., Fleming, J. A., Furumoto, E. J., Roberts, R. F., Kris-Etherton, P. M., and Rogers, C. J. Consumption of Bifidobacterium animalis subsp. lactis BB-12 impacts upper respiratory tract infection and the function of NK and T cells in healthy adults. Mol.Nutr.Food Res. 2016; 60(5):1161-1171.

ABSTRACT: SCOPE: Probiotics can modulate immunity and reduce upper respiratory tract infections (URTI) in humans; however few studies have examined both outcomes in the same trial. The goal of the current study was to investigate the effect of Bifidobacterium animalis subsp. lactis BB-12, on natural killer (NK) and T-cell function in conjunction with self-reported cold/flu outcomes in healthy adults. METHODS AND RESULTS: In a randomized, partially blinded, four-period crossover study, healthy adults (n = 30) were recruited, and received four treatments for 4 weeks in a random order: (i) yogurt smoothies alone (YS); smoothies with BB-12 added (ii) before (PRE) or (iii) after (POST) yogurt fermentation, or (iv) BB-12 capsule (CAP). NK- and T-cell function was assessed at baseline and after each treatment. Incidence and severity of cold/flu infection was quantified using self-reported URTI questionnaires. Participants on YS, PRE, or CAP treatments had elevated IL-2 secretion and NK-cell cytotoxicity, concurrently with fewer days with URTI. However, the POST treatment did not change immune outcomes or the severity of URTI. CONCLUSION: The timing of BB-12 addition to yogurt smoothies in relation to the fermentation process influenced the impact of BB-12 on immune function and cold/flu severity in young healthy adults.

Messora, M. R., Pereira, L. J., Foureaux, R., Oliveira, L. F., Sordi, C. G., Alves, A. J., Napimoga, M. H., Nagata, M. J., Ervolino, E., and Furlaneto, F. A. Favourable effects of Bacillus subtilis and Bacillus licheniformis on experimental periodontitis in rats. Arch.Oral Biol. 2016; 66:108-119.

ABSTRACT: OBJECTIVES: The purposes of this study were to evaluate, in rats: i) the effects of Bacillus species on the development of experimental periodontitis (EP) via microtomographic, immunological and hematological assays (Experiment 1-E1); ii) the

effects of Bacillus species as adjuncts to scaling and root planing (SRP) for the treatment of EP via histomorphometric and immunohistochemical analyses (Experiment 2-E2). METHODS: In E1, 24 rats were divided into groups C1 (control), PROB1, EP1 and EP-PROB1. In groups with EP, the mandibular first molar of each animal received a ligature for 14 days. In groups PROB1, animals received Bacillus species for 44 days, starting 30 days before EP induction in Group EP-PROB1. In E2, 24 rats were assigned to groups C2 (control), PROB2, EP-SRP2 and EP-SRP-PROB2. In groups with SRP, EP was induced as described in E1. The ligatures were removed after 14 days and SRP was performed. In groups PROB2, animals received Bacillus species for 15 days, starting after SRP in Group EP-SRP-PROB2. RESULTS: In E1, Group EP1 presented bone loss (BL) and eosinophil numbers greater than Group EP-PROB1 ($P<0.05$). In Group EP-PROB1, the receptor activator of nuclear factor-kB ligand (RANKL)/osteoprotegerin (OPG) ratio was similar to that of groups without EP. In E2, Group EP-SRP-PROB2 presented fewer TRAP-positive osteoclasts, lower immunolabeling pattern for a proinflammatory cytokine and decreased BL and attachment loss than Group EP-SRP2 ($P<0.05$). CONCLUSIONS: Bacillus species supplementation provided a protective effect against BL and enhanced the effects of SRP in the treatment of EP in rats.

Meunier, M., Guyard-Nicodeme, M., Dory, D., and Chemaly, M. Control strategies against Campylobacter at the poultry production level: biosecurity measures, feed additives and vaccination. J.Appl.Microbiol. 2016; 120(5):1139-1173.

ABSTRACT: Campylobacteriosis is the most prevalent bacterial foodborne gastroenteritis affecting humans in the European Union, and ranks second in the United States only behind salmonellosis. In Europe, there are about nine million cases of campylobacteriosis every year, making the disease a major public health issue. Human cases are mainly caused by the zoonotic pathogen Campylobacter jejuni. The main source of contamination is handling or consumption of poultry meat. Poultry constitutes the main reservoir of Campylobacter, substantial quantities of which are found in the intestines following rapid, intense colonization. Reducing Campylobacter levels in the poultry chain would decrease the incidence of human campylobacteriosis. As primary production is a crucial step in Campylobacter poultry contamination, controlling the infection at this level could impact the following links along the food chain (slaughter, retail and consumption). This review describes the control strategies implemented during the past few decades in primary poultry production, including the most recent studies. In fact, the implementation of biosecurity and hygiene measures is described, as well as the immune strategy with passive immunization and vaccination trials and the nutritional strategy with the administration of organic and fatty acids, essential oil and plant-derived compound, probiotics, bacteriocins and bacteriophages.

Miao, J., Lang, C., Kang, Z., Zhu, H., Wang, S., and Li, M. Oral administration of fermented milk supplemented with synbiotics can influence the physiological condition of Wistar rats in a dose-sensitive and sex-specific manner. Biosci.Microbiota.Food Health. 2016; 35(2):89-96.

ABSTRACT: Fermented milk supplemented with two probiotic strains (Bifidobacterium lactis Bi-07 and Lactobacillus acidophilus NCFM) and a prebiotic (isomaltooligosaccharide) was orally administered to Wistar rats for 30 days using three dosages. A commercial yogurt was used as a placebo. After treatment, the total protein, hemoglobin, and albumin levels in serum were significantly increased in female rats

compared with those in the control group (p<0.05), whereas no significant change occurred in the male rats. A significant decrease in serum glucose levels was observed in male rats administered a low dosage of the tested fermented milk (p<0.05). The serum triglyceride level was significantly decreased in both male and female rats (p<0.05). No significant differences were found between rats groups in body weight, food intake, food utilization rate, red blood cell counts, white blood cell counts, alanine aminotransferase, aspartate aminotransferase, urea nitrogen, creatinine, and total cholesterol. These results suggest that the fermented milk supplemented with synbiotics altered the nutritive status of the host animal and contributed to their health. However, such potent health-promoting effects could be deeply associated with the dose and sex specific. Therefore, different physiological targets and population characteristics should be managed with different combinations of probiotics and prebiotics.

Michael, D. R., Moss, J. W., Calvente, D. L., Garaiova, I., Plummer, S. F., and Ramji, D. P. Lactobacillus plantarum CUL66 can impact cholesterol homeostasis in Caco-2 enterocytes. Benef.Microbes. 2016; 7(3):443-451.

ABSTRACT: Hypercholesterolemia drives the development of cardiovascular disease, the leading cause of mortality in western society. Supplementation with probiotics that interfere with cholesterol metabolism may provide a contribution to disease prevention. Lactobacillus plantarum CUL66 (NCIMB 30280) has been assessed in vitro for its ability to impact cholesterol absorption. L. plantarum CUL66 tested positive for bile salt hydrolase activity and the ability to assimilate cholesterol from culture media. RT-qPCR analysis showed that the bacterium significantly decreased the expression of Niemann-Pick C1-like 1 and ATP-binding cassette transporter-1 in polarised Caco-2 cells after 6 h exposure. Conversely, the expression of ATP-binding cassette sub-family G member (ABCG)-5 and ABCG-8, and 3-hydroxy-3-methylglutaryl-CoA reductase were significantly increased. Using a radiolabelled assay, we also observed significant reductions in the uptake and basolateral efflux of cholesterol by Caco-2 cells exposed to L. plantarum CUL66. This in vitro study identified L. plantarum CUL66 as a cholesterol lowering bacteria by highlighting its ability to beneficially regulate multiple in vitro events associated with intestinal cholesterol metabolism and provides evidence of efficacy for its inclusion in future in vivo studies.

Mikelsaar, M., Sepp, E., Stsepetova, J., Songisepp, E., and Mandar, R. Biodiversity of Intestinal Lactic Acid Bacteria in the Healthy Population. Adv.Exp.Med.Biol. 5-12-2016;

ABSTRACT: The complex ecosystem of the gastrointestinal tract involves tight interrelations among host cells, diet, and billions of microbes, both beneficial and opportunistic pathogens. In spite of advanced genomic, metagenomic, and metabonomic approaches, knowledge is still quite limited regarding the biodiversity of beneficial microbiota, including Lactobacillus spp., and its impact on the main biomarkers of general health. In this paper, Lactobacillus biodiversity is demonstrated through its taxonomy, function, and host-microbial interactions. Its prevalence, composition, abundance, intertwined metabolic properties, and relation to host age, genotype, and socioeconomic factors are reviewed based on the literature and original research experience. The species richness, e.g., the biodiversity of gut microbiota, provides the host with a variety of metabolically active species and strains that predict their response for different health conditions and extrinsic interventions. Metabolically active and safe Lactobacillus species and specific strains with particular functional

properties increase the biodiversity of the whole intestinal microbiota. The elaborated principles for effective application of probiotics are discussed, aimed at regulating the composition of microbiota simultaneously with blood and urine biomarkers at the borderline of normality. This approach targets the impact of probiotic strains to maintenance of health with anti-infectious, cardiovascular, and metabolic support.

Milani, C., Ferrario, C., Turroni, F., Duranti, S., Mangifesta, M., van, Sinderen D., and Ventura, M. The human gut microbiota and its interactive connections to diet. J.Hum.Nutr.Diet. 5-10-2016;

ABSTRACT: The microbiota of the gastrointestinal tract plays an important role in human health. In addition to their metabolic interactions with dietary constituents, gut bacteria may also be involved in more complex host interactions, such as modulation of the immune system. Furthermore, the composition of the gut microbiota may be important in reducing the risk of contracting particular gut infections. Changes in the microbiota during an individual's lifespan are accompanied by modifications in multiple health parameters, and such observations have prompted intense scientific efforts aiming to understand the complex interactions between the microbiota and its human host, as well as how this may be influenced by diet.

Miller, A. W., Oakeson, K. F., Dale, C., and Dearing, M. D. Microbial Community Transplant Results in Increased and Long-Term Oxalate Degradation. Microb.Ecol. 2016; 72(2):470-478.

ABSTRACT: Gut microbes are essential for the degradation of dietary oxalate, and this function may play a role in decreasing the incidence of kidney stones. However, many oxalate-degrading bacteria are susceptible to antibiotics and the use of oxalate-degrading probiotics has only led to an ephemeral reduction in urinary oxalate. The objective of the current study was to determine the efficacy of using whole-community microbial transplants from a wild mammalian herbivore, Neotoma albigula, to increase oxalate degradation over the long term in the laboratory rat, Rattus norvegicus. We quantified the change in total oxalate degradation in lab rats immediately after microbial transplants and at 2- and 9-month intervals following microbial transplants. Additionally, we tracked the fecal microbiota of the lab rats, with and without microbial transplants, using high-throughput Illumina sequencing of a hyper-variable region of the 16S rRNA gene. Microbial transplants resulted in a significant increase in oxalate degradation, an effect that persisted 9 months after the initial transplants. Functional persistence was corroborated by the transfer, and persistence of a group of bacteria previously correlated with oxalate consumption in N. albigula, including an anaerobic bacterium from the genus Oxalobacter known for its ability to use oxalate as a sole carbon source. The results of this study indicate that whole-community microbial transplants are an effective means for the persistent colonization of oxalate-degrading bacteria in the mammalian gut.

Miller, H., Ferris, R., and Phelps, B. R. The effect of probiotics on CD4 counts among people living with HIV: a systematic review. Benef.Microbes. 2016; 7(3):345-351.

ABSTRACT: Probiotics are defined by the WHO as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host'. Ongoing research has shown probiotics provide benefits to humans, including protection and

restoration of the gastrointestinal and other mucosal tracts. As human immunodeficiency virus (HIV) activates gut-associated lymphoid tissue (GALT), several studies have investigated the effect of probiotics on CD4 cell count and related outcomes among those living with HIV. These studies are summarised here. Manuscripts were identified using the search terms 'probiotics', 'synbiotics', 'HIV', and 'CD4', and were reviewed for relevance and inclusion of CD4 count as an immunologic endpoint. Bibliographies of relevant manuscripts were also reviewed for additional studies matching inclusion and exclusion criteria. The search yielded 91 results; 13 included relevant outcomes. Seven of these studies produced beneficial CD4 outcomes, while the remaining 6 reported on insignificant beneficial or negative CD4 outcomes. The studies summarised here collectively suggest that daily consumption of probiotics over a prolonged period of time may improve CD4 count in people living with HIV.

Miller, L. E., Zimmermann, A. K., and Ouwehand, A. C. Contemporary meta-analysis of short-term probiotic consumption on gastrointestinal transit. World J.Gastroenterol. 6-7-2016; 22(21):5122-5131.

ABSTRACT: AIM: To determine the efficacy of probiotic supplementation on intestinal transit time (ITT) in adults and to identify factors that influence these outcomes. METHODS: We conducted a systematic review of randomized controlled trials of probiotic supplementation that measured ITT in adults. Study quality was assessed using the Jadad scale. A random effects meta-analysis was performed with standardized mean difference (SMD) of ITT between probiotic and control groups as the primary outcome. Meta-regression and subgroup analyses examined the impact of moderator variables on SMD of ITT. RESULTS: A total of 15 clinical trials with 17 treatment effects representing 675 subjects were included in this analysis. Probiotic supplementation was moderately efficacious in decreasing ITT compared to control, with an SMD of 0.38 (95%CI: 0.23-0.53, $P < 0.001$). Subgroup analyses demonstrated statistically greater reductions in ITT with probiotics in subjects with vs without constipation (SMD: 0.57 vs 0.22, $P < 0.01$) and in studies with high vs low study quality (SMD: 0.45 vs 0.00, $P = 0.01$). Constipation ($R (2) = 38\%$, $P < 0.01$), higher study quality ($R (2) = 31\%$, $P = 0.01$), older age ($R (2) = 27\%$, $P = 0.02$), higher percentage of female subjects ($R (2) = 26\%$, $P = 0.02$), and fewer probiotic strains ($R (2) = 20\%$, $P < 0.05$) were predictive of decreased ITT with probiotics in meta-regression. Medium to large treatment effects were identified with B. lactis HN019 (SMD: 0.67, $P < 0.001$) and B. lactis DN-173 010 (SMD: 0.54, $P < 0.01$) while other probiotic strains yielded negligible reductions in ITT relative to control. CONCLUSION: Probiotic supplementation is moderately efficacious for reducing ITT in adults. Probiotics were most efficacious in constipated subjects, when evaluated in high-quality studies, and with certain probiotic strains.

Miquel, S., Lagrafeuille, R., Souweine, B., and Forestier, C. Anti-biofilm Activity as a Health Issue. Front Microbiol. 2016; 7:592

ABSTRACT: The formation and persistence of surface-attached microbial communities, known as biofilms, are responsible for 75% of human microbial infections (National Institutes of Health). Biofilm lifestyle confers several advantages to the pathogens, notably during the colonization process of medical devices and/or patients' organs. In addition, sessile bacteria have a high tolerance to exogenous stress including anti-infectious agents. Biofilms are highly competitive communities and some microorganisms exhibit anti-biofilm capacities such as bacterial growth inhibition, exclusion or

competition, which enable them to acquire advantages and become dominant. The deciphering and control of anti-biofilm properties represent future challenges in human infection control. The aim of this review is to compare and discuss the mechanisms of natural bacterial anti-biofilm strategies/mechanisms recently identified in pathogenic, commensal and probiotic bacteria and the main synthetic strategies used in clinical practice, particularly for catheter-related infections.

Mitra, D., Jena, A. K., De, A., Das, M., Das, B., and Samanta, A. Prebiotic potential of gum odina and its impact on gut ecology: in vitro and in vivo assessments. Food Funct. 7-13-2016; 7(7):3064-3072.

ABSTRACT: The use of prebiotics to escalate certain gut flora is a current aspect of research for effective gut ecology. In the present study we appraise the efficacy of gum odina obtained from the bark of Odina wodier (Anacardiaceae), which is not fully degraded (16%) in the upper GI tract and becomes available to the lower region, as a prebiotic. An in vitro prebiotic activity assay established a quantitative score to describe the extent to which gum odina supports the selective growth of probiotics with a maximum of 5.60 +/- 0.11 for Lactobacillus plantarum MTCC 6160. The polysaccharide, upon fermentation, also liberates lactic acid (0.46 +/- 0.003 mg ml(-1)) and acetic acid (1.03 +/- 0.003 mg ml(-1)). In vivo studies revealed that natural gum selectively stimulates Lactobacillus sp., and eliminates enteric pathogens with a C.F.U. of 384.48 +/- 0.11 and 40.56 +/- 0.17 respectively on the 8(th) day. The changes in the level of beta-galactosidase signify maturation of macrophages in the gut environment. It also boosts the immune system by increasing sIgA upon infection from the 5(th) day in the gut, when incorporated into the feed of mice. Moreover an increase in levels of IFNgamma on the 5(th) day also manifest additional protection against various pathogen-induced primary and secondary infections. Thus, gum odina is a potential prebiotic which not only provides nutrition but also improves gut ecology.

Mizuta, M., Endo, I., Yamamoto, S., Inokawa, H., Kubo, M., Udaka, T., Sogabe, O., Maeda, H., Shirakawa, K., Okazaki, E., Odamaki, T., Abe, F., and Xiao, J. Z. Perioperative supplementation with bifidobacteria improves postoperative nutritional recovery, inflammatory response, and fecal microbiota in patients undergoing colorectal surgery: a prospective, randomized clinical trial. Biosci.Microbiota.Food Health. 2016; 35(2):77-87.

ABSTRACT: The use of probiotics has been widely documented to benefit human health, but their clinical value in surgical patients remains unclear. The present study investigated the effect of perioperative oral administration of probiotic bifidobacteria to patients undergoing colorectal surgery. Sixty patients undergoing colorectal resection were randomized to two groups prior to resection. One group (n=31) received a probiotic supplement, Bifidobacterium longum BB536, preoperatively for 7-14 days and postoperatively for 14 days, while the other group (n=29) received no intervention as a control. The occurrences of postoperative infectious complications were recorded. Blood and fecal samples were collected before and after surgery. No significant difference was found in the incidence of postoperative infectious complications and duration of hospital stay between the two groups. In comparison to the control group, the probiotic group tended to have higher postoperative levels of erythrocytes, hemoglobin, lymphocytes, total protein, and albumin and lower levels of high sensitive C-reactive proteins. Postoperatively, the proportions of fecal bacteria changed significantly; Actinobacteria increased in the probiotic group, Bacteroidetes and

Proteobacteria increased in the control group, and Firmicutes decreased in both groups. Significant correlations were found between the proportions of fecal bacteria and blood parameters; Actinobacteria correlated negatively with blood inflammatory parameters, while Bacteroidetes and Proteobacteria correlated positively with blood inflammatory parameters. In the subgroup of patients who received preoperative chemoradiotherapy treatment, the duration of hospital stay was significantly shortened upon probiotic intervention. These results suggest that perioperative oral administration of bifidobacteria may contribute to a balanced intestinal microbiota and attenuated postoperative inflammatory responses, which may subsequently promote a healthy recovery after colorectal resection.

Mohle, L., Mattei, D., Heimesaat, M. M., Bereswill, S., Fischer, A., Alutis, M., French, T., Hambardzumyan, D., Matzinger, P., Dunay, I. R., and Wolf, S. A. Ly6C(hi) Monocytes Provide a Link between Antibiotic-Induced Changes in Gut Microbiota and Adult Hippocampal Neurogenesis. Cell Rep. 5-31-2016; 15(9):1945-1956.

ABSTRACT: Antibiotics, though remarkably useful, can also cause certain adverse effects. We detected that treatment of adult mice with antibiotics decreases hippocampal neurogenesis and memory retention. Reconstitution with normal gut flora (SPF) did not completely reverse the deficits in neurogenesis unless the mice also had access to a running wheel or received probiotics. In parallel to an increase in neurogenesis and memory retention, both SPF-reconstituted mice that ran and mice supplemented with probiotics exhibited higher numbers of Ly6C(hi) monocytes in the brain than antibiotic-treated mice. Elimination of Ly6C(hi) monocytes by antibody depletion or the use of knockout mice resulted in decreased neurogenesis, whereas adoptive transfer of Ly6C(hi) monocytes rescued neurogenesis after antibiotic treatment. We propose that the rescue of neurogenesis and behavior deficits in antibiotic-treated mice by exercise and probiotics is partially mediated by Ly6C(hi) monocytes.

Mokoena, M. P., Mutanda, T., and Olaniran, A. O. Perspectives on the probiotic potential of lactic acid bacteria from African traditional fermented foods and beverages. Food Nutr.Res. 2016; 60:29630

ABSTRACT: Diverse African traditional fermented foods and beverages, produced using different types of fermentation, have been used since antiquity because of their numerous nutritional values. Lactic acid bacteria (LAB) isolated from these products have emerged as a welcome source of antimicrobials and therapeutics, and are accepted as probiotics. Probiotics are defined as live microbial food supplements which beneficially affect the host by improving the intestinal microbial balance. Currently, popular probiotics are derived from fermented milk products. However, with the growing number of consumers with lactose intolerance that are affected by dietary cholesterol from milk products, there is a growing global interest in probiotics from other food sources. The focus of this review is to provide an overview of recent developments on the applications of probiotic LAB globally, and to specifically highlight the suitability of African fermented foods and beverages as a viable source of novel probiotics.

Moos, W. H., Faller, D. V., Harpp, D. N., Kanara, I., Pernokas, J., Powers, W. R., and Steliou, K. Microbiota and Neurological Disorders: A Gut Feeling. Biores.Open.Access. 2016; 5(1):137-145.

ABSTRACT: In the past century, noncommunicable diseases have surpassed infectious diseases as the principal cause of sickness and death, worldwide. Trillions of commensal microbes live in and on our body, and constitute the human microbiome. The vast majority of these microorganisms are maternally derived and live in the gut, where they perform functions essential to our health and survival, including: digesting food, activating certain drugs, producing short-chain fatty acids (which help to modulate gene expression by inhibiting the deacetylation of histone proteins), generating anti-inflammatory substances, and playing a fundamental role in the induction, training, and function of our immune system. Among the many roles the microbiome ultimately plays, it mitigates against untoward effects from our exposure to the environment by forming a biotic shield between us and the outside world. The importance of physical activity coupled with a balanced and healthy diet in the maintenance of our well-being has been recognized since antiquity. However, it is only recently that characterization of the host-microbiome intermetabolic and crosstalk pathways has come to the forefront in studying therapeutic design. As reviewed in this report, synthetic biology shows potential in developing microorganisms for correcting pathogenic dysbiosis (gut microbiota-host maladaptation), although this has yet to be proven. However, the development and use of small molecule drugs have a long and successful history in the clinic, with small molecule histone deacetylase inhibitors representing one relevant example already approved to treat cancer and other disorders. Moreover, preclinical research suggests that epigenetic treatment of neurological conditions holds significant promise. With the mouth being an extension of the digestive tract, it presents a readily accessible diagnostic site for the early detection of potential unhealthy pathogens resident in the gut. Taken together, the data outlined herein provide an encouraging roadmap toward important new medicines and companion diagnostic platforms in a wide range of therapeutic indications.

Morales, A., Carvajal, P., Silva, N., Hernandez, M., Godoy, C., Rodriguez, G., Cabello, R., Garcia-Sesnich, J., Hoare, A., Diaz, P. I., and Gamonal, J. Clinical Effects of Lactobacillus rhamnosus in Non-Surgical Treatment of Chronic Periodontitis: A Randomized Placebo-Controlled Trial With 1-Year Follow-Up. J.Periodontol. 2016; 87(8):944-952.

ABSTRACT: BACKGROUND: Probiotics are living microorganisms that provide beneficial effects for the host when administered in proper quantities. The aim of this double-masked placebo-controlled parallel-arm randomized clinical trial is to evaluate the clinical effects of a Lactobacillus rhamnosus SP1-containing probiotic sachet as an adjunct to non-surgical therapy. METHODS: Twenty-eight systemically healthy volunteers with chronic periodontitis were recruited and monitored clinically at baseline and 3, 6, 9, and 12 months after therapy. Clinical parameters measured included plaque accumulation, bleeding on probing, probing depths (PDs), and clinical attachment loss. Patients received non-surgical therapy, including scaling and root planing (SRP), and were assigned randomly to a test (SRP + probiotic, n = 14) or control (SRP + placebo, n = 14) group. The intake, once a day for 3 months, of an L. rhamnosus SP1 probiotic sachet commenced after the last session of SRP. RESULTS: Both test and control groups showed improvements in clinical parameters at all time points evaluated. However, the test group showed greater reductions in PD than the control. Also, at initial visits and after 1-year follow-up, the test group showed a statistically significant reduction in the number of participants with PD >/=6 mm, indicating a reduced need for surgery, in contrast to the placebo group. CONCLUSION: The results of this trial indicate that oral administration of L. rhamnosus SP1 resulted in similar clinical improvements compared with SRP alone.

Mousa, H. A. Prevention and Treatment of Influenza, Influenza-Like Illness, and Common Cold by Herbal, Complementary, and Natural Therapies. J.Evid.Based.Complementary.Altern.Med. 4-6-2016;

ABSTRACT: In recent years viral respiratory tract infections, especially influenza viruses, have had a major impact on communities worldwide as a result of unavailability of effective treatment or vaccine. The frequent alterations in the antigenic structures of respiratory viruses, particularly for RNA viruses, pose difficulties in production of effective vaccines. The unavailability of optimal medication and shortage of effective vaccines suggests the requirement for alternative natural therapies. Several herbal remedies were used for prevention and treatment viral respiratory illnesses. Among those that were found effective included maoto, licorice roots, antiwei, North American ginseng, berries, Echinacea, plants extracted carnosic acid, pomegranate, guava tea, and Bai Shao. There is scientific evidence regarding the effectiveness of several complementary therapies for colds. Oral zinc may reduce the length and severity of a cold. Taking vitamin C supplements on a regular basis only slightly reduces the length and severity of colds. Probiotics were found better than placebo in reducing the number episodes of acute upper respiratory tract infections, the rate of episodes of acute upper respiratory tract infection and reducing antibiotic use. Alkaline diets or drinks might have antiviral properties as in vitro studies demonstrated inactivation effect of alkaline medium on respiratory virus. Earthing might have a natural anti-inflammatory effect for human body. It is now accepted that an overwhelming inflammatory response is the cause of human deaths from avian H5N1 influenza infection. Earthing accelerates immune response following vaccination, as demonstrated by increases of gamma globulin concentration. No in vivo or clinical studies were found that investigate the role of alkalization or earthing on respiratory viral infections. Thus, future studies are recommended to reveal any potential curative effects.

Moyes, D. L., Saxena, D., John, M. D., and Malamud, D. The gut and oral microbiome in HIV disease: a workshop report. Oral Dis. 2016; 22 Suppl 1:166-170.

ABSTRACT: Recent years have seen a massive expansion in our understanding of how we interact with our microbial colonists. The development of new, rapid sequencing techniques such as pyrosequencing and other next-generation sequencing systems have enabled us to begin to characterise the constituents of our diverse microbial communities, revealing the astonishing genetic richness that is our microbiome. Despite this, our ignorance of how these communities change over the course of an HIV infection is profound. Whilst some steps have been made to characterise the HIV microbiome at selected sites, these reports are still limited and much remains to be done. It has become apparent, however, that host-microbiota interactions are perturbed during HIV infections, with microbial translocation of potential pathogens linked to a variety of different HIV complications, including more rapid progression of disease. The use of probiotics and prebiotics has been investigated as treatments to alleviate symptoms for a variety of conditions, and is now being proposed for the treatment of symptoms associated with HIV. However, this is a new area of investigations and many questions remain unanswered. What we know about both of these topics is a drop in the ocean compared with what we need to know. In this article, we report on a workshop where these two major under-investigated research areas were presented, and future directions explored and discussed.

Muhleisen, A. L. and Herbst-Kralovetz, M. M. Menopause and the vaginal microbiome. Maturitas. 2016; 91:42-50.

ABSTRACT: For over a century it has been well documented that bacteria in the vagina maintain vaginal homeostasis, and that an imbalance or dysbiosis may be associated with poor reproductive and gynecologic health outcomes. Vaginal microbiota are of particular significance to postmenopausal women and may have a profound effect on vulvovaginal atrophy, vaginal dryness, sexual health and overall quality of life. As molecular-based techniques have evolved, our understanding of the diversity and complexity of this bacterial community has expanded. The objective of this review is to compare the changes that have been identified in the vaginal microbiota of menopausal women, outline alterations in the microbiome associated with specific menopausal symptoms, and define how hormone replacement therapy impacts the vaginal microbiome and menopausal symptoms; it concludes by considering the potential of probiotics to reinstate vaginal homeostasis following menopause. This review details the studies that support the role of Lactobacillus species in maintaining vaginal homeostasis and how the vaginal microbiome structure in postmenopausal women changes with decreasing levels of circulating estrogen. In addition, the associated transformations in the microanatomical features of the vaginal epithelium that can lead to vaginal symptoms associated with menopause are described. Furthermore, hormone replacement therapy directly influences the dominance of Lactobacillus in the microbiota and can resolve vaginal symptoms. Oral and vaginal probiotics hold great promise and initial studies complement the findings of previous research efforts concerning menopause and the vaginal microbiome; however, additional trials are required to determine the efficacy of bacterial therapeutics to modulate or restore vaginal homeostasis.

Mukdsi, M. C., Arganaraz, Martinez E., Chaia, A. P., and Medina, R. B. Feruloyl esterase activity is influenced by bile, probiotic intestinal adhesion and milk fat. Benef.Microbes. 4-19-2016; 1-12.

ABSTRACT: Cinnamoyl esterases (CE) are microbial and mammalian intestinal enzymes able to release antioxidant hydroxycinnamic acids from their non-digestible ester-linked forms naturally present in vegetable foods. Previous findings showed that oral administration of Lactobacillus fermentum CRL1446 increased intestinal CE activity and improved oxidative status in mice. The aim of this work was to evaluate the in vitro CE activity of L. fermentum CRL1446 and the effect of bile on this activity, as well as strain resistance to simulated gastrointestinal tract (GIT) conditions and its ability to adhere to intestinal epithelium and influence its basal CE activity. L. fermentum CRL1446 and L. fermentum ATCC14932 (positive control for CE activity) were able to hydrolyse different synthetic hydroxycinnamates, with higher specificity toward methyl ferulate (3,853.73 and 899.19 U/g, respectively). Feruloyl esterase (FE) activity was mainly intracellular in L. fermentum CRL1446 and cell-surface associated in L. fermentum ATCC14932. Both strains tolerated simulated GIT conditions and were able to adhere ex vivo to intestinal epithelium. Pre-incubation of L. fermentum strains with bile increased FE activity in both whole cells and supernatants (~2-fold), compared to controls, suggesting that cells were permeabilised by bile, allowing more substrate to enter the cell and/or leakage of FE enzymes. Three-fold higher FE activities were detected in intestinal tissue fragments with adhered L. fermentum CRL1446 cells compared to control fragments (without bacteria),

indicating that this strain provides exogenous FE activity and could stimulate esterase activity in the intestinal mucosa. Finally, we found that milk fat had a negative effect on FE activity of intestinal tissue, in absence or presence of adhered L. fermentum. These results help explaining the increase in intestinal FE activity previously observed in mice fed with L. fermentum CRL1446, and support the potential use of this strain for the development of new functional foods directed to oxidative stress-related ailments.

Myintzu, Hlaing M., Wood, B., McNaughton, D., Ying, D., and Augustin, M. A. Raman spectroscopic analysis of Lactobacillus rhamnosus GG in response to dehydration reveals DNA conformation changes. J.Biophotonics. 5-31-2016;

ABSTRACT: Dehydration of bacterial cells elicits cellular stress responses in bacteria. Microencapsulation has been used to protect cells against the environmental stress. In this study, Confocal Raman Spectroscopy was used to examine DNA changes in the chemical composition of non-encapsulated and microencapsulated Lactobacillus rhamnosus GG and the reversibility of these changes upon freeze drying and rehydration. The viability of cells upon freeze drying was also enumerated using culture methods and membrane integrity was measured using BacLight Live/Dead staining. Raman analyses show changes in the spectral features associated with various biochemical compounds, which are interpreted as the result of detrimental freeze drying effects on the bacterial cells. Specifically, analyses based on Principal Components Analysis (PCA) of Raman spectra, confirm that microencapsulation protects cells from environmental stress. The results also reveal a B- to A-like DNA conformation change in dormant cells that provided insights into the extent of reversibility of this transition upon rehydration. The extent of this reversibility is less in non-encapsulated than in microencapsulated cells. These findings indicate the potential application of Raman spectroscopy in rapid sensing of microbial dehydration stress responses.

Nagpal, R., Kumar, M., Yadav, A. K., Hemalatha, R., Yadav, H., Marotta, F., and Yamashiro, Y. Gut microbiota in health and disease: an overview focused on metabolic inflammation. Benef.Microbes. 2016; 7(2):181-194.

ABSTRACT: In concern to the continuously rising global prevalence of obesity, diabetes and associated diseases, novel preventive and therapeutic approaches are urgently required. However, to explore and develop such innovative strategies, a meticulous comprehension of the biological basis of these diseases is extremely important. Past decade has witnessed an enormous amount of research investigation and advancement in the field of obesity, diabetes and metabolic syndrome, with the gut microbiota receiving a special focus in the triangle of nutrition, health and diseases. In particular, the role of gut microbiota in health and diseases has been one of the most vigorous and intriguing field of recent research; however, much still remains to be elucidated about its precise role in host metabolism and immune functions and its implication in the onset, progression as well as in the amelioration of metabolic ailments. Recent investigations have suggested a significant contribution of the gut microbiota in the regulation and impairment of energy homeostasis, thereby causing metabolic disorders, such as metabolic endotoxemia, insulin resistance and type 2 diabetes. Numerous inflammatory biomarkers have been found to be associated with obesity, diabetes and risk of other associated adverse outcomes, thereby suggesting that a persistent low-grade inflammatory response is a potential risk factor. In this milieu, this review intends to discuss potential evidences supporting the disturbance of the gut

microbiota balance and the intestinal barrier permeability as a potential triggering factor for systemic inflammation in the onset and progression of obesity, type 2 diabetes and metabolic syndrome.

Nair, M. R., Chouhan, D., Sen, Gupta S., and Chattopadhyay, S. Fermented Foods: Are They Tasty Medicines for Helicobacter pylori Associated Peptic Ulcer and Gastric Cancer? Front Microbiol. 2016; 7:1148

ABSTRACT: More than a million people die every year due to gastric cancer and peptic ulcer. Helicobacter pylori infection in stomach is the most important reason for these diseases. Interestingly, only 10-20% of the H. pylori infected individuals suffer from these gastric diseases and rest of the infected individuals remain asymptomatic. The genotypes of H. pylori, host genetic background, lifestyle including smoking and diet may determine clinical outcomes. People from different geographical regions have different food habits, which also include several unique fermented products of plant and animal origins. When consumed raw, the fermented foods bring in fresh inocula of microbes to gastrointestinal tract and several strains of these microbes, like Lactobacillus and Saccharomyces are known probiotics. In vitro and in vivo experiments as well as clinical trials suggest that several probiotics have anti-H. pylori effects. Here we discuss the possibility of using natural probiotics present in traditional fermented food and beverages to obtain protection against H. pylori induced gastric diseases.

Nankervis, H., Thomas, K. S., Delamere, F. M., Barbarot, S., Rogers, N. K., and Williams, H. C. 2016;

ABSTRACT: Eczema is a very common chronic inflammatory skin condition. To update the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) systematic review of treatments for atopic eczema, published in 2000, and to inform health-care professionals, commissioners and patients about key treatment developments and research gaps. Electronic databases including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Skin Group Specialised Register, Latin American and Caribbean Health Sciences Literature (LILACS), Allied and Complementary Medicine Database (AMED) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from the end of 2000 to 31 August 2013. Retrieved articles were used to identify further randomised controlled trials (RCTs). Studies were filtered according to inclusion criteria and agreed by consensus in cases of uncertainty. Abstracts were excluded and non-English-language papers were screened by international colleagues and data were extracted. Only RCTs of treatments for eczema were included, as other forms of evidence are associated with higher risks of bias. Inclusion criteria for studies included availability of data relevant to the therapeutic management of eczema; mention of randomisation; comparison of two or more treatments; and prospective data collection. Participants of all ages were included. Eczema diagnosis was determined by a clinician or according to published diagnostic criteria. The risk of bias was assessed using the Cochrane Collaboration risk-of-bias tool. We used a standardised approach to summarising the data and the assessment of risk of bias and we made a clear distinction between what the studies found and our own interpretation of study findings. Of 7198 references screened, 287 new trials were identified spanning 92 treatments. Trial reporting was generally poor (randomisation method: 2% high, 36% low, 62% unclear risk of bias; allocation concealment: 3% high, 15% low, 82% unclear risk of bias; blinding of the intervention: 15% high, 28% low, 57% unclear risk of bias). Only 22 (8%) trials were considered to be at low risk of bias for all three

criteria. There was reasonable evidence of benefit for the topical medications tacrolimus, pimecrolimus and various corticosteroids (with tacrolimus superior to pimecrolimus and corticosteroids) for both treatment and flare prevention; oral ciclosporin; oral azathioprine; narrow band ultraviolet B (UVB) light; Atopiclair and education. There was reasonable evidence to suggest no clinically useful benefit for twice-daily compared with once-daily topical corticosteroids; corticosteroids containing antibiotics for non-infected eczema; probiotics; evening primrose and borage oil; ion-exchange water softeners; protease inhibitor SRD441 (Serentis Ltd); furfuryl palmitate in emollient; cipamfylline cream; and Mycobacterium vaccae vaccine. Additional research evidence is needed for emollients, bath additives, antibacterials, specialist clothing and complementary and alternative therapies. There was no RCT evidence for topical corticosteroid dilution, impregnated bandages, soap avoidance, bathing frequency or allergy testing. The large scope of the review coupled with the heterogeneity of outcomes precluded formal meta-analyses. Our conclusions are still limited by a profusion of small, poorly reported studies. Although the evidence base of RCTs has increased considerably since the last NIHR HTA systematic review, the field is still severely hampered by poor design and reporting problems including failure to register trials and declare primary outcomes, small sample size, short follow-up duration and poor reporting of risk of bias. Key areas for further research identified by the review include the optimum use of emollients, bathing frequency, wash products, allergy testing and antiseptic treatments. Perhaps the greatest benefit identified is the use of twice weekly anti-inflammatory treatment to maintain disease remission. More studies need to be conducted in a primary care setting where most people with eczema are seen in the UK. Future studies need to use the same core set of outcomes that capture patient symptoms, clinical signs, quality of life and the chronic nature of the disease. The National Institute for Health Research Programme Grants for Applied Research programme.

Narang, R., Hull, T., Perrins, S., Garcia, J. S., and Wexner, S. D. Should Immunomodulation Therapy Alter the Surgical Management in Patients With Rectovaginal Fistula and Crohn's Disease? Dis.Colon Rectum. 2016; 59(7):670-676.

ABSTRACT: BACKGROUND: Rectovaginal fistula in Crohn's disease is challenging for both healthcare providers and patients. The impact of immunomodulation therapy on healing after surgery is unclear. OBJECTIVE: The purpose of this study was to examine whether immunomodulation therapy impacts healing after surgery for rectovaginal fistula in Crohn's disease. DESIGN: This was a retrospective analysis with a follow-up telephone survey. SETTINGS: The study was conducted at two major tertiary referral centers. PATIENTS: All of the patients who underwent rectovaginal fistula repair from 1997 to 2013 at our centers were included. MAIN OUTCOME MEASURES: A chi test and logistical regression analysis were used to study treatment outcomes according to type of procedure, recent use of immunosuppressives, and number of previous attempted repairs. Age, BMI, smoking, comorbidities, previous vaginal delivery/obstetric injury, use of probiotics, diverting stoma, and use of seton were also analyzed. RESULTS: A total of 120 (62%) patients were contacted, and 99 (51%) of them agreed to participate in the study. Mean follow-up after surgical repair was 39 months. Procedures included advancement flap (n = 59), transvaginal repair (n = 14), muscle interposition (n = 14), episioproctotomy (n = 6), sphincteroplasty (n = 3), and other (n = 3); overall, 63% of patients experienced healing. Sixty-eight patients underwent recent immunomodulation therapy but did not exhibit statistical significance in outcome after surgical repair. In the subset of patients with fistula related to obstetric injury, a 74% (n = 26) healing rate after surgical repair was

observed. Age, BMI, diabetes mellitus, use of steroids, probiotics, seton before repair, fecal diversion, and number of repairs did not affect healing. LIMITATIONS: This was a retrospective analysis; the high volume tertiary referral inflammatory bowel disease centers studied may not be reflective of rectovaginal fistula presentation, treatment, or results in all patients, and the 3-year follow-up may not be sufficiently long. CONCLUSIONS: Despite a relatively low success rate (63%) in healing after surgical repair of a rectovaginal fistula, the recent use of immunomodulation therapy did not negatively impact healing. However, tissue interposition techniques had the highest success rates.

Nardone, R., Taylor, A. C., Holler, Y., Brigo, F., Lochner, P., and Trinka, E. Minimal hepatic encephalopathy: A review. Neurosci.Res. 5-3-2016;

ABSTRACT: Minimal hepatic encephalopathy (MHE) is the earliest form of hepatic encephalopathy and can affect up to 80% of patients with liver cirrhosis. By definition, MHE is characterized by cognitive function impairment in the domains of attention, vigilance and integrative function, but obvious clinical manifestation are lacking. MHE has been shown to affect daily functioning, quality of life, driving and overall mortality. The diagnosis can be achieved through neuropsychological testing, recently developed computerized psychometric tests, such as the critical flicker frequency and the inhibitory control tests, as well as neurophysiological procedures. Event related potentials can reveal subtle changes in patients with normal neuropsychological performances. Spectral analysis of electroencephalography (EEG) and quantitative analysis of sleep EEG provide early markers of cerebral dysfunction in cirrhotic patients with MHE. Neuroimaging, in particular MRI, also increasingly reveals diffuse abnormalities in intrinsic brain activity and altered organization of functional connectivity networks. Medical treatment for MHE to date has been focused on reducing serum ammonia levels and includes non-absorbable disaccharides, probiotics or rifaximin. Liver transplantation may not reverse the cognitive deficits associated with MHE. We performed here an updated review on epidemiology, burden and quality of life, neuropsychological testing, neuroimaging, neurophysiology and therapy in subjects with MHE.

Nelson, H. S. Allergen immunotherapy now and in the future. Allergy Asthma Proc. 2016; 37(4):268-272.

ABSTRACT: BACKGROUND: Subcutaneous (SCIT) and sublingual (SLIT) immunotherapy provide effective treatment for allergic rhinitis and allergic asthma with clinical improvement following an adequate course of therapy persisting in most patients for years after treatment is discontinued. However, both require prolonged courses of therapy and many or most patients either do not begin or stop long before they have completed the prescribed course of treatment. METHODS: Based on review of the recent medical literature, the current status of SCIT and SLIT was reviewed as well as new approaches to allergy immunotherapy (AIT) that have promise to overcome the safety and inconvenience concerns of both the current approaches. RESULTS: New approaches to AIT include application of extracts to the skin with patches, injection into inguinal lymph nodes, alterations in the allergen molecules by chemical treatment or recombinant technology to make them less reactive with specific IgE, shifting the immune response by stimulation of toll-like receptors or suppression of Th2 responses, and finally by adjuvants such as probiotics and vitamin D. CONCLUSIONS: Current forms of immunotherapy require years of treatment. New approaches, although differing markedly in their approach to AIT, all offer marked reduction in the required period of

treatment. Hopefully, some of these new approaches will prove safe and effective and obtain approval for general use. If approved, they should make AIT more widely utilized to the benefit of the allergic population.

Nguyen, H. T., Truong, D. H., Kouhounde, S., Ly, S., Razafindralambo, H., and Delvigne, F. Biochemical Engineering Approaches for Increasing Viability and Functionality of Probiotic Bacteria. Int.J.Mol.Sci. 2016; 17(6)

ABSTRACT: The literature presents a growing body of evidence demonstrating the positive effect of probiotics on health. Probiotic consumption levels are rising quickly in the world despite the fluctuation of their viability and functionality. Technological methods aiming at improving probiotic characteristics are thus highly wanted. However, microbial metabolic engineering toolbox is not available for this kind of application. On the other hand, basic microbiology teaches us that bacteria are able to exhibit adaptation to external stresses. It is known that adequately applied sub-lethal stress, i.e., controlled in amplitude and frequency at a given stage of the culture, is able to enhance microbial robustness. This property could be potentially used to improve the viability of probiotic bacteria, but some technical challenges still need to be overcome before any industrial implementation. This review paper investigates the different technical tools that can be used in order to define the proper condition for improving viability of probiotic bacteria and their implementation at the industrial scale. Based on the example of Bifidobacterium bifidum, potentialities for simultaneously improving viability, but also functionality of probiotics will be described.

Nido, S. A., Shituleni, S. A., Mengistu, B. M., Liu, Y., Khan, A. Z., Gan, F., Kumbhar, S., and Huang, K. Effects of Selenium-Enriched Probiotics on Lipid Metabolism, Antioxidative Status, Histopathological Lesions, and Related Gene Expression in Mice Fed a High-Fat Diet. Biol.Trace Elem.Res. 2016; 171(2):399-409.

ABSTRACT: A total of 80 female albino mice were randomly allotted into five groups (n = 16) as follows: (A) normal control, (B) high-fat diet (HFD),; (C) HFD + probiotics (P), (D) HFD + sodium selenite (SS), and (E) HFD + selenium-enriched probiotics (SP). The selenium content of diets in groups A, B, C, D, and E was 0.05, 0.05, 0.05, 0.3, and 0.3 mug/g, respectively. The amount of probiotics contained in groups C and E was similar (Lactobacillus acidophilus 0.25 x 10(11)/mL and Saccharomyces cerevisiae 0.25 x 10(9)/mL colony-forming units (CFU)). The high-fat diet was composed of 15 % lard, 1 % cholesterol, 0.3 % cholic acid, and 83.7 % basal diet. At the end of the 4-week experiment, blood and liver samples were collected for the measurements of lipid metabolism, antioxidative status, histopathological lesions, and related gene expressions. The result shows that HFD significantly increased the body weights and liver damages compared to control, while P, SS, or SP supplementation attenuated the body weights and liver damages in mice. P, SS, or SP supplementation also significantly reversed the changes of alanine aminotransferase (AST), aspartate aminotransferase (ALT), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), total protein (TP), high-density lipoprotein (HDL), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), catalasa (CAT), and malondialdehyde (MDA) levels induced by HFD. Generally, adding P, SS, or SP up-regulated mRNA expression of carnitine palmitoyltransferase-I (CPT1), carnitine palmitoyltransferase II (CPT2), acetyl-CoA acetyltransferase II (ACAT2), acyl-coenzyme A oxidase (ACOX2), and peroxisome proliferator-activated receptor alpha (PPARalpha) and down-regulated mRNA expression of fatty acid synthase (FAS),

lipoprotein lipase (LPL), peroxisome proliferator-activated receptor gamma (PPARgamma), and sterol regulatory element-binding protein-1 (SREBP1) involved in lipid metabolism. Among the group, adding SP has a maximum effect in improving lipid metabolism, antioxidative status, histopathological lesions, and related gene expression in mice fed a HFD.

Nova, E., Perez de, Heredia F., Gomez-Martinez, S., and Marcos, A. The Role of Probiotics on the Microbiota: Effect on Obesity. Nutr.Clin.Pract. 2016; 31(3):387-400.

ABSTRACT: The microbiota and the human host maintain a symbiotic association. Nowadays, metagenomic analyses are providing valuable knowledge on the diversity and functionality of the gut microbiota. However, with regard to the definition of a "healthy microbiota" and the characterization of the dysbiosis linked to obesity, there is still not a clear answer. Despite this fact, attempts have been made to counteract obesity through probiotic supplementation. A literature search of experimental studies relevant to the topic was performed in PubMed database with the keywords "probiotic" and "obesity" and restricted to those with "Lactobacillus" or "Bifidobacterium" in the title. So far, evidence of an antiobesity effect of different lactobacilli and bifidobacteria has been mainly obtained from animal models of dietary-induced obesity. Using these experimental models, a substantial number of studies have reported reductions in weight gain and, in particular, fat tissue mass at different locations following administration of bacteria, as compared with controls. Antiatherogenic and anti-inflammatory effects-including regulation of expression of lipogenic and lipolytic genes in the liver, reduction in liver steatosis, improvement of blood lipid profile and glucose tolerance, decreased endotoxemia, and regulation of inflammatory pathways-are also reported in many of them. The number of human studies focused on probiotic administration for obesity management is still very scarce, and it is too soon to judge their potential efficacy, especially when considering the fact that the actions of probiotics are always strain specific and the individual response varies according to intrinsic factors, the overall composition of diet, and their interactions.

Nowak, A., Czyzowska, A., Huben, K., Sojka, M., Kuberski, S., Otlewska, A., and Slizewska, K. Prebiotics and age, but not probiotics affect the transformation of 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (IQ) by fecal microbiota - An in vitro study. Anaerobe. 2016; 39:124-135.

ABSTRACT: Heterocyclic aromatic amines (HAAs) are carcinogens which are formed in meat cooked using high-temperature methods. The human gastrointestinal (GI) microbiota plays a crucial role in maintaining health in humans of different ages, and especially in the elderly. However, the GI microbiota, whose metabolism and composition changes with age, may also be responsible for the activation of mutagenic substances reaching the colon with diet. Probiotics and prebiotics are promising in terms of reducing the destructive effects of HAAs. The aim of the study was to determine if fecal microbiota derived from the feces of 27 volunteers: infants (up to 18 months), adults (aged 23-39 years), the sub-elderly (aged 64-65 years), and the elderly (aged 76-87 years), and the presence of probiotics or prebiotics, affected the transformation of IQ (2-amino-3-methylimidazo[4,5-f]quinoline) to 7-OH-IQ (2-amino-3,6-dihydro-3-methyl-7H-imidazo[4,5-f]quinoline-7-one). The compounds were identified using LC-MS(n), NMR, and FTIR. Their genotoxicity was compared in the comet assay. Individual strains capable of IQ transformation were also identified. 7-OH-IQ was detected in six persons (two children

and four elderly individuals). The degree of IQ conversion ranged from 26% (4-month-old girl) to 94% (81-year-old woman) of the initial quantity. Four Enterococcus isolates: two Enterococcus faecium and two Enterococcus faecalis strains, as well as one Clostridium difficile strain (LOCK 1030, from the culture collection) converted IQ to 7-OH-IQ. The genotoxicity of samples containing 7-OH-IQ was even three times higher ($P < 0.05$) than those with IQ and was correlated with the degree of IQ conversion and 7-OH-IQ concentration.

O'Brien, K. V., Aryana, K. J., Prinyawiwatkul, W., Ordonez, K. M., and Boeneke, C. A. Short communication: The effects of frozen storage on the survival of probiotic microorganisms found in traditionally and commercially manufactured kefir. J.Dairy Sci. 6-8-2016;

ABSTRACT: Kefir is a fermented milk traditionally made from a unique starter culture, which consists of numerous bacteria and yeast species bound together in an exopolysaccharide matrix produced by certain lactic acid bacteria. Many health benefits are associated with traditionally produced kefir; however, bulging and leaking packaging, caused by secondary yeast fermentation during storage, has limited large-scale manufacture. Commercial kefir products have been designed to reduce these effects by using a pure starter culture consisting of a mixture of bacteria and yeast species that give a flavor similar to traditional kefir, but some health benefits may be lost in commercial production due to reduced microbial diversity and lack of beneficial exopolysaccharides. In this study, traditional and commercial kefir was frozen to study the effects of frozen storage on the viability of probiotic bacteria over time. Traditional kefir was prepared by inoculating 1 L of pasteurized whole goat milk with approximately 30 g of kefir grains. Commercial kefir was prepared by inoculating 1 L of full-fat, pasteurized goat milk with a commercial kefir starter. The milk was allowed to ferment at room temperature (24-28 degrees C) until pH 4.6 was reached. Samples were frozen (-8 to -14 degrees C) immediately following the completion of fermentation and were thawed and plated for lactobacilli, lactococci, and yeasts on d 0, 7, 14, and 30 of frozen storage. Lactobacilli, lactococci, and yeasts were significantly reduced in number during frozen storage; however, the traditionally produced kefir was shown to have significantly higher counts of bacteria and yeast at each sampling. We concluded that frozen storage and the development of frozen kefir products could eliminate most packaging concerns associated with the large-scale manufacture of traditionally produced kefir, resulting in increased production and marketability of this healthful product.

O'Callaghan, A. and van, Sinderen D. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. Front Microbiol. 2016; 7:925

ABSTRACT: Members of the genus Bifidobacterium are among the first microbes to colonize the human gastrointestinal tract and are believed to exert positive health benefits on their host. Due to their purported health-promoting properties, bifidobacteria have been incorporated into many functional foods as active ingredients. Bifidobacteria naturally occur in a range of ecological niches that are either directly or indirectly connected to the animal gastrointestinal tract, such as the human oral cavity, the insect gut and sewage. To be able to survive in these particular ecological niches, bifidobacteria must possess specific adaptations to be competitive. Determination of genome sequences has revealed genetic attributes that may explain bifidobacterial ecological fitness, such as metabolic abilities, evasion of the host adaptive immune system and colonization of the host through specific appendages. However, genetic

modification is crucial toward fully elucidating the mechanisms by which bifidobacteria exert their adaptive abilities and beneficial properties. In this review we provide an up to date summary of the general features of bifidobacteria, whilst paying particular attention to the metabolic abilities of this species. We also describe methods that have allowed successful genetic manipulation of bifidobacteria.

Oh, B., Kim, B. S., Kim, J. W., Kim, J. S., Koh, S. J., Kim, B. G., Lee, K. L., and Chun, J. The Effect of Probiotics on Gut Microbiota during the Helicobacter pylori Eradication: Randomized Controlled Trial. Helicobacter. 2016; 21(3):165-174.

ABSTRACT: BACKGROUND: Helicobacter pylori causes chronic gastritis, gastroduodenal ulcers, and gastric cancer, and has been treated with two antibiotics (amoxicillin and clarithromycin) and proton-pump inhibitors (PPIs). However, antibiotic treatment alters the indigenous gut microbiota to cause side effects. Therefore, the effects of probiotic supplementation on therapy have been studied. Although several studies have covered the probiotics' effects, details about the gut microbiota changes after H. pylori eradication have not been evaluated. Therefore, we analyzed the influences of antibiotics and their combination with probiotics on the composition of the gut microbiota using high-throughput sequencing. METHODS: Subjects were divided into two groups. The antibiotics group was treated with general therapy, and the probiotics group with general therapy and probiotic supplementation. Fecal samples were collected from all subjects during treatments, and the influences on gut microbiota were analyzed by 16S rRNA gene-pyrosequencing. RESULTS: Three phyla, Firmicutes, Bacteroidetes, and Proteobacteria, were predominant in the gut microbiota of all subjects. After treatment, the relative abundances of Firmicutes were reduced, whereas those of Proteobacteria were increased in both groups. However, the changed proportions of the gut microbiota in the antibiotics group were higher than those in the probiotics group. In addition, the increase in the levels of antibiotic-resistant bacteria was higher in the antibiotics group than in the probiotics one. CONCLUSION: Probiotic supplementation can reduce the antibiotic-induced alteration and imbalance of the gut microbiota composition. This effect may restrict the growth of antibiotic-resistant bacteria in the gut and improve the H. pylori eradication success rate.

Ohshima, T., Kojima, Y., Seneviratne, C. J., and Maeda, N. Therapeutic Application of Synbiotics, a Fusion of Probiotics and Prebiotics, and Biogenics as a New Concept for Oral Candida Infections: A Mini Review. Front Microbiol. 2016; 7:10

ABSTRACT: Candida is a major human fungal pathogen causing infectious conditions predominantly in the elderly and immunocompromised hosts. Although Candida resides as a member of the oral indigenous microbiota in symbiosis, some circumstances may cause microbial imbalance leading to dysbiosis and resultant oral candidiasis. Therefore, oral microbial symbiosis that suppresses the overgrowth of Candida is important for a healthy oral ecosystem. In this regard, probiotics, prebiotics, and synbiotics can be considered a potential therapeutic and preventive strategy against oral candidiasis. Prebiotics have a direct effect on microbial growth as they stimulate the growth of beneficial bacteria and suppress the growth of pathogens. Probiotics render a local protective effect against pathogens and a systemic indirect effect on immunological amelioration. Synbiotics are fusion products of prebiotics and probiotics. This mini review discusses the potential use and associated limitations of probiotics, prebiotics, and synbiotics for the prevention and treatment of oral candidiasis. We will also introduce

biogenics, a recent concept derived from the work on probiotics. Biogenics advocates the use of beneficial bioactive substances produced by probiotic bacteria, whose activities are independent from the viability of probiotic bacteria in human bodies.

Ojha, K. S., Kerry, J. P., Alvarez, C., Walsh, D., and Tiwari, B. K. Effect of high intensity ultrasound on the fermentation profile of Lactobacillus sakei in a meat model system. Ultrason.Sonochem. 2016; 31:539-545.

ABSTRACT: The objective of this study was to investigate the efficacy of high intensity ultrasound on the fermentation profile of Lactobacillus sakei in a meat model system. Ultrasound power level (0-68.5 W) and sonication time (0-9 min) at 20 degrees C were assessed against the growth of L. sakei using a Microplate reader over a period of 24h. The L. sakei growth data showed a good fit with the Gompertz model (R(2)>0.90; SE<0.042). Second order polynomial models demonstrated the effect of ultrasonic power and sonication time on the specific growth rate (SGR, mu, h(-1)) and lag phase (lambda, h). A higher SGR and a shorter lag phase were observed at low power (2.99 W for 5 min) compared to control. Conversely, a decrease ($p<0.05$) in SGR with an increase in lag phase was observed with an increase in ultrasonic power level. Cell-free extracts obtained after 24h fermentation of ultrasound treated samples showed antimicrobial activity against Staphylococcus aureus, Listeria monocytogenes, Escherichia coli and Salmonella typhimurium at lower concentrations compared to control. No significant difference ($p<0.05$) among treatments was observed for lactic acid content after a 24h fermentation period. This study showed that both stimulation and retardation of L. sakei is possible, depending on the ultrasonic power and sonication time employed. Hence, fermentation process involving probiotics to develop functional food products can be tailored by selection of ultrasound processing parameters.

Olaya Galan, N. N., Ulloa Rubiano, J. C., Velez Reyes, F. A., Fernandez Duarte, K. P., Salas Cardenas, S. P., and Gutierrez Fernandez, M. F. In vitro antiviral activity of Lactobacillus casei and Bifidobacterium adolescentis against rotavirus infection monitored by NSP4 protein production. J.Appl.Microbiol. 2016; 120(4):1041-1051.

ABSTRACT: AIMS: The aim of this study was to determine the antiviral activity of four probiotic metabolites (Lactobacillus and Bifidobacetrium species) against rotavirus in vitro infection monitored by the NSP4 protein production and Ca(2+) release. METHODS AND RESULTS: The antiviral effect of the metabolites was performed due a comparison between a blocking model and an intracelullar model on MA104 cells, with the response of NSP4 production and Ca(2+) liberation measured by flow cytometry. Significant results were obtained with the metabolites of Lactobacillus casei, and Bifidobacterium adolescentis in the reduction of the protein production ($P = 0.04$ and $P = 0.014$) and Ca(2+) liberation ($P = 0.094$ and $P = 0.020$) in the intracellular model, which suggests a successful antiviral activity against RV infection. CONCLUSIONS: This study demonstrates that probiotic metabolites were able to interfere with the final amount of intracellular NSP4 protein and a successful Ca(2+) regulation, which suggests a new approach to the mechanism exerted by probiotics against the rotavirus infection. SIGNIFICANCE AND IMPACT OF THE STUDY: A novel anti-rotaviral effect exerted by probiotic metabolites monitored by the NSP4 protein during the RV in vitro infection and the effect on the Ca(2+) release is reported; suggesting a reduction on the impact of the infection by decreasing the damage of the cells preventing the electrolyte loss.

Ollech, J. E., Shen, N. T., Crawford, C. V., and Ringel, Y. Use of probiotics in prevention and treatment of patients with Clostridium difficile infection. Best.Pract.Res.Clin.Gastroenterol. 2016; 30(1):111-118.

ABSTRACT: Clostridium difficile is an anaerobic, gram positive, sporulating, toxin-producing bacillus which causes a spectrum of clinical disease ranging from an asymptomatic carrier state to toxic megacolon and fulminant disease. Infection with C. difficile is an expensive and pervasive health care burden. The current theory regarding the development of C. difficile infection (CDI) suggests that disruption of the structure and/or function of an individual's normal intestinal microbiota enables colonization by C. difficile, and in the absence of an effective immune response, the bacteria causes illness. In this article we discuss the role of the colonic microbiota in the development of CDI and the potential role of probiotics in preventing and treating CDI. We review the evidence from in vitro laboratory and pre-clinical studies, as well as evidence from clinical studies and discuss the current recommendations for the use of probiotics for CDI in clinical practice.

Olsen, R., Greisen, G., Schroder, M., and Brok, J. Prophylactic Probiotics for Preterm Infants: A Systematic Review and Meta-Analysis of Observational Studies. Neonatology. 2016; 109(2):105-112.

ABSTRACT: BACKGROUND: Necrotizing enterocolitis (NEC) is a major morbidity and cause of mortality in preterm neonates. Probiotics seem to have a beneficial role in preventing NEC, which is confirmed in meta-analyses of randomized controlled trials (RCTs). We therefore aimed to review and confirm the efficacy of probiotics in preterm neonates obtained in observational studies. OBJECTIVE: To assess the effects of prophylactic probiotics in preterm infants. METHODS: A meta-analysis was performed searching PubMed, EMBASE, CENTRAL (the Cochrane Library) and www.clinicaltrials.gov. Reference lists of reviews of RCTs were also searched. Included studies were observational studies that enrolled preterm infants <37 weeks of gestational age. Trials were included if they administered any probiotics and measured at least one clinical outcome (e.g. NEC, all-cause mortality, sepsis or long-term development scores). Two authors extracted characteristics and outcomes from included studies. The Newcastle-Ottawa Scale was used for quality assessment. A random-effects meta-analysis model was used, and heterogeneity was assessed by the I2 test. RESULTS: We included 12 studies with 10,800 premature neonates (5,144 receiving prophylactic probiotics and 5,656 controls). The meta-analysis showed a significantly decreased incidence of NEC (risk ratio, RR = 0.55, 95% confidence interval, 95% CI, 0.39-0.78; p = 0.0006) and mortality (RR = 0.72, 95% CI, 0.61-0.85; p < 0.0001). Sepsis did not differ significantly between the two groups (RR = 0.86, 95% CI, 0.74-1.00; p = 0.05). CONCLUSIONS: Probiotic supplementation reduces the risk of NEC and mortality in preterm infants. The effect sizes are similar to findings in meta-analyses of RCTs. However, the optimal strain, dose and timing need further investigation.

Olson, J. K., Rager, T. M., Navarro, J. B., Mashburn-Warren, L., Goodman, S. D., and Besner, G. E. Harvesting the benefits of biofilms: A novel probiotic delivery system for the prevention of necrotizing enterocolitis. J.Pediatr.Surg. 2016; 51(6):936-941.

ABSTRACT: BACKGROUND/PURPOSE: Probiotics reduce the incidence of necrotizing enterocolitis (NEC) albeit only when administered at high frequency (at least daily). We have developed a novel probiotic delivery system in which probiotics are grown as a biofilm on microspheres, allowing enhanced efficacy with only a single treatment. METHODS: Neonatal rats were subjected to experimental NEC. Pups received a single enteral dose of: (1) vehicle only, (2) unloaded microspheres, (3) MRS (broth)-loaded microspheres, (4) Lactobacillus reuteri, (5) L. reuteri grown on unloaded microspheres, or (6) L. reuteri grown on MRS-loaded microspheres. Intestinal injury was graded histologically and intestinal permeability determined by serum levels of enterally administered fluorescein isothiocyanate-labeled dextran. RESULTS: 69% of untreated pups developed NEC, whereas 32% of pups treated with L. reuteri grown as a biofilm on unloaded microspheres (p=0.009) and 33% of pups treated with L. reuteri grown as a biofilm on MRS-loaded microspheres (p=0.005) developed NEC. No other group had a significant reduction in NEC. Furthermore, pups treated with L. reuteri grown as a biofilm had significantly reduced intestinal permeability. CONCLUSIONS: A single dose of Lactobacillus biofilm grown on biocompatible microspheres significantly reduces NEC incidence and severity. This novel probiotic delivery system may be beneficial in the prevention of NEC in the future.

Orlando, A., Linsalata, M., and Russo, F. Antiproliferative effects on colon adenocarcinoma cells induced by co-administration of vitamin K1 and Lactobacillus rhamnosus GG. Int.J.Oncol. 2016; 48(6):2629-2638.

ABSTRACT: Vitamin K (VK), an essential nutrient associated with the clotting cascade, has also been demonstrated to have anticancer properties in various cancer cells including colon cancer cells. Also probiotics have gained interest as potential anticancer agents. Among them, Lactobacillus rhamnosus GG (L.GG) has been shown to inhibit cell proliferation and polyamine biosynthesis as well as to induce apoptosis in different human gastrointestinal cancer cells. Nevertheless, the exact mechanisms involved in these actions are not completely elucidated. Therefore, the aims of the present study were to evaluate in three differently graded human colon cancer cells (namely Caco-2, HT-29 and SW480) the effects of increasing VK1 concentrations, administered alone or in combination with viable L.GG, on the cell proliferation evaluated by MTT test, apoptosis investigated by Bax/Bcl-2 ratio and the percentage of the apoptotic cells, and the cell cycle evaluated by MUSE cell analyzer. Both VK1 and L.GG administered alone up to 72 h, caused inhibition of proliferation, induction of apoptosis and the cell cycle arrest in all the tested colon cancer cells. When VK1 and L.GG were co-administered, the addition of increasing VK1 concentrations potentiated the probiotic antiproliferative effect in a dose-dependent manner, being also related to the individual features of each cell line. The effect was more evident in Caco-2 and HT-29 cells compared to the less differentiated SW480. The enhanced antiproliferative efficacy due to co-administration of L.GG and VK1 could represent a suitable option in a functional food strategy for cancer growth inhibition and chemoprevention.

Ostan, R., Bene, M. C., Spazzafumo, L., Pinto, A., Donini, L. M., Pryen, F., Charrouf, Z., Valentini, L., Lochs, H., Bourdel-Marchasson, I., Blanc-Bisson, C., Buccolini, F., Brigidi, P., Franceschi, C., and d'Alessio, P. A. Impact of diet and nutraceutical supplementation on inflammation in elderly people. Results from the RISTOMED study, an open-label randomized control trial. Clin.Nutr. 2016; 35(4):812-818.

ABSTRACT: BACKGROUND & AIMS: Eating habits may influence the life span and the quality of ageing process by modulating inflammation. The RISTOMED project was developed to provide a personalized and balanced diet, enriched with or without nutraceutical compounds, to decrease and prevent inflammageing, oxidative stress and gut microbiota alteration in healthy elderly people. This paper focused on the effect on inflammation and metabolism markers after 56 days of RISTOMED diet alone or supplementation with three nutraceutical compounds. METHODS: A cohort of 125 healthy elderly subjects was recruited and randomized into 4 arms (Arm A, RISTOMED diet; Arm B, RISTOMED diet plus VSL#3 probiotic blend; Arm C, RISTOMED diet plus AISA d-Limonene; Arm D, RISTOMED diet plus Argan oil). Inflammatory and metabolism parameters as well as the ratio between Clostridium cluster IV and Bifidobacteria (CL/B) were collected before and after 56 days of dietary intervention, and their evolution compared among the arms. Moreover, participants were subdivided according to their baseline inflammatory parameters (erythrocytes sedimentation rate (ESR), C-Reactive Protein, fibrinogen, Tumor Necrosis Factor-alfa (TNF-alpha), and Interleukin 6) in two clusters with low or medium-high level of inflammation. The evolution of the measured parameters was then examined separately in each cluster. RESULTS: Overall, RISTOMED diet alone or with each nutraceutical supplementation significantly decreased ESR. RISTOMED diet supplemented with d-Limonene resulted in a decrease in fibrinogen, glucose, insulin levels and HOMA-IR. The most beneficial effects were observed in subjects with a medium-high inflammatory status who received RISTOMED diet with AISA d-Limonene supplementation. Moreover, RISTOMED diet associated with VSL#3 probiotic blend induced a decrease in the CL/B ratio. CONCLUSIONS: Overall, this study emphasizes the beneficial anti-inflammageing effect of RISTOMED diet supplemented with nutraceuticals to control the inflammatory status of elderly individuals.

Ouwehand, A. C., Forssten, S., Hibberd, A. A., Lyra, A., and Stahl, B. Probiotic approach to prevent antibiotic resistance. Ann.Med. 2016; 48(4):246-255.

ABSTRACT: Probiotics are live microorganisms, mainly belonging to the genera Lactobacillus and Bifidobacterium, although also strain of other species are commercialized, that have a beneficial effect on the host. From the perspective of antibiotic use, probiotics have been observed to reduce the risk of certain infectious disease such as certain types of diarrhea and respiratory tract infection. This may be accompanied with a reduced need of antibiotics for secondary infections. Antibiotics tend to be effective against most common diseases, but increasingly resistance is being observed among pathogens. Probiotics are specifically selected to not contribute to the spread of antibiotic resistance and not carry transferable antibiotic resistance. Concomitant use of probiotics with antibiotics has been observed to reduce the incidence, duration and/or severity of antibiotic-associated diarrhea. This contributes to better adherence to the antibiotic prescription and thereby reduces the evolution of resistance. To what extent probiotics directly reduce the spread of antibiotic resistance is still much under investigation; but maintaining a balanced microbiota during antibiotic use may certainly provide opportunities for reducing the spread of resistances. Key messages Probiotics may reduce the risk for certain infectious diseases and thereby reduce the need for antibiotics. Probiotics may reduce the risk for antibiotic-associated diarrhea Probiotics do not contribute to the spread of antibiotic resistance and may even reduce it.

Padua, D. and Pothoulakis, C. Novel approaches to treating Clostridium difficile-associated colitis. Expert.Rev.Gastroenterol.Hepatol. 2016; 10(2):193-204.

ABSTRACT: Clostridium difficile is being recognized as a growing threat to many health-care systems. Epidemiology data shows that infection rates are soaring and the disease burden is increasing. Despite the efficacy of standard treatments, it is becoming evident that novel therapeutics will be required to tackle this disease. These new treatments aim to enhance the intestinal microbial barrier, activate the immune system and neutralize the toxins that mediate this disease. Many of these therapies are still in the beginning stages of investigation, however, in the next few years, more clinical data will become available to help implement many of these exciting new therapeutic approaches.

Pakdaman, M. N., Udani, J. K., Molina, J. P., and Shahani, M. The effects of the DDS-1 strain of lactobacillus on symptomatic relief for lactose intolerance - a randomized, double-blind, placebo-controlled, crossover clinical trial. Nutr.J. 2016; 15(1):56

ABSTRACT: BACKGROUND: Lactose intolerance is a form of lactose maldigestion where individuals experience symptoms such as diarrhea, abdominal cramping, flatulence, vomiting and bowel sounds following lactose consumption. Lactobacillus acidophilus is a species of bacteria known for its sugar fermenting properties. Preclinical studies have found that Lactobacillus acidophilus supplementation may assist in breaking down lactose; however, no human clinical trials exist evaluating its efficacy in alleviating symptoms related to lactose intolerance. OBJECTIVE: The aim of this randomized, double-blind, placebo-controlled, crossover study was to evaluate the effect of a proprietary strain of Lactobacillus acidophilus on relieving discomfort related to lactose intolerance. METHODS: The study enrolled healthy volunteers between 18 and 75 years of age who complained of lactose intolerance. Screening visits included a lactose challenge visit to confirm eligibility based on a score of 10 or higher on subjective assessment of the following symptoms after lactose challenge: diarrhea, abdominal cramping, vomiting, audible bowel sounds, flatulence, and overall symptoms. Qualified subjects participated in a 2-arm crossover design, with each arm consisting of 4 weeks of intervention of either active or placebo product, with a 2-week washout period during crossover. The study product consisted of the DDS-1 strain of Lactobacillus acidophilus (Nebraska Cultures, Walnut Creek, California). The placebo was formulated from maltodextrin. Study participants were instructed to take the product once daily for 4 weeks. Data collected included subjective symptom scores related to lactose intolerance. RESULTS: Longitudinal comparison between the DDS-1 group and placebo group demonstrated statistically significant reductions in abdominal symptom scores during the 6-h Lactose Challenge at week 4 for diarrhea ($p = 0.033$), abdominal cramping ($p = 0.012$), vomiting ($p = 0.0002$), and overall symptom score ($p = 0.037$). No adverse events were reported. CONCLUSIONS: The present study has found that this unique DDS-1 strain of Lactobacillus acidophilus, manufactured by Nebraska Cultures, is safe to consume and improves abdominal symptom scores compared to placebo with respect to diarrhea, cramping, and vomiting during an acute lactose challenge.

Pamer, E. G. Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens. Science. 4-29-2016; 352(6285):535-538.

ABSTRACT: The intestinal microbiota, which is composed of diverse populations of commensal bacterial species, provides resistance against colonization and invasion by

pathogens. Antibiotic treatment can damage the intestinal microbiota and, paradoxically, increase susceptibility to infections. Reestablishing microbiota-mediated colonization resistance after antibiotic treatment could markedly reduce infections, particularly those caused by antibiotic-resistant bacteria. Ongoing studies are identifying commensal bacterial species that can be developed into next-generation probiotics to reestablish or enhance colonization resistance. These live medicines are at various stages of discovery, testing, and production and are being subjected to existing regulatory gauntlets for eventual introduction into clinical practice. The development of next-generation probiotics to reestablish colonization resistance and eliminate potential pathogens from the gut is warranted and will reduce health care-associated infections caused by highly antibiotic-resistant bacteria.

Panahi, Y., Ghanei, M., Vahedi, E., Mousavi, S. H., Imani, S., and Sahebkar, A. Efficacy of probiotic supplementation on quality of life and pulmonary symptoms due to sulfur mustard exposure: a randomized double-blind placebo-controlled trial. Drug Chem.Toxicol. 4-14-2016; 1-6.

ABSTRACT: OBJECTIVE: This study investigated the efficacy and safety of supplementation with probiotics in improving chronic pulmonary symptoms due to sulfur mustard (SM) exposure. METHODS: In a randomized double-blind placebo-controlled study, 65 subjects suffering from chronic pulmonary complications of SM were assigned to one probiotic capsule (1 x 109 CFU containing seven strains of lactic acid-producing bacteria) every 12 h or an identical placebo for six weeks. Serum high-sensitivity C-reactive protein (CRP) concentrations, pulmonary function tests (FEV1, FEV1/FVC and MMEF 25-75%) and COPD assessment test (CAT) were assessed at baseline and at the end of trial. RESULTS: The groups were comparable in baseline characteristics. There were significant improvements in FEV1/FVC in the probiotic but not in placebo group. CAT scores were decreased in both study groups. However, between-group comparison of changes in the assessed parameters reached statistical significance only for CAT score ($p < 0.001$). There was no report of adverse events during the course of trial. CONCLUSIONS: Findings of the present trial favor the efficacy of probiotic supplementation in improving the pulmonary symptoms of SM-exposed subjects.

Pandey, S., Senthilguru, K., Uvanesh, K., Sagiri, S. S., Behera, B., Babu, N., Bhattacharyya, M. K., Pal, K., and Banerjee, I. Natural gum modified emulsion gel as single carrier for the oral delivery of probiotic-drug combination. Int.J.Biol.Macromol. 7-16-2016; 92:504-514.

ABSTRACT: Single formulation based delivery of probiotic-drug combination is envisioned as a superior therapeutic delivery modality for the diseases like Crohn's diseases, ulceritive colitis and Recurrent Clostridium difficile-Associated Diarrhoea (RCDAD). Keeping this perspective in mind, here we have developed natural gum [using a combination of aqueous solution of xantham gum (X) and guar gum (G)] modified sunflower oil based emulsion gels for the delivery of probiotics-drugs combination. FT-IR analysis and fluorescence microscopy together confirmed the formation of oil-in-water type emulsion gel by physical gelation in presence of the physical gelator sorbitan monopalmitate (SM). Other studies (XRD, DSC, mechanical properties and disintegration study) revealed that the variation in relative proportion of the two gums has a sporadic but significant effect on the physico-chemical properties of the gel. Post storage viability of commercially used probiotic Lactobacillus plantarum 299v (Lp 299v) at different storage conditions (4 degrees C, -20 degrees C, -196 degrees C) was found higher in the

emulsion gels with respect to the control. Moreover, the gels were found suitable for sustained delivery of metronidazole (the lipophilic drug often used with Lp 299v). In conclusion, the natural gum modified emulsion gel may be used as a delivery system for the probiotic-drug combination.

Parekh, H. and Bahna, S. L. Infant Formulas for Food Allergy Treatment and Prevention. Pediatr.Ann. 4-1-2016; 45(4):e150-e156.

ABSTRACT: The number of infant formulas intended for food allergy treatment or prevention has been increasing. Some products fulfill the criteria for hypoallergenicity, such as extensively hydrolyzed protein (casein or whey) and synthesized amino acid formulas (elemental diet). Numerous partially hydrolyzed formulas have been derived from bovine milk, soybean, and rice. They are not hypoallergenic and are not recommended for children allergic to the parent protein, yet certain preparations have shown efficacy for allergy prevention. Soybean-derived preparations, although not hypoallergenic, have been tolerated by a majority of children allergic to bovine milk. Studies on the addition of probiotics or prebiotics to infant formulas have shown inconsistent findings. Numerous hypoallergenic formulas or milk substitutes are available for pediatricians to choose for children with food allergy. Caution is needed in prescribing formulas that are erroneously marketed as hypoallergenic. [Pediatr Ann. 2016;45(4):e150-e156.].

Parekh, P. J., Nayi, V. R., Johnson, D. A., and Vinik, A. I. The Role of Gut Microflora and the Cholinergic Anti-inflammatory Neuroendocrine System in Diabetes Mellitus. Front Endocrinol.(Lausanne). 2016; 7:55

ABSTRACT: The obesity epidemic has drastically impacted the state of health care in the United States. Paralleling this epidemic is the incidence of diabetes mellitus, with a notable shift toward a much younger age of onset. While central to the pathogenesis of diabetes associated with obesity is the role of inflammation attributed to "adiposopathy." Emerging data suggest that changes in sympathetic/parasympathetic balance regulated by the brain precede changes in the inflammatory cascade. It has now been established that the gut microflora contributes significantly to the activation and inhibition of autonomic control and impact the set of the neuroinflammatory inhibitory reflex mediated by the cholinergic nervous system. There has been a paradigm shift toward further investigating commensal bacteria in the pathogenesis of obesity and diabetes mellitus and its complications, as dysbiosis is thought to play a pivotal role in diabetic-associated disorders. This paper is intended to evaluate the role of intestinal dysbiosis in the pathogenesis of diabetes mellitus and examine the potential for restoration of balance via use of probiotics.

Parian, A. and Limketkai, B. N. Dietary Supplement Therapies for Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis. Curr.Pharm.Des. 2016; 22(2):180-188.

ABSTRACT: Inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease are chronic relapsing and remitting chronic diseases for which there is no cure. The treatment of IBD frequently requires immunosuppressive and biologic therapies which carry an increased risk of infections and possible malignancy. There is a continued search for safer and more natural therapies in the treatment of IBD. This review aims to

summarize the most current literature on the use of dietary supplements for the treatment of IBD. Specifically, the efficacy and adverse effects of vitamin D, fish oil, probiotics, prebiotics, curcumin, Boswellia serrata, aloe vera and cannabis sativa are reviewed.

Park, H. J., Lee, G. H., Jun, J., Son, M., and Kang, M. J. Multiple-unit tablet of probiotic bacteria for improved storage stability, acid tolerability, and in vivo intestinal protective effect. Drug Des Devel.Ther. 2016; 10:1355-1364.

ABSTRACT: The aim of this study was to formulate probiotics-loaded pellets in a tablet form to improve storage stability, acid tolerability, and in vivo intestinal protective effect. Bacteria-loaded pellets primarily prepared with hydroxypropyl methylcellulose acetate succinate were compressed into tablets with highly compressible excipients and optimized for flow properties, hardness, and disintegration time. The optimized probiotic tablet consisted of enteric-coated pellets (335 mg), microcrystalline cellulose (Avicel PH102, 37.5 mg), and porous calcium silicate (25 mg) and allowed whole survival of living bacteria during the compaction process with sufficient tablet hardness (13 kp) and disintegration time (14 minutes). The multiple-unit tablet showed remarkably higher storage stability under ambient conditions (25 degrees C/60% relative humidity) over 6 months and resistance to acidic medium compared to uncoated strains or pellets. Repeated intake of this multiple-unit tablet significantly lowered plasma level of endotoxin, a pathogenic material, compared to repeated intake of bare probiotics or marketed products in rats. These results, therefore, suggest that the multiple-unit tablet is advantageous to better bacterial viability and gain the beneficial effects on the gut flora, including the improvement of intestinal barrier function.

Park, J. W., Jeong, J. S., Lee, S. I., and Kim, I. H. Effect of dietary supplementation with a probiotic (Enterococcus faecium) on production performance, excreta microflora, ammonia emission, and nutrient utilization in ISA brown laying hens. Poult.Sci. 7-14-2016;

ABSTRACT: The ban on the use of antibiotics as growth promoters due to resistance issues has urged scientists to find alternatives to antibiotics. Entercoccus faecium is one of the probiotics which have been used as an alternative to antibiotics in the livestock industry. This study was conducted to evaluate the effect of probiotic (Enterococcus faecium DSM 7134) supplementation on production performance, feed intake, egg quality, excreta microflora, ammonia emission, and nutrient utilization in laying hens. A total of 288 ISA brown laying hens were used in a 27 wk feeding experiment and randomly assigned to 3 dietary treatments with 8 replicates of 12 birds each. The treatments were CON (basal diet), PB1 (basal diet + 0.005% E. faecium), and PB2 (basal diet + 0.01% E. faecium). Overall, our results demonstrated that E. faecium supplementation resulted in a significant increase in egg production, egg shell thickness, and nutrient digestibility (dry matter, nitrogen, and energy) in laying hens, and a significant reduction in fecal coliform counts as compared with CON. The shift of excreta fecal microbial composition by E. faecium supplementation was accompanied by increased nutrient retention and reduction in nutrient excretion, leading to improved nutrient digestibility and reduced excreta ammonia emission. Overall, E. faecium supplementation appears to have a beneficial effect in ISA brown laying hens and should be considered as a positive diet supplement to use in the industry.

Partty, A., Kalliomaki, M., Salminen, S., and Isolauri, E. Infantile Colic is Associated with Low-grade Systemic Inflammation. J.Pediatr.Gastroenterol.Nutr. 7-14-2016;

ABSTRACT: OBJECTIVE: Dysbiosis, an imbalance in the taxonomic composition of the gut bacteria occurring during the critical stages of development, induces lasting shifts in the immunological and metabolic phenotype if accompanied by an inflammatory response. As altered gut microbiota and successful treatment with probiotics have both been demonstrated in cases of colic, we hypothesized here that infants with colic might have low-grade inflammation. METHODS: In 28 infants with colic and in 12 healthy controls at the age of one month, we measured the following serum immunological biomarkers: cytokines interleukin 1beta (IL-1beta); IL-6; IL-10; tumor necrosis factor alpha (TNF-alpha); interferon gamma (IFN-gamma); chemokines IL-8; monocyte chemotactic protein-1 (MCP-1); macrophage inflammatory protein1beta (MIP-1beta) and chemokine (C-X-C motif) ligand 16 (CXCL16); intestinal-fatty-acid-binding protein (ifabp), a biomarker of enterocyte damage and zonulin, a biomarker of intestinal permeability. In addition, intestinal microbiota composition was correlated with immunological biomarkers. RESULTS: Infants with colic had increased concentrations of IL-8, MCP-1 and MIP-1beta in serum as compared with healthy children. All the other immunological biomarkers were comparable between the groups. Fecal levels of Clostridium leptum correlated negatively with the pro-inflammatory markers MCP-1 ($r = -0.44$, $p = 0.02$), MIP-1beta ($r = -0.43$, $p = 0.02$) and TNF-alpha ($r = -0.38$, $p = 0.04$). In addition, Clostridium coccoides group levels correlated negatively with MCP-1 ($r = -0.43$, $p = 0.02$) and Bifidobacterium breve levels positively with CXCL16 ($r = 0.38$, $p = 0.04$). CONCLUSIONS: In addition to gut microbiota alterations, colic in infants is associated with low-grade systemic inflammation. Specific bacterial species beyond conventional probiotics may have anti-inflammatory properties that may help to modulate microbiota and alleviate colic-related inflammation.

Patel, B., Kumar, P., Banerjee, R., Basu, M., Pal, A., Samanta, M., and Das, S. Lactobacillus acidophilus attenuates Aeromonas hydrophila induced cytotoxicity in catla thymus macrophages by modulating oxidative stress and inflammation. Mol.Immunol. 2016; 75:69-83.

ABSTRACT: The pathogenesis of Aeromonas hydrophila, a potent fish pathogen, is attributed to its ability to cause motile aeromonad septicaemia leading to apoptosis in a myriad of fish species, including freshwater carp Catla catla. However, the underlying mechanism of antagonistic activity of probiotics against A. hydrophila induced apoptosis is not elucidated due to lack of appropriate in-vitro models. This study reported that the exposure of catla thymus macrophages (CTM) to A. hydrophila markedly induced cellular injuries as evidenced by elevated levels of reactive oxygen species (ROS), reactive nitrogen species (RNS), increased apoptosis, DNA damage and decreased cellular viability. Flow cytometry analysis and Annexin-V/propidium iodide assay further confirmed increased ROS positive cells leading to cell death after infection. The quantitative real-time PCR analysis, also revealed upregulation of inducible nitric-oxide synthase (iNOS), pro-inflammatory cytokine (TNFalpha), cyclooxygenase2 (COX-2) and downregulation of anti-inflammatory cytokine (IL-10). Pretreatment of cells with probiotic, Lactobacillus acidophilus attenuated A. hydrophila induced apoptosis as evident from the decrease in the levels of ROS, RNS and DNA damage. Significant increase ($P</=0.05$) in expression of TNFalpha and IL-10 and decrease in iNOS and COX-2 was observed on probiotic stimulation. In-vivo study using catla fingerlings confirmed similar pattern of ROS, iNOS, NO production and cytokine expression in thymus. This study provides a

comprehensive insight into the mechanistic basis of L. acidophilus induced macrophage mediated inflammatory response against A. hydrophila in CTM cells. Further, it speculates the possibility of using cost-effective in-vitro models for screening probiotic candidates of therapeutic potential in aquaculture industry.

Patel, T., Bhattacharya, P., and Das, S. Gut microbiota: an Indicator to Gastrointestinal Tract Diseases. J.Gastrointest.Cancer. 2016; 47(3):232-238.

ABSTRACT: PURPOSE: Gut microbiota is predicted to play a key role in manifestation of gastrointestinal tract cancers. The human gastrointestinal tract is a complex and abundant network of microbial community. Gut microbiota depicts the microbe population living in our intestine. Humans harbour more than 10(14) microbes in the gut, and the diversity and densities of the microbiota increase from stomach to colon. METHODS: The beneficial relationship between endogenous microbiota and the eukaryotic hosts helps in maintaining various metabolic activities of the body as well as temperature and pH balance. Studies using culturing methods have suggested that the oesophagus is either sterile or contains only a few transient microbes that originates from the oropharynx by swallowing or from the stomach by gastroesophageal reflux. However, metagenomics suggest that large numbers of uncultured organisms are harboured in the human gut. RESULTS: Observations suggest that research directed towards manipulation of the gut microbiota can be employed in prevention as well as treatment of these conditions. Well-designed, randomized, placebo-controlled human studies using probiotics and/or prebiotics are necessary to formulate the directions for prevention and therapy. CONCLUSIONS: Change in gut microbes in gastrointestinal (GI) tract may have major implication in gastric cancer, the fifth most occurring malignancy in the world. Affected population manifests multiple conditions and diseases, which majorly includes inflammatory bowel disease and colorectal malignancy.

Patole, S. K., Rao, S. C., Keil, A. D., Nathan, E. A., Doherty, D. A., and Simmer, K. N. Benefits of Bifidobacterium breve M-16V Supplementation in Preterm Neonates - A Retrospective Cohort Study. PLoS.One. 2016; 11(3):e0150775

ABSTRACT: BACKGROUND: Systematic reviews of randomised controlled trials report that probiotics reduce the risk of necrotising enterocolitis (NEC) in preterm neonates. AIM: To determine whether routine probiotic supplementation (RPS) to preterm neonates would reduce the incidence of NEC. METHODS: The incidence of NEC >/= Stage II and all-cause mortality was compared for an equal period of 24 months 'before' (Epoch 1) and 'after' (Epoch 2) RPS with Bifidobacterium breve M-16V in neonates <34 weeks. Multivariate logistic regression analysis was conducted to adjust for relevant confounders. RESULTS: A total of 1755 neonates (Epoch I vs. II: 835 vs. 920) with comparable gestation and birth weights were admitted. There was a significant reduction in NEC >/= Stage II: 3% vs. 1%, adjusted odds ratio (aOR) = 0.43 (95%CI: 0.21-0.87); 'NEC >/= Stage II or all-cause mortality': 9% vs. 5%, aOR = 0.53 (95%CI: 0.32-0.88); but not all-cause mortality alone: 7% vs. 4%, aOR = 0.58 (95% CI: 0.31-1.06) in Epoch II. The benefits in neonates <28 weeks did not reach statistical significance: NEC >/= Stage II: 6% vs. 3%, aOR 0.51 (95%CI: 0.20-1.27), 'NEC >/= Stage II or all-cause mortality', 21% vs. 14%, aOR = 0.59 (95%CI: 0.29-1.18); all-cause mortality: 17% vs. 11%, aOR = 0.63 (95%CI: 0.28-1.41). There was no probiotic sepsis. CONCLUSION: RPS with Bifidobacterium breve M-16V was associated with decreased NEC>/= Stage II and 'NEC>/= Stage II or all-cause mortality' in neonates <34 weeks. Large sample size is required to assess the potential benefits of RPS in neonates <28 weeks.

Patterson, E., Ryan, P. M., Cryan, J. F., Dinan, T. G., Ross, R. P., Fitzgerald, G. F., and Stanton, C. Gut microbiota, obesity and diabetes. Postgrad.Med.J. 2016; 92(1087):286-300.

ABSTRACT: The central role of the intestinal microbiota in the progression and, equally, prevention of metabolic dysfunction is becoming abundantly apparent. The symbiotic relationship between intestinal microbiota and host ensures appropriate development of the metabolic system in humans. However, disturbances in composition and, in turn, functionality of the intestinal microbiota can disrupt gut barrier function, a trip switch for metabolic endotoxemia. This low-grade chronic inflammation, brought about by the influx of inflammatory bacterial fragments into circulation through a malfunctioning gut barrier, has considerable knock-on effects for host adiposity and insulin resistance. Conversely, recent evidence suggests that there are certain bacterial species that may interact with host metabolism through metabolite-mediated stimulation of enteric hormones and other systems outside of the gastrointestinal tract, such as the endocannabinoid system. When the abundance of these keystone species begins to decline, we see a collapse of the symbiosis, reflected in a deterioration of host metabolic health. This review will investigate the intricate axis between the microbiota and host metabolism, while also addressing the promising and novel field of probiotics as metabolic therapies.

Pavlova, I., Milanova, A., Danova, S., and Fink-Gremmels, J. Enrofloxacin and Probiotic Lactobacilli Influence PepT1 and LEAP-2 mRNA Expression in Poultry. Probiotics.Antimicrob.Proteins. 8-9-2016;

ABSTRACT: Expression of peptide transporter 1 (PepT1) and liver-expressed antimicrobial peptide 2 (LEAP-2) in chickens can be influenced by food deprivation, pathological conditions and drug administration. Effect of three putative probiotic Lactobacillus strains and enrofloxacin on the expression of PepT1 and LEAP-2 mRNA was investigated in Ross 308 chickens. One-day-old chicks (n = 24) were allocated to following groups: control (without treatment); group treated with probiotics via feed; group treated with a combination of probiotics and enrofloxacin; and a group given enrofloxacin only. The drug was administered at a dose of 10 mg kg-1, via drinking water for 5 days. Samples from liver, duodenum and jejunum were collected 126 h after the start of the treatment. Expression levels of PepT1 and LEAP-2 were determined by real-time polymerase chain reaction and were statistically evaluated by Mann-Whitney test. Enrofloxacin administered alone or in combination with probiotics provoked a statistically significant up-regulation of PepT1 mRNA levels in the measured organ sites. These changes can be attributed to a tendency of improvement in utilization of dietary peptide and in body weight gain. LEAP-2 mRNA expression levels did not change significantly in enrofloxacin-treated chickens in comparison with control group.

Penala, S., Kalakonda, B., Pathakota, K. R., Jayakumar, A., Koppolu, P., Lakshmi, B. V., Pandey, R., and Mishra, A. Efficacy of local use of probiotics as an adjunct to scaling and root planing in chronic periodontitis and halitosis: A randomized controlled trial. J.Res.Pharm.Pract. 2016; 5(2):86-93.

ABSTRACT: OBJECTIVE: Periodontitis is known to have multifactorial etiology, involving interplay between environmental, host and microbial factors. The current treatment

approaches are aimed at reducing the pathogenic microorganisms. Administration of beneficial bacteria (probiotics) has emerged as a promising concept in the prevention and treatment of periodontitis. Thus, the aim of the present study is to evaluate the efficacy of the local use of probiotics as an adjunct to scaling and root planing (SRP) in the treatment of patients with chronic periodontitis and halitosis. METHODS: This is a randomized, placebo-controlled, double-blinded trial involving 32 systemically healthy chronic periodontitis patients. After SRP, the subjects were randomly assigned into the test and control groups. Test group (SRP + probiotics) received subgingival delivery of probiotics and probiotic mouthwash, and control group (SRP + placebo) received subgingival delivery of placebo and placebo mouthwash for 15 days. Plaque index (PI), modified gingival index (MGI), and bleeding index (BI) were assessed at baseline, 1 and 3 months thereafter, whereas probing depth (PD) and clinical attachment level were assessed at baseline and after 3 months. Microbial assessment using N-benzoyl-DL-arginine-naphthylamide (BANA) and halitosis assessment using organoleptic scores (ORG) was done at baseline, 1 and 3 months. FINDINGS: All the clinical and microbiological parameters were significantly reduced in both groups at the end of the study. Inter-group comparison of PD reduction (PDR) and clinical attachment gain (CAG) revealed no statistical significance except for PDR in moderate pockets for the test group. Test group has shown statistically significant improvement in PI, MGI, and BI at 3 months compared to control group. Inter-group comparison revealed a significant reduction in BANA in test group at 1 month. ORG were significantly reduced in test group when compared to control group. CONCLUSION: Within the limitations of the study, the present investigation showed that the adjunctive use of probiotics offers clinical benefit in terms of pocket depth reduction in moderate pockets and reduced oral malodor parameters.

Perez-Cornago, A., Sanchez-Villegas, A., Bes-Rastrollo, M., Gea, A., Molero, P., Lahortiga-Ramos, F., and Martinez-Gonzalez, M. A. Intake of High-Fat Yogurt, but Not of Low-Fat Yogurt or Prebiotics, Is Related to Lower Risk of Depression in Women of the SUN Cohort Study. J.Nutr. 7-27-2016;

ABSTRACT: BACKGROUND: Yogurt and prebiotic consumption has been linked to better health. However, to our knowledge, no longitudinal study has assessed the association of yogurt and prebiotic consumption with depression risk. OBJECTIVE: We longitudinally evaluated the association of yogurt and prebiotic consumption with depression risk in a Mediterranean cohort. METHODS: The SUN (Seguimiento Universidad de Navarra) Project is a dynamic, prospective cohort of Spanish university graduates. A total of 14,539 men and women (mean age: 37 y) initially free of depression were assessed during a median follow-up period of 9.3 y. Validated food-frequency questionnaires at baseline and after a 10-y follow-up were used to assess prebiotic (fructans and galacto-oligosaccharide) intake and yogurt consumption (<0.5, >/=0.5 to <3, >/=3 to <7, and >/=7 servings/wk). Participants were classified as incident cases of depression when they reported a new clinical diagnosis of depression by a physician (previously validated). Multivariable Cox proportional hazards models were used to calculate HRs and 95% CIs. RESULTS: We identified 727 incident cases of depression during follow-up. Whole-fat yogurt intake was associated with reduced depression risk: HR for the highest [>/=7 servings/wk (1 serving = 125 g)] compared with the lowest (<0.5 servings/wk) consumption: 0.78 (95% CI: 0.63, 0.98; P-trend = 0.020). When stratified by sex, this association was significant only in women (HR: 0.66; 95% CI: 0.50, 0.87; P-trend = 0.004). Low-fat yogurt consumption was associated with a higher incidence of depression (HR: 1.32; 95% CI: 1.06, 1.65; P-trend = 0.001), although this association lost significance after the exclusion of early incident

cases, suggesting possible reverse causation bias. Prebiotic consumption was not significantly associated with depression risk. CONCLUSIONS: Our study suggests that high consumption of whole-fat yogurt was related to a lower risk of depression in women of the SUN cohort. No association was observed for prebiotics. Further studies are needed to clarify why the yogurt-depression association may differ by fat content of the yogurt.

Pessione, E. and Cirrincione, S. Bioactive Molecules Released in Food by Lactic Acid Bacteria: Encrypted Peptides and Biogenic Amines. Front Microbiol. 2016; 7:876

ABSTRACT: Lactic acid bacteria (LAB) can produce a huge amount of bioactive compounds. Since their elective habitat is food, especially dairy but also vegetal food, it is frequent to find bioactive molecules in fermented products. Sometimes these compounds can have adverse effects on human health such as biogenic amines (tyramine and histamine), causing allergies, hypertensive crises, and headache. However, some LAB products also display benefits for the consumers. In the present review article, the main nitrogen compounds produced by LAB are considered. Besides biogenic amines derived from the amino acids tyrosine, histidine, phenylalanine, lysine, ornithine, and glutamate by decarboxylation, interesting peptides can be decrypted by the proteolytic activity of LAB. LAB proteolytic system is very efficient in releasing encrypted molecules from several proteins present in different food matrices. Alpha and beta-caseins, albumin and globulin from milk and dairy products, rubisco from spinach, beta-conglycinin from soy and gluten from cereals constitute a good source of important bioactive compounds. These encrypted peptides are able to control nutrition (mineral absorption and oxidative stress protection), metabolism (blood glucose and cholesterol lowering) cardiovascular function (antithrombotic and hypotensive action), infection (microbial inhibition and immunomodulation) and gut-brain axis (opioids and anti-opioids controlling mood and food intake). Very recent results underline the role of food-encrypted peptides in protein folding (chaperone-like molecules) as well as in cell cycle and apoptosis control, suggesting new and positive aspects of fermented food, still unexplored. In this context, the detailed (transcriptomic, proteomic, and metabolomic) characterization of LAB of food interest (as starters, biocontrol agents, nutraceuticals, and probiotics) can supply a solid evidence-based science to support beneficial effects and it is a promising approach as well to obtain functional food. The detailed knowledge of the modulation of human physiology, exploiting the health-promoting properties of fermented food, is an open field of investigation that will constitute the next challenge.

Pontonio, E., Mahony, J., Di, Cagno R., O'Connell, Motherway M., Lugli, G. A., O'Callaghan, A., De, Angelis M., Ventura, M., Gobbetti, M., and van, Sinderen D. Cloning, expression and characterization of a beta-D-xylosidase from Lactobacillus rossiae DSM 15814(T). Microb.Cell Fact. 2016; 15:72

ABSTRACT: BACKGROUND: Among the oligosaccharides that may positively affect the gut microbiota, xylo-oligosaccharides (XOS) and arabinoxylan oligosaccharides (AXOS) possess promising functional properties. Ingestion of XOS has been reported to contribute to anti-oxidant, anti-bacterial, immune-modulatory and anti-diabetic activities. Because of the structural complexity and chemical heterogeneity, complete degradation of xylan-containing plant polymers requires the synergistic activity of several enzymes. Endo-xylanases and beta-D-xylosidases, collectively termed xylanases, represent the two key enzymes responsible for the sequential hydrolysis of xylan. Xylanase cocktails are used on an industrial scale for biotechnological purposes. Lactobacillus rossiae DSM 15814(T) can

utilize an extensive set of carbon sources, an ability that is likely to contribute to its adaptive ability. In this study, the capacity of this strain to utilize XOS, xylan, D-xylose and L-arabinose was investigated. RESULTS: Genomic and transcriptomic analyses revealed the presence of two gene clusters, designated xyl and ara, encoding proteins predicted to be responsible for XOS uptake and hydrolysis and D-xylose utilization, and L-arabinose metabolism, respectively. The deduced amino acid sequence of one of the genes of the xyl gene cluster, LROS_1108 (designated here as xylA), shows high similarity to (predicted) beta-D-xylosidases encoded by various lactic acid bacteria, and belongs to glycosyl hydrolase family 43. Heterologously expressed XylA was shown to completely hydrolyse XOS to xylose and showed optimal activity at pH 6.0 and 40 degrees C. Furthermore, beta-D-xylosidase activity of L. rossiae DSM 15814(T) was also measured under sourdough conditions. CONCLUSIONS: This study highlights the ability of L. rossiae DSM 15814(T) to utilize XOS, which is a very useful trait when selecting starters with specific metabolic performances for sourdough fermentation or as probiotics.

Pourakbari, M., Seidavi, A., Asadpour, L., and Martinez, A. Probiotic level effects on growth performance, carcass traits, blood parameters, cecal microbiota, and immune response of broilers. An.Acad.Bras.Cienc. 5-31-2016; 88(2):1011-1021.

ABSTRACT: Probiotic effects on growth performance, carcass traits, blood parameters, cecal microbiota, and immune response of broilers were studied. Two hundred one-day-old male chickens were allocated to one of five treatments (four replicates of 10 birds per treatment): control, and the same control diet supplemented with 0.005%, 0.01%, 0.015% and 0.02% probiotics. Probiotics in feed at 0.01% or higher levels of supplementation improved body weight gain (+12%) and feed conversion rate (-5%) compared with the control. There were no effects on carcass traits, but the relative weights of drumsticks and wings showed increasing and decreasing linear responses, respectively, to probiotic supplementation level. Blood plasma glucose and albumin contents linearly increased (from 167.1 to 200.5 mg dl-1, and from 1.70 to 3.25 g dl-1) with increasing probiotic supplementation. Triglycerides and cholesterol contents were lower in probiotic supplemented treatments (average contents 71.3 and 125.3 mg dl-1 vs. 92.6 and 149.9 mg dl-1 in the control). Probiotics decreased cecal Escherichia coli counts, but had no effects on immunity related organs or immune response. The linear trends, either positive or negative, observed in many of the parameters studied, suggest that more studies are needed to establish the optimal concentration of probiotics in broiler feed.

Pradhan, B., Guha, D., Ray, P., Das, D., and Aich, P. Comparative Analysis of the Effects of Two Probiotic Bacterial Strains on Metabolism and Innate Immunity in the RAW 264.7 Murine Macrophage Cell Line. Probiotics.Antimicrob.Proteins. 2016; 8(2):73-84.

ABSTRACT: Probiotic and potential probiotic bacterial strains are routinely prescribed and used as supplementary therapy for a variety infectious diseases, including enteric disorders among a wide range of individuals. While there are an increasing number of studies defining the possible mechanisms of probiotic activity, a great deal remains unknown regarding the diverse modes of action attributed to these therapeutic agents. More precise information is required to support the appropriate application of probiotics. To address this objective, we selected two probiotics strains, Lactobacillus acidophilus MTCC-10307 (LA) and Bacillus clausii MTCC-8326 (BC) that are frequently prescribed for the treatment of intestinal disorders and investigated their effects on the RAW 264.7 murine macrophage cell line. Our results reveal that LA and BC are potent activators of

both metabolic activity and innate immune responses in these cells. We also observed that LA and BC possessed similar activity in preventing infection simulated in vitro in murine macrophages by Salmonella typhimurium serovar enterica.

Pranckute, R., Kaunietis, A., Kuisiene, N., and Citavicius, D. J. Combining prebiotics with probiotic bacteria can enhance bacterial growth and secretion of bacteriocins. Int.J.Biol.Macromol. 2016; 89:669-676.

ABSTRACT: There is a growing interest in supporting human health by using prebiotics, such as oligosaccharides, and beneficial bacteria, also called probiotics. Combining these two components we can develop synbiotics. In order to create successful combination of synbiotic it is very important to evaluate the influence of prebiotic oligosaccharides to probiotic bacteria and their behavior, such as growth and secretion of health related biomolecules, including bacteriocins. In this study seven type strains of probiotic bacteria (five Lactobacillus sp. and two Lactococcus sp.) and two Lactobacillus sp. strains, isolated from probiotic yoghurt, were cultivated with various commercially available and extracted oligosaccharides (OS). The aim of this study was to evaluate the influence of these OS on type and isolated bacterial strains growth and antibacterial activity. Obtained results suggest that combination of certain OS with probiotic strains may considerably improve their growth and/or antibacterial activity. We also determined the antibacterial activity spectrum of investigated strains with combination of OS against common food borne pathogens. Results of this work show that prebiotic OS can be useful for modulating probiotic bacteria growth, antibacterial activity and even specificity of this activity.

Priyamvada, S., Anbazhagan, A. N., Kumar, A., Soni, V., Alrefai, W. A., Gill, R. K., Dudeja, P. K., and Saksena, S. Lactobacillus acidophilus stimulates intestinal P-glycoprotein expression via a c-Fos/c-Jun-dependent mechanism in intestinal epithelial cells. Am.J.Physiol Gastrointest.Liver Physiol. 4-15-2016; 310(8):G599-G608.

ABSTRACT: Our previous studies showed that Lactobacillus acidophilus (LA) culture supernatant (CS) increased P-glycoprotein [Pgp/multidrug resistance 1 (MDR1)] function, expression, and promoter activity in Caco-2 cells. The current studies were designed to elucidate the molecular mechanisms mediating the stimulatory effects of LA CS on Pgp promoter activity. Deletion analysis indicated that the LA CS response element(s) is located in the -172/+428-bp region, and sequence analysis of this region revealed three potential binding sites for c-Fos or c-Jun: proximal activating protein (AP) 1a (-119/-98 bp), distal AP1b (-99/-78 bp), and AP1c (+175/+196 bp). LA CS (24 h) showed an approximately twofold increase in the protein expression of c-Fos and c-Jun in Caco-2 cells. Electrophoretic mobility shift assay showed that LA CS markedly increased the binding of Caco-2 nuclear proteins to AP1a and AP1b, but not AP1c. The DNA-protein complex was completely eliminated by c-Fos antibody, while c-Jun antibody partially eliminated the complex. Chromatin immunoprecipitation analysis also showed that LA CS enhanced the association of c-Fos and c-Jun (by approximately 4- and 1.5-fold, respectively) with endogenous Pgp promoter in Caco-2 cells (p-172/+1). Interestingly, overexpression of c-Fos or c-Jun activated Pgp promoter by nearly twofold each. This increase was further enhanced (approximately 14-fold) when c-Fos and c-Jun were simultaneously overexpressed, suggesting that the presence of one of these transcription factors potentiates the effect of the other. These studies, for the first time, provide

evidence for the involvement of c-Fos/c-Jun in stimulation of Pgp gene expression by LA CS in the human intestine.

Przemska-Kosicka, A., Childs, C. E., Enani, S., Maidens, C., Dong, H., Dayel, I. B., Tuohy, K., Todd, S., Gosney, M. A., and Yaqoob, P. Effect of a synbiotic on the response to seasonal influenza vaccination is strongly influenced by degree of immunosenescence. Immun.Ageing. 2016; 13:6

ABSTRACT: BACKGROUND: Ageing increases risk of respiratory infections and impairs the response to influenza vaccination. Pre- and probiotics offer an opportunity to modulate anti-viral defenses and the response to vaccination via alteration of the gut microbiota. This study investigated the effect of a novel probiotic, Bifidobacterium longum bv. infantis CCUG 52,486, combined with a prebiotic, gluco-oligosaccharide (B. longum + GI-OS), on the response to seasonal influenza vaccination in young and older subjects in a double-blind, randomized controlled trial, taking into account the influence of immunosenescence markers at baseline. RESULTS: Vaccination resulted in a significant increase in total antibody titres, vaccine-specific IgA, IgM and IgG and seroprotection to all three subunits of the vaccine in both young and older subjects, and in general, the increases in young subjects were greater. There was little effect of the synbiotic, although it tended to reduce seroconversion to the Brisbane subunit of the vaccine and the vaccine-specific IgG response in older subjects. Immunological characterization revealed that older subjects randomized to the synbiotic had a significantly higher number of senescent (CD28(-)CD57(+)) helper T cells at baseline compared with those randomized to the placebo, and they also had significantly higher plasma levels of anti-CMV IgG and a greater tendency for CMV seropositivity. Moreover, higher numbers of CD28(-)CD57(+) helper T cells were associated with failure to seroconvert to Brisbane, strongly suggesting that the subjects randomized to the synbiotic were already at a significant disadvantage in terms of likely ability to respond to the vaccine compared with those randomized to the placebo. CONCLUSIONS: Ageing was associated with marked impairment of the antibody response to influenza vaccination in older subjects and the synbiotic failed to reverse this impairment. However, the older subjects randomized to the synbiotic were at a significant disadvantage due to a greater degree of immunosenscence at baseline compared with those randomized to the placebo. Thus, baseline differences in immunosenescence between the randomized groups are likely to have influenced the outcome of the intervention, highlighting the need for detailed immunological characterization of subjects prior to interventions. TRIAL REGISTRATION: Clinicaltrials.gov NCT01066377.

Putignani, L., Alisi, A., and Nobili, V. Pediatric NAFLD: the Future role of Patient-Tailored Probiotics Therapy. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S6-S8.

ABSTRACT: PURPOSE OF REVIEW: Clinical evidence of the use of probiotics in pediatric NAFLD, framed within gut microbiota response, is herein discussed. RECENT FINDINGS: The assistance of a new microbiological approach in probiotics' design is playing a central role in NAFLD clinical management. Experimental studies demonstrated the effect of gut microbiota manipulation in NAFLD and recent clinical evidence reported their beneficial effect in pediatric patients. SUMMARY: Epidemiology suggests that NAFLD is the most frequent pediatric chronic liver disease evolving from simple steatosis to a more severe form that may progress toward fibrosis. The goal of pharmacological treatment of NAFLD-related fibrosis is to stop and eventually to reverse liver damage, but no drug

tested so far seem to be able to reach this endpoint. A few encouraging clinical studies demonstrated an improvement of hepato-metabolic milieu under probiotic treatment suggesting that they could exert an anti-fibrotic activity.Currently, new insights onto probiotics can be deduced by ad hoc generated NAFLD gut microbiota profiles. These functional maps may unveil gut ecosystem dynamics under probiotics' treatment, selecting the most appropriate for NAFLD gut microbiota amelioration.

Qiu, J. W., He, X. L., Zhang, B., DU, L., Zeng, Q., Li, S., Xiong, H. H., Long, M., Luo, J., and Cao, H. [Effect on Muc2 gene knockdown in Ht29 cells by CRISPR/Cas9 on probiotics-mediated inhibition of E.coli K1 adhesion and invasion]. Nan.Fang Yi.Ke.Da.Xue.Xue.Bao. 2016; 36(6):819-823.

ABSTRACT: OBJECTIVE: To investigate the effects of Lactobacillus rhamnosus GG (LGG) for inhibiting E.coli K1 (E44) adhesion and invasion of an intestinal epithelial cell model with Muc2 gene knockdown established using CRISPR-Cas9 system. METHODS: Two 20-25 bp sgRNAs targeting Muc2 were chemically synthesized to construct CRISPR expression vectors for transfection in wild-type human colonic cancer cell line Ht29. The efficiency of Muc2 knockdown was determined using Western blotting. After assessment of the viability and proliferation of the transfected cells with MTT assay, we evaluated the effects of the probiotics against E44 adhesion and invasion of the cells through a competitive exclusion assay. RESULTS: Transfection of the cells with Lenticrisprv2 plasmid vectors resulted in a cell line with stable Muc2 knockdown by 81%. The inhibitory effects of probiotics against E44 adhesion and invasion of the transfected cells were markedly attenuated, and the relative adhesion and invasion rates of E44 were 72.23% ($P<0.05$) and 81.49% ($P<0.05$), respectively. CONCLUSION: Muc2 knockdown causes attenuation of the inhibitory effects of probiotics against E44 adhesion and invasion of the intestinal epithelial cells, suggesting that up-regulation of Muc2 may serve as an important mechanism for the probiotics to reinforce the intestinal barrier and antagonize the pathogenic bacteria, which sheds light on a new strategy for prevention and treatment of bacterial intestinal infections.

Quilodran-Vega, S. R., Villena, J., Valdebenito, J., Salas, M. J., Parra, C., Ruiz, A., Kitazawa, H., and Garcia, A. Isolation of lactic acid bacteria from swine milk and characterization of potential probiotic strains with antagonistic effects against swine-associated gastrointestinal pathogens. Can.J.Microbiol. 2016; 62(6):514-524.

ABSTRACT: Probiotics are usually isolated from the gastrointestinal tract of humans and animals. The search of probiotics in human milk is a recent field of research, as the existence of the human milk microbiome was discovered only about a decade ago. To our knowledge, no reports regarding the potential probiotic effect of bacteria from swine milk have been published. In this work, we isolated several lactic acid bacteria from swine milk and evaluated them for them potential as probiotics. Among the isolated strains, Lactobacillus curvatus TUCO-5E showed antagonistic effects against swine-associated gastrointestinal pathogens. TUCO-5E was able to reduce the growth of enterotoxigenic and enterohemorrhagic Escherichia coli strains as well as pathogenic salmonella. In vitro exclusion and displacement assays in intestinal epithelial cells showed a remarkable antagonistic effect for L. curvatus TUCO-5E against Salmonella sp. strain TUCO-I7 and Salmonella enterica ATCC 13096. Moreover, by using a mouse model of Salmonella infection, we were able to demonstrate that preventative administration of L. curvatus TUCO-5E for 5 consecutive days was capable of decreasing the number of

Salmonella enterica serovar Typhimurium in the liver and spleen of treated mice, compared with the controls, and prevented dissemination of the pathogen to the blood stream. Therefore, we have demonstrated here that swine milk is an interesting source of beneficial bacteria. In addition, the results of this work suggest that L. curvatus TUCO-5E is a good candidate to study in vivo the protective effect of probiotics against intestinal infection and damage induced by Salmonella infection in the porcine host.

Raes, J. Microbiome-based companion diagnostics: no longer science fiction? Gut. 2016; 65(6):896-897.

No abstract currently available.

Ramakrishnan, V. and Luthria, D. L. Recent applications of NMR in food and dietary studies. J.Sci.Food Agric. 7-20-2016;

ABSTRACT: Over the last decade, a wide variety of new foods have been introduced into the global market place, many with health benefits that exceed those of traditional foods. Simultaneously, a wide range of analytical technologies have evolved that allow greater capability for the determination of food composition. Thus, the world is being offered an unprecedented number of healthful foods and an unprecedented ability to characterize these foods. Nuclear magnetic resonance (NMR), traditionally a research tool used for structural elucidation, is now being used frequently for metabolomics and chemical fingerprinting. Its stability and inherent ease of quantification have been exploited extensively to identify and quantify bioactive components in foods and dietary supplements. In addition, NMR fingerprints have been used to differentiate cultivars, evaluate sensory properties of food, and investigate the influence of growing conditions on food crops. Here we review the latest applications of NMR in food analysis.

Ran, C., Huang, L., Hu, J., Tacon, P., He, S., Li, Z., Wang, Y., Liu, Z., Xu, L., Yang, Y., and Zhou, Z. Effects of dietary live and heat-inactive baker's yeast on growth, gut health, and disease resistance of Nile tilapia under high rearing density. Fish.Shellfish.Immunol. 7-5-2016; 56:263-271.

ABSTRACT: In this study, the effects of baker's yeast as probiotics was evaluated in Nile tilapia reared at high density. Juvenile tilapia were distributed to tanks at high density (436 fish/m3) and fed with basal diet (CK) or diets supplemented with live (LY) or heat-inactivated yeast (HIY). Another group of fish reared at low density (218 fish/m3) and fed with basal diet was also included (LowCK). After 8 weeks of feeding, growth, feed utilization, gut microvilli morphology, digestive enzymes, and expressions of hsp70 and inflammation-related cytokines in the intestine were assessed. Intestinal microbiota was investigated using 16S rRNA gene pyrosequencing. Fish were challenged with Aeromonas hydrophila to evaluate disease resistance. High rearing density significantly decreased the growth, feed utilization, microvilli length, and disease resistance of fish (CK versus LowCK). Moreover, the intestinal hsp70 expression was increased in fish reared at high density, supporting a stress condition. Compared to CK group, supplementation of live yeast significantly increased gut microvilli length and trypsin activity, decreased intestinal hsp70 expression, and enhanced resistance of fish against A. hydrophila (reflected by reduced intestinal alkaline phosphatase activity 24 h post infection). The gut microbiota was not markedly influenced by either rearing density or yeast

supplementation. Heat-inactivated yeast (HIY) didn't display the beneficial effects observed in LY except an increase in gut trypsin activity, suggesting the importance of yeast viability and thus secretory metabolites of yeast. In conclusion, live baker's yeast may alleviate the negative effects induced by crowding stress, and has the potential to be used as probiotics for tilapia reared at high density.

Rasmussen, B. B., Grotkjaer, T., D'Alvise, P. W., Yin, G., Zhang, F., Bunk, B., Sproer, C., tzon-Tilia, M., and Gram, L. Vibrio anguillarum Is Genetically and Phenotypically Unaffected by Long-Term Continuous Exposure to the Antibacterial Compound Tropodithietic Acid. Appl.Environ.Microbiol. 8-1-2016; 82(15):4802-4810.

ABSTRACT: Minimizing the use of antibiotics in the food production chain is essential for limiting the development and spread of antibiotic-resistant bacteria. One alternative intervention strategy is the use of probiotic bacteria, and bacteria of the marine Roseobacter clade are capable of antagonizing fish-pathogenic vibrios in fish larvae and live feed cultures for fish larvae. The antibacterial compound tropodithietic acid (TDA), an antiporter that disrupts the proton motive force, is key in the antibacterial activity of several roseobacters. Introducing probiotics on a larger scale requires understanding of any potential side effects of long-term exposure of the pathogen to the probionts or any compounds they produce. Here we exposed the fish pathogen Vibrio anguillarum to TDA for several hundred generations in an adaptive evolution experiment. No tolerance or resistance arose during the 90 days of exposure, and whole-genome sequencing of TDA-exposed lineages and clones revealed few mutational changes, compared to lineages grown without TDA. Amino acid-changing mutations were found in two to six different genes per clone; however, no mutations appeared unique to the TDA-exposed lineages or clones. None of the virulence genes of V. anguillarum was affected, and infectivity assays using fish cell lines indicated that the TDA-exposed lineages and clones were less invasive than the wild-type strain. Thus, long-term TDA exposure does not appear to result in TDA resistance and the physiology of V. anguillarum appears unaffected, supporting the application of TDA-producing roseobacters as probiotics in aquaculture. IMPORTANCE: It is important to limit the use of antibiotics in our food production, to reduce the risk of bacteria developing antibiotic resistance. We showed previously that marine bacteria of the Roseobacter clade can prevent or reduce bacterial diseases in fish larvae, acting as probiotics. Roseobacters produce the antimicrobial compound tropodithietic acid (TDA), and we were concerned regarding whether long-term exposure to this compound could induce resistance or affect the disease-causing ability of the fish pathogen. Therefore, we exposed the fish pathogen Vibrio anguillarum to increasing TDA concentrations over 3 months. We did not see the development of any resistance to TDA, and subsequent infection assays revealed that none of the TDA-exposed clones had increased virulence toward fish cells. Hence, this study supports the use of roseobacters as a non-risk-based disease control measure in aquaculture.

Rather, I. A., Bajpai, V. K., Kumar, S., Lim, J., Paek, W. K., and Park, Y. H. Probiotics and Atopic Dermatitis: An Overview. Front Microbiol. 2016; 7:507

ABSTRACT: Atopic dermatitis (AD) is a common, recurrent, chronic inflammatory skin disease that is a cause of considerable economic and social burden. Its prevalence varies substantially among different countries with an incidence rate proclaimed to reach up to 20% of children in developed countries and continues to escalate in

developing nations. This increased rate of incidence has changed the focus of research on AD toward epidemiology, prevention, and treatment. The effects of probiotics in the prevention and treatment of AD remain elusive. However, evidence from different research groups show that probiotics could have positive effect on AD treatment, if any, that depend on multiple factors, such as specific probiotic strains, time of administration (onset time), duration of exposure, and dosage. However, till date we still lack strong evidence to advocate the use of probiotics in the treatment of AD, and questions remain to be answered considering its clinical use in future. Based on updated information, the processes that facilitate the development of AD and the topic of the administration of probiotics are addressed in this review.

Rawski, M., Kieronczyk, B., Dlugosz, J., Swiatkiewicz, S., and Jozefiak, D. Dietary Probiotics Affect Gastrointestinal Microbiota, Histological Structure and Shell Mineralization in Turtles. PLoS.One. 2016; 11(2):e0147859

ABSTRACT: Probiotics are widely used in nutrition, and their mode of action is intensively studied in mammals and birds; however, it is almost unknown in reptiles. In the present study, Trachemys scripta scripta and Sternotherus odoratus were used to assess the effects of dietary probiotics on chelonian gastrointestinal tract microecology. In the first, 20-week experiment, 40 young T. s. scripta were randomly distributed to four experimental groups: 1st, (CON)--with no additives; 2nd, (SSPA) with Bacillus subtilis PB6; 3rd, (MSP)--with multiple strain probiotic; and 4th, (SSPB) with Bacillus subtilis C-3102. The first study has shown that SSPA and MSP decreased the numbers of total bacteria, Enterobacteriace, Staphylococcus sp. and Streptococcus sp. excreted to water and increased the villous height and mucosa thickness in duodenum. SSPB improved the duodenal microstructure; however, it also increased numbers of kanamycin and vancomycin resistant bacteria, Staphylococcus sp. and Streptococcus sp., in water. In the second, 52-week experiment, 30 S. odoratus were randomly assigned to three dietary treatments. CON, SSPA and MSP groups. The MSP preparation increased the body weight gain, crude ash, Ca and P share in the turtles' shells. Both probiotics affected duodenal histomorphology. SSPA decreased the villous height, while MSP increased the villous height and mucosa thickness, and decreased the crypt depth. SSPA decreased the concentrations of bacteria excreted to water. In the case of intestinal microbiota, bacteria suppressing effects were observed in the case of both probiotics. MSP increased the number of Bifidobacterium sp. and Lactobacillus sp./Enteroccoccus sp., and decreased the number of Clostridium perfringens and Campylobacter sp. in the small intestine. In the large intestine it lowered, amongst others, Bacteroides-Pervotella cluster, Clostridium leptum subgroup and Clostridium perfringens numbers. The above-mentioned results suggest that probiotics are useful in turtle nutrition due to their positive effects on growth performance, shell mineralization, duodenal histomorphology and microbiota.

Razmpoosh, E., Javadi, M., Ejtahed, H. S., and Mirmiran, P. Probiotics as beneficial agents in the management of diabetes mellitus: a systematic review. Diabetes Metab Res.Rev. 2016; 32(2):143-168.

ABSTRACT: Probiotics have been suggested to play an important role in the management of diabetes. We conducted a systematic review on the role of probiotics in modulating parameters related to diabetes in animal and human experiments. We searched Pubmed, Scopus and Cochrane central until June 2014, concerning the

effects of probiotics on hyperglycemia, hyperinsulinemia and their anti-diabetic efficacies by modulating the activities of proinflammatory and antioxidant factors. Our initial search retrieved 1120 reports. After screening titles and abstracts, 72 full-text articles were reviewed for eligibility. Ultimately, 33 articles met our inclusion criteria consisting of five human and twenty eight animal reports. Lactobacillus strains were, in particular, used in all studies with or without other strains. We found that probiotics have beneficial effects on glycemic controls, as all human studies showed significant reductions in at least one of the primary outcome endpoints which were the levels of fasting plasma glucose, postprandial blood glucose, glycated haemoglobin, insulin, insulin resistance and onset of diabetes; similarly, all the animal reports, except for two, documented significant changes in these parameters. Regarding secondary outcome measures, that is, lipid profiles, pro-inflammatory and anti-oxidant factors, only one human and one animal study failed to show any significant changes in any of these parameters. This systematic review generally demonstrated beneficial effects of the probiotic administration, especially Lactobacillus sub-strains, on the management of diabetes-related blood parameters, although, more evidence, especially from human trials, is needed to confirm these effects and also to conduct a meta-analysis. Copyright (c) 2015 John Wiley & Sons, Ltd.

Rebollar, E. A., Antwis, R. E., Becker, M. H., Belden, L. K., Bletz, M. C., Brucker, R. M., Harrison, X. A., Hughey, M. C., Kueneman, J. G., Loudon, A. H., McKenzie, V., Medina, D., Minbiole, K. P., Rollins-Smith, L. A., Walke, J. B., Weiss, S., Woodhams, D. C., and Harris, R. N. Using "Omics" and Integrated Multi-Omics Approaches to Guide Probiotic Selection to Mitigate Chytridiomycosis and Other Emerging Infectious Diseases. Front Microbiol. 2016; 7:68

ABSTRACT: Emerging infectious diseases in wildlife are responsible for massive population declines. In amphibians, chytridiomycosis caused by Batrachochytrium dendrobatidis, Bd, has severely affected many amphibian populations and species around the world. One promising management strategy is probiotic bioaugmentation of antifungal bacteria on amphibian skin. In vivo experimental trials using bioaugmentation strategies have had mixed results, and therefore a more informed strategy is needed to select successful probiotic candidates. Metagenomic, transcriptomic, and metabolomic methods, colloquially called "omics," are approaches that can better inform probiotic selection and optimize selection protocols. The integration of multiple omic data using bioinformatic and statistical tools and in silico models that link bacterial community structure with bacterial defensive function can allow the identification of species involved in pathogen inhibition. We recommend using 16S rRNA gene amplicon sequencing and methods such as indicator species analysis, the Kolmogorov-Smirnov Measure, and co-occurrence networks to identify bacteria that are associated with pathogen resistance in field surveys and experimental trials. In addition to 16S amplicon sequencing, we recommend approaches that give insight into symbiont function such as shotgun metagenomics, metatranscriptomics, or metabolomics to maximize the probability of finding effective probiotic candidates, which can then be isolated in culture and tested in persistence and clinical trials. An effective mitigation strategy to ameliorate chytridiomycosis and other emerging infectious diseases is necessary; the advancement of omic methods and the integration of multiple omic data provide a promising avenue toward conservation of imperiled species.

Reid, G., Kumar, H., Khan, A. I., Rautava, S., Tobin, J., and Salminen, S. The case in favour of probiotics before, during and after pregnancy: insights from the first 1,500 days. Benef.Microbes. 2016; 7(3):353-362.

ABSTRACT: Successful human reproduction requires microbial homeostasis in the female reproductive tract, and colonisation of the newborn with beneficial microbes. In order to prevent several complications associated with dysbiosis, the administration of probiotics is more often being considered. The objective of the enclosed review was to examine the rationale for probiotic utility before and during pregnancy and in the early phase of infant life. The conclusions emerged from a panel of researchers who met during the International Scientific Association for Probiotics and Prebiotics (ISAPP) workshop held in Washington, DC, USA in 2015. The group concluded based upon the current literature, that a case can be made for the use of a specific sets of probiotic organisms during the first 1,500 days of life, with the goal of a healthy pregnancy to term, and a healthy start to life with lowered risk of infections and inflammatory events. The key to successfully translating these recommendations to practice is that products be made available and affordable to women in developed and developing countries.

Reis, N. A., Saraiva, M. A., Duarte, E. A., de Carvalho, E. A., Vieira, B. B., and Evangelista-Barreto, N. S. Probiotic properties of lactic acid bacteria isolated from human milk. J.Appl.Microbiol. 5-9-2016;

ABSTRACT: AIM: The objective of this study was to identify and characterize lactic acid bacteria isolated from human milk, with an emphasis on their probiotic properties. METHODS AND RESULTS: The strains were tested for their ability to inhibit growth of Enterococcus faecalis, Salmonella enterica subsp. enterica serotype Enteritidis, Listeria monocytogenes, Staphylococcus aureus and Escherichia coli, as well as for susceptibility to antimicrobial agents and for acid pH and bile salt tolerance. Gram-positive and catalase-negative were selected and identified as Enterococcus (83.3%) after sequencing the 16S rDNA gene. All the isolates inhibited growth of Ent. faecalis and S. serotype Enteritidis, 97% inhibited growth of L. monocytogenes and Staph. aureus and 78.8% inhibited growth of E. coli. Most of the isolates were resistant to gentamicin (50%) and vancomycin (47%). Twelve isolates grew when subjected to pH 3.0 and 0.1% bile salts. At lower pH (2.5-2.0), Ent. faecalis F1 and Weissella confusa F8 were more efficient. CONCLUSION: It was possible to isolate from human milk the lactic acid bacteria with potential for use as probiotics. SIGNIFICANCE AND IMPACT OF THE STUDY: Lactic acid bacteria isolated of nursing mothers have probiotic properties.

Ribeiro, Cde M., Zorgi, N. E., Meireles, L. R., Garcia, J. L., and de Andrade Junior, H. F. CD19 LYMPHOCYTE PROLIFERATION INDUCED BY Bifidobacterium animalis subsp. lactis IN C57BL/6 MICE EXPERIMENTALLY INFECTED WITH Toxoplasma gondii. Rev.Inst.Med.Trop.Sao Paulo. 2016; 58:26

ABSTRACT: Toxoplasmosis is frequently acquired through the oral route by the ingestion of cysts or oocysts of Toxoplasma gondii. Once ingested, the parasites penetrate the intestinal epithelial cells and rapidly disseminate to all organs in the host. During T. gondii infection, the intestinal microbiota plays an important role in stimulating a protective immune response against the parasite. In this sense the use of probiotics is worthy of note since they are live microorganisms that have beneficial effects on the host through stimulation of the immune response that can be important in the control of T. gondii

proliferation and dissemination in the host. In the present study, the action of the probiotic Bifidobacterium animalis subsp. lactis was investigated in C57BL/6 mice infected with oocysts of ME49 strain of T. gondii. The probiotic had an immunomodulatory action, inducing CD19 lymphocyte proliferation and consequently increasing anti-T. gondii antibody level. Bifidobacterium animalis subsp. lactis provided protection in supplemented mice, compared to the control group. In addition, supplemented animals had milder inflammatory process in the small intestine, indicating that the probiotic protects the intestinal mucosa during infection with T. gondii. It was concluded that the probiotic B. animalis subsp. lactis induces humoral immune response capable of providing protection against T. gondii infection.

Ricci, G., Cipriani, F., Cuello-Garcia, C. A., Brozek, J. L., Fiocchi, A., Pawankar, R., Yepes-Nunes, J. J., Terraciano, L., Gandhi, S., Agarwal, A., Zhang, Y., and Schunemann, H. J. A clinical reading on "World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics". World Allergy Organ J. 2016; 9:9.

No abstract currently available.

Richards, J. L., Yap, Y. A., McLeod, K. H., Mackay, C. R., and Marino, E. Dietary metabolites and the gut microbiota: an alternative approach to control inflammatory and autoimmune diseases. Clin.Transl.Immunology. 2016; 5(5):e82

ABSTRACT: It is now convincingly clear that diet is one of the most influential lifestyle factors contributing to the rise of inflammatory diseases and autoimmunity in both developed and developing countries. In addition, the modern 'Western diet' has changed in recent years with increased caloric intake, and changes in the relative amounts of dietary components, including lower fibre and higher levels of fat and poor quality of carbohydrates. Diet shapes large-bowel microbial ecology, and this may be highly relevant to human diseases, as changes in the gut microbiota composition are associated with many inflammatory diseases. Recent studies have demonstrated a remarkable role for diet, the gut microbiota and their metabolites-the short-chain fatty acids (SCFAs)-in the pathogenesis of several inflammatory diseases, such as asthma, arthritis, inflammatory bowel disease, colon cancer and wound-healing. This review summarizes how diet, microbiota and gut microbial metabolites (particularly SCFAs) can modulate the progression of inflammatory diseases and autoimmunity, and reveal the molecular mechanisms (metabolite-sensing G protein-coupled receptor (GPCRs) and inhibition of histone deacetylases (HDACs)). Therefore, considerable benefit could be achieved simply through the use of diet, probiotics and metabolites for the prevention and treatment of inflammatory diseases and autoimmunity.

Riddle, M. S. and Connor, B. A. The Traveling Microbiome. Curr.Infect.Dis.Rep. 2016; 18(9):29

ABSTRACT: Given the recent interest in the human gut microbiome in health and disease, we have undertaken a review of the role of the gut microbiome as it relates to travel. Considering the microbiome as the interface with the external world of the traveler, not only from the perspective of protection from enteric infection by colonization resistance but also the possibility that a traveler's unique microbiome may place him or her at lesser or greater risk for enteric infection. We review available data on travel, travelers' diarrhea, and the use of antibiotics as it relates to changes in the microbiome and the acquisition of multi-drug-resistant bacteria and explore the interplay of these factors in

the development of dysbiosis and the post-infectious sequelae of TD, specifically PI-IBS. In addition, we explore whether dietary changes in travel affect the gut microbiome in a way which modulates gastrointestinal function and susceptibility to infection and discuss whether pre- or probiotics have any meaningful role in prevention or treatment of TD. Finally, a discussion of important research gaps and opportunities in this area is identified.

Rigo-Adrover, M., Saldana-Ruiz, S., van, Limpt K., Knipping, K., Garssen, J., Knol, J., Franch, A., Castell, M., and Perez-Cano, F. J. A combination of scGOS/lcFOS with Bifidobacterium breve M-16V protects suckling rats from rotavirus gastroenteritis. Eur.J.Nutr. 4-25-2016;

ABSTRACT: PURPOSE: Rotavirus (RV) is the leading cause of severe diarrhoea among infants and young children, and although more standardized studies are needed, there is evidence that probiotics can help to fight against RV and other infectious and intestinal pathologies. On the other hand, the effects of prebiotics have not been properly addressed in the context of an RV infection. The aim of this study was to demonstrate a protective role for a specific scGOS/lcFOS 9:1 prebiotic mixture (PRE) separately, the probiotic Bifidobacterium breve M-16V (PRO) separately and the combination of the prebiotic mixture and the probiotic (synbiotic, SYN) in a suckling rat RV infection model. METHODS: The animals received the intervention from the 3rd to the 21st day of life by oral gavage. On day 7, RV was orally administered. Clinical parameters and immune response were evaluated. RESULTS: The intervention with the PRO reduced the incidence, severity and duration of the diarrhoea ($p < 0.05$). The PRE and SYN products improved clinical parameters as well, but a change in stool consistency induced by the PRE intervention hindered the observation of this effect. Both the PRE and the SYN, but not the PRO, significantly reduced viral shedding. All interventions modulated the specific antibody response in serum and intestinal washes at day 14 and 21 of life. CONCLUSIONS: A daily supplement of a scGOS/lcFOS 9:1 prebiotic mixture, Bifidobacterium breve M-16V or a combination of both is highly effective in modulating RV-induced diarrhoea in this preclinical model.

Ripert, G., Racedo, S. M., Elie, A. M., Jacquot, C., Bressollier, P., and Urdaci, M. C. Secreted Compounds of the Probiotic Bacillus clausii Strain O/C Inhibit the Cytotoxic Effects Induced by Clostridium difficile and Bacillus cereus Toxins. Antimicrob.Agents Chemother. 2016; 60(6):3445-3454.

ABSTRACT: Although the use of probiotics based on Bacillus strains to fight off intestinal pathogens and antibiotic-associated diarrhea is widespread, the mechanisms involved in producing their beneficial effects remain unclear. Here, we studied the ability of compounds secreted by the probiotic Bacillus clausii strain O/C to counteract the cytotoxic effects induced by toxins of two pathogens, Clostridium difficile and Bacillus cereus, by evaluating eukaryotic cell viability and expression of selected genes. Coincubation of C. difficile and B. cereus toxic culture supernatants with the B. clausii supernatant completely prevented the damage induced by toxins in Vero and Caco-2 cells. The hemolytic effect of B. cereus was also avoided by the probiotic supernatant. Moreover, in these cells, the expression of rhoB, encoding a Rho GTPase target for C. difficile toxins, was normalized when C. difficile supernatant was pretreated using the B. clausii supernatant. All of the beneficial effects observed with the probiotic were abolished by the serine protease inhibitor phenylmethylsulfonyl fluoride (PMSF). Suspecting the involvement of a secreted protease in this protective effect, a protease was purified from the B. clausii supernatant and identified as a serine protease (M-

protease; GenBank accession number Q99405). Experiments on Vero cells demonstrated the antitoxic activity of the purified protease against pathogen supernatants. This is the first report showing the capacity of a protease secreted by probiotic bacteria to inhibit the cytotoxic effects of toxinogenic C. difficile and B. cereus strains. This extracellular compound could be responsible, at least in part, for the protective effects observed for this human probiotic in antibiotic-associated diarrhea.

Riviere, A., Selak, M., Lantin, D., Leroy, F., and De, Vuyst L. Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and Strategies for Their Stimulation in the Human Gut. Front Microbiol. 2016; 7:979

ABSTRACT: With the increasing amount of evidence linking certain disorders of the human body to a disturbed gut microbiota, there is a growing interest for compounds that positively influence its composition and activity through diet. Besides the consumption of probiotics to stimulate favorable bacterial communities in the human gastrointestinal tract, prebiotics such as inulin-type fructans (ITF) and arabinoxylan-oligosaccharides (AXOS) can be consumed to increase the number of bifidobacteria in the colon. Several functions have been attributed to bifidobacteria, encompassing degradation of non-digestible carbohydrates, protection against pathogens, production of vitamin B, antioxidants, and conjugated linoleic acids, and stimulation of the immune system. During life, the numbers of bifidobacteria decrease from up to 90% of the total colon microbiota in vaginally delivered breast-fed infants to <5% in the colon of adults and they decrease even more in that of elderly as well as in patients with certain disorders such as antibiotic-associated diarrhea, inflammatory bowel disease, irritable bowel syndrome, obesity, allergies, and regressive autism. It has been suggested that the bifidogenic effects of ITF and AXOS are the result of strain-specific yet complementary carbohydrate degradation mechanisms within cooperating bifidobacterial consortia. Except for a bifidogenic effect, ITF and AXOS also have shown to cause a butyrogenic effect in the human colon, i.e., an enhancement of colon butyrate production. Butyrate is an essential metabolite in the human colon, as it is the preferred energy source for the colon epithelial cells, contributes to the maintenance of the gut barrier functions, and has immunomodulatory and anti-inflammatory properties. It has been shown that the butyrogenic effects of ITF and AXOS are the result of cross-feeding interactions between bifidobacteria and butyrate-producing colon bacteria, such as Faecalibacterium prausnitzii (clostridial cluster IV) and Anaerostipes, Eubacterium, and Roseburia species (clostridial cluster XIVa). These kinds of interactions possibly favor the co-existence of bifidobacterial strains with other bifidobacteria and with butyrate-producing colon bacteria in the human colon.

Rolny, I. S., Tiscornia, I., Racedo, S. M., Perez, P. F., and Bollati-Fogolin, M. Lactobacillus delbrueckii subsp lactis CIDCA 133 modulates response of human epithelial and dendritic cells infected with Bacillus cereus. Benef.Microbes. 7-26-2016; 1-12.

ABSTRACT: It is known that probiotic microorganisms are able to modulate pathogen virulence. This ability is strain dependent and involves multiple interactions between microorganisms and relevant host's cell populations. In the present work we focus on the effect of a potentially probiotic lactobacillus strain (Lactobacillus delbrueckii subsp. lactis CIDCA 133) in an in vitro model of Bacillus cereus infection. Our results showed that infection of intestinal epithelial HT-29 cells by B. cereus induces nuclear factor kappa B (NF-kappaB) pathway. Noteworthy, the presence of strain L. delbrueckii subsp.lactis

CIDCA 133 increases stimulation. However, B. cereus-induced interleukin (IL)-8 production by epithelial cells is partially abrogated by L. delbrueckii subsp. lactis CIDCA 133. These findings suggest that signalling pathways other than that of NF-kappaB are involved. In a co-culture system (HT-29 and monocyte-derived dendritic cells), B. cereus was able to translocate from the epithelial (upper) to the dendritic cell compartment (lower). This translocation was partially abrogated by the presence of lactobacilli in the upper compartment. In addition, infection of epithelial cells in the co-culture model, led to an increase in the expression of CD86 by dendritic cells. This effect could not be modified in the presence of lactobacilli. Interestingly, infection of enterocytes with B. cereus triggers production of proinflammatory cytokines by dendritic cells (IL-8, IL-6 and tumour necrosis factor alpha (TNF-alpha)). The production of TNF-alpha (a protective cytokine in B. cereus infections) by dendritic cells was increased in the presence of lactobacilli. The present work demonstrates for the first time the effect of L. delbrueckii subsp. lactis CIDCA 133, a potentially probiotic strain, in an in vitro model of B. cereus infection. The presence of the probiotic strain modulates cell response both in infected epithelial and dendritic cells thus suggesting a possible beneficial effect of selected lactobacilli strains on the course of B. cereus infection.

Rossi, M., Martinez-Martinez, D., Amaretti, A., Ulrici, A., Raimondi, S., and Moya, A. Mining metagenomic whole genome sequences revealed subdominant but constant Lactobacillus population in the human gut microbiota. Environ.Microbiol.Rep. 2016; 8(3):399-406.

ABSTRACT: The genus Lactobacillus includes over 215 species that colonize plants, foods, sewage and the gastrointestinal tract (GIT) of humans and animals. In the GIT, Lactobacillus population can be made by true inhabitants or by bacteria occasionally ingested with fermented or spoiled foods, or with probiotics. This study longitudinally surveyed Lactobacillus species and strains in the feces of a healthy subject through whole genome sequencing (WGS) data-mining, in order to identify members of the permanent or transient populations. In three time-points (0, 670 and 700 d), 58 different species were identified, 16 of them being retrieved for the first time in human feces. L. rhamnosus, L. ruminis, L. delbrueckii, L. plantarum, L. casei and L. acidophilus were the most represented, with estimated amounts ranging between 6 and 8 Log (cells g(-1)), while the other were detected at 4 or 5 Log (cells g(-1)). 86 Lactobacillus strains belonging to 52 species were identified. 43 seemingly occupied the GIT as true residents, since were detected in a time span of almost 2 years in all the three samples or in 2 samples separated by 670 or 700 d. As a whole, a stable community of lactobacilli was disclosed, with wide and understudied biodiversity.

Saab, S., Suraweera, D., Au, J., Saab, E. G., Alper, T. S., and Tong, M. J. Probiotics are helpful in hepatic encephalopathy: a meta-analysis of randomized trials. Liver Int. 2016; 36(7):986-993.

ABSTRACT: BACKGROUND: Hepatic encephalopathy (HE) is a major complication of cirrhosis and is associated with decreased survival and increased health care utilization. AIM: The aim of this study was to evaluate the efficacy of probiotics in the management minimal hepatic encephalopathy HE (MHE) and overt HE (OHE) in comparison to no treatment/placebo and lactulose. METHODS: The main outcomes measured were mortality, improvement in MHE, progression to OHE in patients with MHE and hospitalization. We calculated odds ratios (OR) with 95% confidence intervals (CI). Study

heterogeneity was assessed using the I(2) statistic. RESULTS: Fourteen studies totalling 1152 patients were included in the analysis. The use of probiotics had no impact on the overall mortality when compared to either lactulose (OR: 1.07, 95% CI: 0.47-2.44, P = 0.88) or no treatment/placebo (OR: 0.69, 95% CI: 0.42-1.14, P = 0.15). When probiotics was compared to no treatment/placebo, it was associated with a significant improvement in MHE (OR: 3.91, 95% CI: 2.25-6.80, P < 0.00001), decreased hospitalization rates (OR: 0.53, 95% CI: 0.33-0.86, P = 0.01) and decreased progression to overt hepatic encephalopathy (OR: 0.40, 95% CI: 0.26-0.60, P < 0.0001). However when compared to lactulose, probiotics did not show a significant difference in improvement of MHE (OR: 0.81, 95% CI: 0.52-1.27, P = 0.35), hospitalization rates (OR: 1.02, 95% CI: 0.52-1.99, P = 0.96) or progression to overt hepatic encephalopathy (OR: 1.24, 95% CI 0.73-2.10, P = 0.42). CONCLUSIONS: Overall the use of probiotics was more effective in decreasing hospitalization rates, improving MHE and preventing progression to OHE in patients with underlying MHE than placebo, but similar to that seen with lactulose. The use of probiotics did not affect mortality rates.

Saez-Lara, M. J., Robles-Sanchez, C., Ruiz-Ojeda, F. J., Plaza-Diaz, J., and Gil, A. Effects of Probiotics and Synbiotics on Obesity, Insulin Resistance Syndrome, Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease: A Review of Human Clinical Trials. Int.J.Mol.Sci. 2016; 17(6)

ABSTRACT: The use of probiotics and synbiotics in the prevention and treatment of different disorders has dramatically increased over the last decade. Both probiotics and synbiotics are well known ingredients of functional foods and nutraceuticals and may provide beneficial health effects because they can influence the intestinal microbial ecology and immunity. The present study reviews the effects of probiotics and synbiotics on obesity, insulin resistance syndrome (IRS), type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) in human randomized clinical trials. Select probiotics and synbiotics provided beneficial effects in patients with obesity, mainly affecting the body mass index and fat mass. Some probiotics had beneficial effects on IRS, decreasing the cell adhesion molecule-1 levels, and the synbiotics decreased the insulin resistance and plasma lipid levels. Moreover, select probiotics improved the carbohydrate metabolism, fasting blood glucose, insulin sensitivity and antioxidant status and also reduced metabolic stress in subjects with T2D. Some probiotics and synbiotics improved the liver and metabolic parameters in patients with NAFLD. The oral intake of probiotics and synbiotics as co-adjuvants for the prevention and treatment of obesity, IRS, T2D and NAFLD is partially supported by the data shown in the present review. However, further studies are required to understand the precise mechanism of how probiotics and synbiotics affect these metabolic disorders.

Safari, R., Adel, M., Lazado, C. C., Caipang, C. M., and Dadar, M. Host-derived probiotics Enterococcus casseliflavus improves resistance against Streptococcus iniae infection in rainbow trout (Oncorhynchus mykiss) via immunomodulation. Fish.Shellfish.Immunol. 2016; 52:198-205.

ABSTRACT: The present study evaluated the benefits of dietary administration of host-derived candidate probiotics Enterococcus casseliflavus in juvenile rainbow trout Oncorhynchus mykiss. Experimental diets were prepared by incorporating the microorganisms in the basal feed at 3 inclusion levels (i.e. 10(7) CFU g(-1) of feed [T1], 10(8) CFU g(-1) of feed [T2], 10(9) CFU g(-1) of feed [T3]). The probiotic feeds were administered for 8 weeks, with a group fed with the basal diet serving as control. The

effects on growth performance, gut health, innate immunity and disease resistance were evaluated. Results showed that growth performance parameters were significantly improved in T2 and T3 groups. Activities of digestive enzymes such as trypsin and lipase were significantly higher in these two groups as well. Gut micro-ecology was influenced by probiotic feeding as shown by the significant increase in intestinal lactic acid bacteria and total viable aerobic counts in T2 and T3. Humoral immunity was impacted by dietary probiotics as total serum protein and albumin were significantly elevated in T3. The levels of serum IgM significantly increased in all probiotic fed groups at week 8; with the T3 group registering the highest increment. Respiratory burst activity of blood leukocytes were significantly improved in T2 and T3. Hematological profiling further revealed that neutrophil counts significantly increased in all probiotic fed groups. Challenge test showed that probiotic feeding significantly improved host resistance to Streptococcus iniae infection, specifically in T2 and T3 where a considerable modulation of immune responses was observed. Taken together, this study demonstrated E. casseliflavus as a potential probiotics for rainbow trout with the capability of improving growth performance and enhancing disease resistance by immunomodulation.

Sah, B. N., Vasiljevic, T., McKechnie, S., and Donkor, O. N. Antibacterial and antiproliferative peptides in synbiotic yogurt-Release and stability during refrigerated storage. J.Dairy Sci. 2016; 99(6):4233-4242.

ABSTRACT: The search for alternative therapeutics is on the rise due to the extensive increase in bacterial resistance to various conventional antibiotics and side effects of conventional cancer therapies. Bioactive peptides released from natural sources such as dairy foods by lactic acid bacteria have received attention as a potential source of biotherapeutic peptides. However, liberation of peptides in yogurt depends on proteolytic activities of the cultures used. Thus, this research was conducted to establish generation of inhibitory peptides in yogurt against pathogenic bacteria and cancer cells during storage at 4 degrees C for 28d. Water-soluble crude peptide extracts were prepared by high-speed centrifugation of plain and probiotic yogurts supplemented with or without pineapple peel powder (PPP). The inhibition zones against Escherichia coli and Staphylococcus aureus by PPP-fortified probiotic yogurt at 28d of storage were, respectively, 25.89 and 11.72mm in diameter, significantly higher than that of nonsupplemented control yogurts. Antiproliferative activity against HT29 colon cancer cells was also significantly higher in probiotic yogurt with PPP than in nonsupplemented probiotic yogurt. Overall, crude water-soluble peptide extracts of the probiotic yogurt with PPP possessed stronger inhibitory activities against bacteria and cancer cells than controls, and these activities were maintained during storage. However, activities were lowered substantially during in vitro gastrointestinal digestion. These findings support the possibility of utilizing dairy-derived bioactive peptides in the development of a superior alternative to the current generation of antibacterial and anticancer agents, as well as a functional ingredient in foods, nutraceuticals, and pharmaceuticals.

Saha, C., Mukherjee, G., Agarwal, Banka P., and Seal, A. A consortium of non-rhizobial endophytic microbes from Typha angustifolia functions as probiotics in rice and improves nitrogen metabolism. Plant Biol.(Stuttg). 7-25-2016;

ABSTRACT: 1.Endophytic microbes isolated from plants growing in nutrient poor environments often possess properties that improve nutrition when applied to agriculturally important plants. 2.Ten endophytic bacteria isolated from Typha

angustifolia growing in the marginal wetlands associated with a Uranium mine in India were characterized for their plant growth promoting mechanisms and were found to have biological nitrogen (N) fixing properties. These were used as a consortium for their ability to function as bio-fertilizer and their effect on N-metabolism in rice was tested. 3.Evidence of recent horizontal gene transfer events of dinitrogen reductase gene from a Pseudomonas stutzeri strain within the consortium was found among these microbes. The consortium behaved as plant probiotic and showed substantial growth benefits to Typha, their natural host as well as to rice. Plant biomass, shoot length and chlorophyll content were increased in rice plants in response to microbe treatment under N-sufficient as well as deficient conditions. At least some of these microbes inhabited the rice endosphere indicating their broad host range. 4.Up-regulation of nitrate and ammonium uptake genes together with the N-assimilation genes, increased N-content and relative nitrogen use efficiency suggested that the endophytic consortium triggered a long term nitrogen deficiency response in the treated plants improving both uptake and assimilation of nitrogen. This article is protected by copyright. All rights reserved.

Saiki, A., Ishida, Y., Segawa, S., Hirota, R., Nakamura, T., and Kuroda, A. A Lactobacillus mutant capable of accumulating long-chain polyphosphates that enhance intestinal barrier function. Biosci.Biotechnol.Biochem. 2016; 80(5):955-961.

ABSTRACT: Inorganic polyphosphate (polyP) was previously identified as a probiotic-derived substance that enhances intestinal barrier function. PolyP-accumulating bacteria are expected to have beneficial effects on the human gastrointestinal tract. In this study, we selected Lactobacillus paracasei JCM 1163 as a strain with the potential to accumulate polyP, because among the probiotic bacteria stored in our laboratory, it had the largest amount of polyP. The chain length of polyP accumulated in L. paracasei JCM 1163 was approximately 700 phosphate (Pi) residues. L. paracasei JCM 1163 accumulated polyP when Pi was added to Pi-starved cells. We further improved the ability of L. paracasei JCM 1163 to accumulate polyP by nitrosoguanidine mutagenesis. The mutant accumulated polyP at a level of 1500 nmol/mg protein-approximately 190 times that of the wild-type strain. PolyP extracted from the L. paracasei JCM 1163 significantly suppressed the oxidant-induced intestinal permeability in mouse small intestine. In conclusion, we have succeeded in breeding the polyP-accumulating Lactobacillus mutant that is expected to enhance intestinal barrier function.

Saint-Cyr, M. J., Guyard-Nicodeme, M., Messaoudi, S., Chemaly, M., Cappelier, J. M., Dousset, X., and Haddad, N. Recent Advances in Screening of Anti-Campylobacter Activity in Probiotics for Use in Poultry. Front Microbiol. 2016; 7:553

ABSTRACT: Campylobacteriosis is the most common cause of bacterial gastroenteritis worldwide. Campylobacter species involved in this infection usually include the thermotolerant species Campylobacter jejuni. The major reservoir for C. jejuni leading to human infections is commercial broiler chickens. Poultry flocks are frequently colonized by C. jejuni without any apparent symptoms. Risk assessment analyses have identified the handling and consumption of poultry meat as one of the most important sources of human campylobacteriosis, so elimination of Campylobacter in the poultry reservoir is a crucial step in the control of this foodborne infection. To date, the use of probiotics has demonstrated promising results to reduce Campylobacter colonization. This review provides recent insights into methods used for probiotic screening to reduce the prevalence and colonization of Campylobacter at the farm level. Different eukaryotic

epithelial cell lines are employed to screen probiotics with an anti-Campylobacter activity and yield useful information about the inhibition mechanism involved. These in vitro virulence models involve only human intestinal or cervical cell lines whereas the use of avian cell lines could be a preliminary step to investigate mechanisms of C. jejuni colonization in poultry in the presence of probiotics. In addition, in vivo trials to evaluate the effect of probiotics on Campylobacter colonization are conducted, taking into account the complexity introduced by the host, the feed, and the microbiota. However, the heterogeneity of the protocols used and the short time duration of the experiments lead to results that are difficult to compare and draw conclusions at the slaughter-age of broilers. Nevertheless, the combined approach using complementary in vitro and in vivo tools (cell cultures and animal experiments) leads to a better characterization of probiotic strains and could be employed to assess reduced Campylobacter spp. colonization in chickens if some parameters are optimized.

Salazar, N., Gueimonde, M., de Los Reyes-Gavilan CG, and Ruas-Madiedo, P. Exopolysaccharides Produced by Lactic Acid Bacteria and Bifidobacteria as Fermentable Substrates by the Intestinal Microbiota. Crit Rev.Food Sci.Nutr. 7-3-2016; 56(9):1440-1453.

ABSTRACT: The functional food market, including products formulated to maintain a "healthy" gut microbiota, i.e. probiotics and prebiotics, has increased enormously since the end of the last century. In order to favor the competitiveness of this sector, as well as to increase our knowledge of the mechanisms of action upon human health, new probiotic strains and prebiotic substrates are being studied. This review discusses the use of exopolysaccharides (EPS), both homopolysaccharides (HoPS) and heteropolysaccharides (HePS), synthesized by lactic acid bacteria and bifidobacteria as potential prebiotics. These extracellular carbohydrate polymers synthesized by some gut inhabitants seem to be resistant to gastrointestinal digestion; these are susceptible as well to biodegradability by the intestinal microbiota depending on both the physicochemical characteristics of EPS and the pool of glycolytic enzymes harbored by microbiota. Therefore, although the chemical composition of these HoPS and HePS is different, both can be fermentable substrates by intestinal inhabitants and good candidates as prebiotic substrates. However, there are limitations for their use as additives in the food industry due to, on the one hand, their low production yield and, on the other hand, a lack of clinical studies demonstrating the functionality of these biopolymers.

Saliganti, V., Kapila, R., and Kapila, S. Consumption of probiotic Lactobacillus rhamnosus (MTCC: 5897) containing fermented milk plays a key role in development of the immune system in newborn mice during the suckling-weaning transition. Microbiol.Immunol. 2016; 60(4):261-267.

ABSTRACT: Early infancy, the period when offspring rely not only on their own immunity to combat food-borne antigens but also acquire immunity through maternal sources (via transplacental routes and breast milk), is critical for immune system development Hence the present study was designed to evaluate the effect on offspring of administration of probiotic-containing fermented milk (PFM) either to mothers during the suckling period or to their offspring after weaning either separately or sequentially. PFM-fed mice showed enhanced leukocyte functionality in offspring as evidenced by significantly ($P < 0.05$) increased release of lysosomal enzymes (beta-galactosidase, beta-glucuronidase) in peritoneal fluid and nitric oxide production in culture supernatants of activated

macrophages. Further, remarkably reduced levels ($P < 0.01$) of inflammatory markers (TNF-alpha, monocyte chemotactic protein-1) and allergic antibodies (total and milk specific IgE) were observed in offspring where PFM was fed either to them or to their mothers. However, considerably increased levels ($P < 0.05$) of SIgA were found in the guts of control and experimental groups animals irrespective of their exposure to PFM. Restoration of Th1/Th2 homeostasis further confirmed the useful effects of PFM supplementation by shifting the cytokine profile (IL-4, IFN-gamma and IL-10) with increased IFN-gamma/IL-4 and reduced IgE/Ig2Ga ratios. Hence, it is logical to conclude that administration of Lactobacillus rhamnosus-containing (MTCC:5897) fermented milk to mothers during the suckling period and to their offspring after weaning has beneficial effects on the development of newborns immune systems; this effect appears to be more pronounced when mothers are fed with it.

Salvetti, E., Orru, L., Capozzi, V., Martina, A., Lamontanara, A., Keller, D., Cash, H., Felis, G. E., Cattivelli, L., Torriani, S., and Spano, G. Integrate genome-based assessment of safety for probiotic strains: Bacillus coagulans GBI-30, 6086 as a case study. Appl.Microbiol.Biotechnol. 2016; 100(10):4595-4605.

ABSTRACT: Probiotics are microorganisms that confer beneficial effects on the host; nevertheless, before being allowed for human consumption, their safety must be verified with accurate protocols. In the genomic era, such procedures should take into account the genomic-based approaches. This study aims at assessing the safety traits of Bacillus coagulans GBI-30, 6086 integrating the most updated genomics-based procedures and conventional phenotypic assays. Special attention was paid to putative virulence factors (VF), antibiotic resistance (AR) genes and genes encoding enzymes responsible for harmful metabolites (i.e. biogenic amines, BAs). This probiotic strain was phenotypically resistant to streptomycin and kanamycin, although the genome analysis suggested that the AR-related genes were not easily transferrable to other bacteria, and no other genes with potential safety risks, such as those related to VF or BA production, were retrieved. Furthermore, no unstable elements that could potentially lead to genomic rearrangements were detected. Moreover, a workflow is proposed to allow the proper taxonomic identification of a microbial strain and the accurate evaluation of risk-related gene traits, combining whole genome sequencing analysis with updated bioinformatics tools and standard phenotypic assays. The workflow presented can be generalized as a guideline for the safety investigation of novel probiotic strains to help stakeholders (from scientists to manufacturers and consumers) to meet regulatory requirements and avoid misleading information.

Samah, S., Ramasamy, K., Lim, S. M., and Neoh, C. F. Probiotics for the management of type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Res.Clin.Pract. 2016; 118:172-182.

ABSTRACT: AIMS: To systematically review evidence of probiotic interventions against type 2 diabetes mellitus (T2DM) and analyse the effects of probiotics on glycaemic control among T2DM patients. METHODS: Electronic search using five electronic databases was performed until October 2015. Relevant studies were identified, extracted and assessed for risk of bias. The primary outcomes of this review were glycated haemoglobin (HbA1c) and fasting blood glucose (FBG). Fasting plasma insulin, homeostasis model assessment-insulin resistance, C-reactive protein, interleukin-6 and malondialdehyde, were identified as the secondary outcomes. Mean differences (MD)

between probiotics and control groups for all outcomes were pooled using either Fixed- or Random-Effect Model. Statistical heterogeneity was assessed using I(2) and Chi(2) tests. RESULTS: Six randomised controlled trials (RCTs) were included in the systematic review, whereas only five were included in meta-analysis. Most RCTs were presented with low or unclear risk of bias. When compared to placebo, FBG was significantly lower with probiotic consumption (MD=-0.98mmol/L; 95% CI: -1.17, 0.78, p<0.00001), with moderate but insignificant heterogeneity noted. Insignificant changes between the groups were also noted for HbA1c and other secondary outcomes. CONCLUSIONS: A moderate hypoglycaemic effect of probiotics, with a significantly lower FBG was noted. Findings on HbA1c, anti-inflammatory and anti-oxidative effects of probiotics in the clinical setting, however, remain inconsistent. The findings imply the need for well-designed clinical studies to further assess the potential beneficial effects of probiotics in management of T2DM.

Sanchart, C., Rattanaporn, O., Haltrich, D., Phukpattaranont, P., and Maneerat, S. Technological and safety properties of newly isolated GABA-producing Lactobacillus futsaii strains. J.Appl.Microbiol. 5-4-2016;

ABSTRACT: AIM: To evaluate the technological and safety properties of Lactobacillus futsaii CS3 and CS5 isolated from Thai fermented shrimp products (Kung-Som) in order to develop a valuable gamma-aminobutyric acid (GABA)-producing starter culture. METHODS AND RESULTS: Both strains showed a high GABA-producing ability (>8 mg ml-1) in MRS broth containing 20 mg ml-1 monosodium glutamate (MSG) for 120 h. They also exhibited inhibitory activity against foodborne pathogens and spoilage bacteria. Cell surface hydrophobicity and proteolytic activity were observed in both strains. Strain CS3 survived better under simulated gastrointestinal tract conditions with only 1.5 log-units cell decrease over 8 h. Both strains showed the ability to deconjugate taurocholate and taurodeoxycholate acid. Neither virulence genes nor biogenic amine production was detected. Strain CS3 exhibited susceptibility to all tested antibiotics with the exception of vancomycin, while strain CS5 showed resistance to vancomycin, ampicillin and chloramphenicol. CONCLUSIONS: Based on the results obtained, Lact. futsaii CS3 is very promising as a GABA-producing and potentially probiotic starter culture strain for applications in functional fermented foods. SIGNIFICANCE AND IMPACT OF THE STUDY: This study focuses on the technological and safety characteristics of Lact. futsaii CS3 and CS5 including their high GABA-producing capacity for the first time. This provides a way of replacing chemical GABA by natural GABA using a GABA-producing starter culture candidate, at the same time offering the consumer new attractive food products.

Sanchez-Tamayo, T., Espinosa Fernandez, M. G., Affumicato, L., Gonzalez, Lopez M., Fernandez, Romero, V, Moreno Algarra, M. C., and Salguero, Garcia E. [Reduction in necrotising enterocolitis after implementing an evidence-based enteral nutrition protocol in very low birth weight newborns]. An.Pediatr.(Barc.). 7-18-2016;

ABSTRACT: INTRODUCTION: An unexpected increase in the incidence of necrotising enterocolitis (NEC) cases was observed in our hospital. Just in case, our feeding policy could be responsible, it was decided to conduct a systematic review and develop a clinical guideline regarding enteral nutrition of very low birth weight infants (VLBW). OBJECTIVE: To assess the impact of the new feeding protocol in the incidence of NEC. METHOD: A "before" (2011) and "after" (May 2.

Sanchez, B., Delgado, S., Blanco-Miguez, A., Lourenco, A., Gueimonde, M., and Margolles, A. Probiotics, gut microbiota and their influence on host health and disease. Mol.Nutr.Food Res. 8-8-2016;

ABSTRACT: The gastrointestinal tract (GIT) of mammals hosts a high and diverse number of different microorganisms, known as intestinal microbiota. Many probiotics were originally isolated from the GIT, and they were defined by the FAO/WHO as "live microorganisms which when administered in adequate amounts confer a health benefit on the host". Probiotics exert their beneficial effects on the host through four main mechanisms: interference with potential pathogens, improvement of barrier function, immunomodulation and production of neurotransmitters, and their host targets vary from the resident microbiota to cellular components of the gut-brain axis. However, in spite of the wide array of beneficial mechanisms deployed by probiotic bacteria, relatively few effects have been supported by clinical data. In this regard, different probiotic strains have been effective in Antibiotic-Associated Diarrhea or Inflammatory Bowel Disease for instance. The aim of this review was to compile the molecular mechanisms underlying the beneficial effects of probiotics, mainly through their interaction with the intestinal microbiota and with the intestinal mucosa. The specific benefits discuss in this paper include among others those elicited directly through dietary modulation of the human gut microbiota. This article is protected by copyright. All rights reserved.

Sanders, M. E. Probiotics and microbiota composition. BMC.Med. 2016; 14(1):82

ABSTRACT: Accumulated evidence, corroborated by a new systematic review by Kristensen et al. (Genome Med 8:52, 2016), suggests that probiotics do not significantly impact the fecal microbiota composition of healthy subjects. Nevertheless, physiological benefits have been associated with probiotic consumption by healthy people. Some studies have suggested that probiotics may impact the function of colonizing microbes, although this needs to be further studied. An alternative hypothesis is that probiotics may promote homeostasis of the gut microbiota, rather than change its composition. This hypothesis warrants investigation as a possible mechanism for how probiotics may benefit healthy people.Please see related article: http://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0300-5.

Santocchi, E., Guiducci, L., Fulceri, F., Billeci, L., Buzzigoli, E., Apicella, F., Calderoni, S., Grossi, E., Morales, M. A., and Muratori, F. Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. BMC.Psychiatry. 2016; 16:183

ABSTRACT: BACKGROUND: A high prevalence of a variety of gastrointestinal (GI) symptoms is frequently reported in patients with Autism Spectrum Disorders (ASD). The GI disturbances in ASD might be linked to gut dysbiosis representing the observable phenotype of a "gut-brain axis" disruption. The exploitation of strategies which can restore normal gut microbiota and reduce the gut production and absorption of toxins, such as probiotics addition/supplementation in a diet, may represent a non-pharmacological option in the treatment of GI disturbances in ASD. The aim of this randomized controlled trial is to determine the effects of supplementation with a probiotic mixture (Vivomixx(R)) in ASD children not only on specific GI symptoms, but also on the core deficits of the disorder, on cognitive and language development, and on

brain function and connectivity. An ancillary aim is to evaluate possible effects of probiotic supplementation on urinary concentrations of phthalates (chemical pollutants) which have been previously linked to ASD. METHODS: A group of 100 preschoolers with ASD will be classified as belonging to a GI group or to a Non-GI (NGI) group on the basis of a symptom severity index specific to GI disorders. In order to obtain four arms, subjects belonging to the two groups (GI and NGI) will be blind randomized 1:1 to regular diet with probiotics or with placebo for 6 months. All participants will be assessed at baseline, after three months and after six months from baseline in order to evaluate the possible changes in: (1) GI symptoms; (2) autism symptoms severity; (3) affective and behavioral comorbid symptoms; (4) plasmatic, urinary and fecal biomarkers related to abnormal intestinal function; (5) neurophysiological patterns. DISCUSSION: The effects of treatments with probiotics on children with ASD need to be evaluated through rigorous controlled trials. Examining the impact of probiotics not only on clinical but also on neurophysiological patterns, the current trial sets out to provide new insights into the gut-brain connection in ASD patients. Moreover, results could add information to the relationship between phthalates levels, clinical features and neurophysiological patterns in ASD. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02708901 . Retrospectively registered: March 4, 2016.

Santos, C. M., Pires, M. C., Leao, T. L., Hernandez, Z. P., Rodriguez, M. L., Martins, A. K., Miranda, L. S., Martins, F. S., and Nicoli, J. R. Selection of Lactobacillus strains as potential probiotics for vaginitis treatment. Microbiology. 2016; 162(7):1195-1207.

ABSTRACT: Lactobacilli are the dominant bacteria of the vaginal tract of healthy women, and imbalance of the local microbiota can predispose women to acquire infections, such as bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC). Although antimicrobial therapy is generally effective, there is still a high incidence of recurrence and increase of microbial resistance due to the repetitive use of antimicrobials. Thus, it has been suggested that administration of probiotics incorporating selected Lactobacillus strains may be an effective strategy for preventing vaginal infections. Accordingly, the in vitro probiotic potential of 23 lactobacilli isolated from the vaginal ecosystem of healthy women from Cuba was evaluated for use in BV and VVC treatments. Eight strains were selected based on their antagonist potential against Gardnerella vaginalis, Candida albicansor both. In vitro assays revealed that all these strains reduced the pathogen counts in co-incubation, showed excellent adhesive properties (biofilm formation and auto-aggregation), were able to co-aggregate with G. vaginalis and C. albicans, yielded high amounts of hydrogen peroxide and lactic acid and demonstrated high adhesion rates to epithelial HeLa cells. Interference tests within HeLa cells showed that all strains were able to reduce the adherence of pathogens by exclusion or displacement. Lactobacilli were able to inhibit HeLa cell apoptosis caused by pathogens when the cells were incubated with the probiotics prior to challenge. These results suggest that these strains have a promising probiotic potential and can be used for prevention or treatment of BV and VVC.

Santos, M. Dos, Brito, S. de, de, A. Prado, Oliveira, G. de, Paula, C. De, Melo, C. de, and Ribeiro, A. P. Cinnamon (Cinnamomum sp.) inclusion in diets for Nile tilapia submitted to acute hypoxic stress. Fish.Shellfish.Immunol. 2016; 54:551-555.

ABSTRACT: The aim of this study was to evaluate the possible effects of diets supplemented with probiotics and different cinnamon levels (powder and essential oil)

on immunological parameters of Nile tilapia after being subjected to acute stress by hypoxia. Three hundred and thirty juvenile male tilapia fish (66.08 +/- 2.79 g) were distributed in 30 tanks of 100 L capacity (11/cage) with a water recirculation system. The animals were fed for 71 days with diets containing extruded cinnamon powder at different levels (0.5, 1, 1.5, 2%), cinnamon essential oil (0.05, 0.1, 0.15; 0.2%) and probiotics (0.4%), all in triplicate. At the end of the experiment, the fish (200.36 +/- 19.88 g) of the different groups were subjected to stress by hypoxia. Hypoxia was achieved by capturing the animals with a net, keeping them out of the water for three minutes, and then sampling the blood 30 min after the procedure to determine the levels of cortisol, glucose, haematocrit, lysozyme, bactericidal index, total protein, and its fractions. The animals kept blood homeostasis after hypoxic stress. Diet supplementation with 0.5% cinnamon powder improved the fish immune response, since it resulted in an increase of 0.5% in gamma-globulin level. Administration of 0.15% cinnamon essential oil resulted in an increase of alpha1 and alpha2-globulins, which may be reflected in increased lipid content of the carcass and the hepatosomatic index. More studies are necessary to better understand the effects of these additives for fish immunity.

Sasikumar, P., Paul, E., Gomathi, S., Abhishek, A., Sasikumar, S., and Selvam, G. S. Mobile group II intron based gene targeting in Lactobacillus plantarum WCFS1. J.Basic Microbiol. 4-27-2016;

ABSTRACT: The usage of recombinant lactic acid bacteria for delivery of therapeutic proteins to the mucosa has been emerging. In the present study, an attempt was made to engineer a thyA mutant of Lactobacillus plantarum (L. plantarum) using lactococcal group II intron LI.LtrB for the development of biologically contained recombinant L. plantarum for prevention of calcium oxalate stone disease. The 3 kb LI.LtrB intron donor cassettes from the source vector pACD4C was PCR amplified, ligated into pSIP series of lactobacillus vector pLp_3050sAmyA, yielding a novel vector pLpACD4C (8.6 kb). The quantitative real-time PCR experiment shows 94-fold increased expression of LI.LtrB intron and 14-fold increased expression of ltrA gene in recombinant L. plantarum containing pLpACD4C. In order to target the thyA gene, the potential intron RNA binding sites in the thyA gene of L. plantarum was predicted with help of computer algorithm. The insertion location 188|189s of thyA gene (lowest E-0.134) was chosen and the wild type intron LI.LtrB was PCR modified, yielding a retargeted intron of pLpACDthyA. The retargeted intron was expressed by using induction peptide (sppIP), subsequently the integration of intron in thyA gene was identified by PCR screening and finally ThyA- mutant of L. plantarum (ThyA18) was detected. In vitro growth curve result showed that in the absence of thymidine, colony forming units of mutant ThyA18 was decreased, whereas high thymidine concentration (10 muM) supported the growth of the culture until saturation. In conclusion, ThyA- mutant of L. plantarum (ThyA18) constructed in this study will be used as a biologically contained recombinant probiotic to deliver oxalate decarboxylase into the lumen for treatment of hyperoxaluria and calcium oxalate stone deposition.

Saxami, G., Papadopoulou, O. S., Chorianopoulos, N., Kourkoutas, Y., Tassou, C. C., and Galanis, A. Molecular Detection of Two Potential Probiotic Lactobacilli Strains and Evaluation of Their Performance as Starter Adjuncts in Yogurt Production. Int.J.Mol.Sci. 2016; 17(5)

ABSTRACT: A molecular method for efficient and accurate detection and identification of two potential probiotic lactobacilli strains isolated from fermented olives, namely

Lactobacillus pentosus B281 and Lb. plantarum B282, was developed in the present study. Random Amplified Polymorphic DNA (RAPD) analysis was performed, and strain specific primers were designed and applied in a multiplex polymerase chain reaction (PCR) assay. The specificity of the assay was tested and successfully confirmed in 27 and 22 lactobacilli strains for Lb. pentosus B281 and Lb. plantarum B282, respectively. Moreover, the two strains were used as starter cultures in yogurt production. Cell enumeration followed by multiplex PCR analysis demonstrated that the two strains were present in yogurt samples at levels >/=6 log CFU/g even after 35 days of storage at 4 degrees C. Microbiological analysis showed that lactobacilli and streptococci were present within usual levels, whereas enterobacteriaceae and yeast/mold counts were not detected as expected. Although the pH values of the novel products were slightly lower than the control ones, the yogurt containing the probiotic cultures scored similar values compared to the control in a series of sensory tests. Overall, these results demonstrated the possible use of the two strains as starter adjuncts in the production of yogurt with potential probiotic properties.

Scaldaferri, F., Gerardi, V., Mangiola, F., Lopetuso, L. R., Pizzoferrato, M., Petito, V., Papa, A., Stojanovic, J., Poscia, A., Cammarota, G., and Gasbarrini, A. Role and mechanisms of action of Escherichia coli Nissle 1917 in the maintenance of remission in ulcerative colitis patients: An update. World J.Gastroenterol. 6-28-2016; 22(24):5505-5511.

ABSTRACT: Ulcerative colitis (UC) is a chronic inflammatory disease, whose etiology is still unclear. Its pathogenesis involves an interaction between genetic factors, immune response and the "forgotten organ", Gut Microbiota. Several studies have been conducted to assess the role of antibiotics and probiotics as additional or alternative therapies for Ulcerative Colitis. Escherichia coli Nissle (EcN) is a nonpathogenic Gram-negative strain isolated in 1917 by Alfred Nissle and it is the active component of microbial drug Mutaflor((R)) (Ardeypharm GmbH, Herdecke, Germany and EcN, Cadigroup, In Italy) used in many gastrointestinal disorder including diarrhea, uncomplicated diverticular disease and UC. It is the only probiotic recommended in ECCO guidelines as effective alternative to mesalazine in maintenance of remission in UC patients. In this review we propose an update on the role of EcN 1917 in maintenance of remission in UC patients, including data about efficacy and safety. Further studies may be helpful for this subject to further the full use of potential of EcN.

Schaeffer, D. F., Walsh, J. C., Tyler, A. D., Ben-Bassat, O., Silverberg, M. S., Riddell, R. H., and Kirsch, R. Intraepithelial lymphocytosis is a frequent finding in biopsies from ileal pouch-anal anastomoses. Hum.Pathol. 2016; 54:31-36.

ABSTRACT: Following restorative proctocolectomy with an ileal pouch-anal anastomosis, the small bowel mucosa undergoes several specific histologic adaptions, which may be unrelated to the underlying disease or symptoms of pouchitis. An increase in intraepithelial lymphocytes (IELs) has not been described as part of this spectrum. Mucosal biopsies of the ileal pouch and afferent limb of 230 patients (mean age: 45.7y [18.3-74.7], gender [female/male]: 117/113) with a functioning ileal pouch-anal anastomosis (mean time since ileostomy closure: 10.8months) and associated clinically annotated outcome data were assessed for IELs/100 enterocytes. Forty-two patients (18.3%) showed an increase in IELs (>/=20 IELs/100 enterocytes [range 20-39]), in pouch and/or afferent limb biopsies. Intraepithelial lymphocytosis was more commonly observed in afferent limb compared to pouch biopsies (18.8% vs 8.3%; P = .42) and in

familial adenomatous polyposis compared to ulcerative colitis patients (16% vs 8%; P = 0.36), but neither difference reached statistical significance. No cases with increased IELs displayed severe villous blunting. Increased IELs were not significantly associated with age, sex, ethnicity, smoking history, time since ileostomy, use of antibiotics, biologic agents, anti-diarrheal agents or probiotics, C-reactive protein levels or differential white cell count. None of the 42 patients with increased IELs had positive celiac serology (anti-human tissue transglutaminase IgA [ELISA] with corresponding total serum IgA). Intraepithelial lymphocytosis in pouch biopsies may represent a subclinical response to an altered bacterial microenvironment. Pathologists should be aware that intraepithelial lymphocytosis is part of the spectrum of changes in pouch biopsies, and only rarely is due to celiac disease.

Schulz-Stubner, S., Textor, Z., and Anetseder, M. Fecal Microbiota Therapy as Rescue Therapy for Life-Threatening Clostridium difficile Infection in the Critically Ill: A Small Case Series. Infect.Control Hosp.Epidemiol. 7-25-2016; 1-2.

No abstract currently available.

Settachaimongkon, S., van Valenberg, H. J., Gazi, I., Nout, M. J., van Hooijdonk, T. C., Zwietering, M. H., and Smid, E. J. Influence of Lactobacillus plantarum WCFS1 on post-acidification, metabolite formation and survival of starter bacteria in set-yoghurt. Food Microbiol. 2016; 59:14-22.

ABSTRACT: The objectives of this study were to evaluate the growth and survival of the model probiotic strain Lactobacillus plantarum WCFS1 in co-culture with traditional yoghurt starters and to investigate the impact of preculturing on their survival and metabolite formation in set-yoghurt. L. plantarum WCFS1 was precultured under sublethal stress conditions (combinations of elevated NaCl and low pH) in a batch fermentor before inoculation in milk. Adaptive responses of L. plantarum WCFS1 were evaluated by monitoring bacterial population dynamics, milk acidification and changes in volatile and non-volatile metabolite profiles of set-yoghurt. The results demonstrated that sublethal preculturing did not significantly affect survival of L. plantarum WCFS1. On the other hand, incorporation of sublethally precultured L. plantarum WCFS1 significantly impaired the survival of Lactobacillus delbrueckii subsp. bulgaricus which consequently reduced the post-acidification of yoghurt during refrigerated storage. A complementary metabolomics approach using headspace SPME-GC/MS and (1)H NMR combined with multivariate statistical analysis revealed substantial impact of sublethally precultured L. plantarum WCFS1 on the metabolite profiles of set-yoghurt. This study provides insight in the technological implications of non-dairy model probiotic strain L. plantarum WCFS1, such as its good stability in fermented milk and the inhibitory effect on post-acidification.

Sha, Y., Liu, M., Wang, B., Jiang, K., Qi, C., and Wang, L. Bacterial Population in Intestines of Litopenaeus vannamei Fed Different Probiotics or Probiotic Supernatant. J.Microbiol.Biotechnol. 7-6-2016;

ABSTRACT: The interactions of microbiota in guts play an important role in promoting or maintaining the health of hosts. In this study, in order to investigate and compare the effects of dietary supplementation with Lactobacillus pentosus HC-2 (HC-2), Enterococcus faecium NRW-2, or the bacteria-free supernatant of a HC-2 culture on the

bacterial composition of Litopenaeus vannamei, Illumina sequencing of V1-V2 region of 16S rRNA gene was used. The results showed that unique species exclusively existed in specific dietary group, and the abundance of Actinobacteria was significantly increased in the intestinal bacterial community of shrimp fed with the bacteria-free supernatant of an HC-2 culture compared with the control. In addition, the histology of intestines of the shrimp from four dietary groups were also described, but no obvious improvements in the intestinal histology were observed. The findings in this work will help to promote the understanding of the roles of intestinal bacteria in shrimps when fed with probiotics or probiotic supernatant.

Shah, C., Mokashe, N., and Mishra, V. Preparation, characterization and in vitro antioxidative potential of synbiotic fermented dairy products. J.Food Sci.Technol. 2016; 53(4):1984-1992.

ABSTRACT: The present study, evaluates the antioxidative potential of two synbiotic dairy products viz. synbiotic lassi with honey and whey based synbiotic drink with inulin and orange juice, along with their physicochemical and microbiological activity during storage period. Antioxidative potential of raw ingredients and probiotic cultures used to prepare synbiotic products was also evaluated. Synbiotic lassi with honey was prepared using Streptococcus thermophilus MTCC 5460 (MD2) and Lactobacillus helveticus MTCC 5463 (V3) as probiotics and honey as prebiotic. For preparation of whey based synbiotic drink, Lactobacillus helveticus MTCC 5463 and inulin were used as probiotic and prebiotic, respectively and orange juice was also incorporated. Titratable acidity and pH of both synbiotic products followed a similar pattern of increase or decrease during storage. Furthermore, no major changes were observed in viability of probiotic cultures under storage conditions adapted. The hydroxyl radical scavenging activity of synbiotic lassi with honey was found to significantly decrease from 107.76 to 79.41 % at the end of storage whereas, the activity of whey based synbiotic drink was 100.32 % which declined sharply to 79.21 % on 7th day but further increased to 102.59 % on 14th day. The DPPH (alpha, alpha-Diphenyl-beta-Picrylhydrazyl) radical scavenging activity of freshly prepared synbiotic lassi with honey was 28.43 % which decreased to 23.03 % on 7th day while for whey based synbiotic drink decreased from 26.85 % (0 day) to 17.12 % (7th day) and continued to decline. Moreover, probiotic strains used for synbiotic preparation also demonstrated good antioxidative activity.

Shandilya, U. K., Sharma, A., Kapila, R., and Kansal, V. K. Probiotic Dahi containing Lactobacillus acidophilus and Bifidobacterium bifidum modulates immunoglobulin levels and cytokines expression in whey proteins sensitised mice. J.Sci.Food Agric. 2016; 96(9):3180-3187.

ABSTRACT: BACKGROUND: Cow milk allergy is the most common food allergy in children. So far, no effective treatment is available to prevent or cure food allergy. This study investigated whether orally administrated probiotics could suppress sensitisation in whey proteins (WP)-induced allergy mouse model. Two types of probiotic Dahi were prepared by co-culturing Dahi bacteria (Lactococcus lactis ssp. cremoris NCDC-86 and Lactococcus lactis ssp. lactis biovar diacetylactis NCDC-60) along with selected strain of Lactobacillus acidophilus LaVK2 and Bifidobacterium bifidum BbVK3. Mice were fed with probiotic Dahi (La-Dahi and LaBb-Dahi) from 7 days before sensitisation with WP, respectively, in addition to milk protein-free basal diet, and control group received no supplements. RESULTS: Feeding of probiotic Dahi suppressed the elevation of whey

proteins-specific IgE and IgG response of WP-sensitised mice. In addition, sIgA levels were significantly (P < 0.001) increased in intestinal fluid collected from mice fed with La-Dahi. Production of T helper (Th)-1 cell-specific cytokines, i.e. interferon-gamma (IFN-gamma), interleukin (IL)-12, and IL-10 increased, while Th2-specific cytokines, i.e. IL-4 decreased in the supernatant of cultured splenocytes collected from mice fed with probiotic Dahi as compared to the other groups. Moreover, the splenic mRNA levels of IFN-gamma, interleukin-10 were found to be significantly increased, while that of IL-4 decreased significantly in La-Dahi groups, as compared to control groups. CONCLUSION: Results of the present study indicate that probiotic Dahi skewed Th2-specific immune response towards Th1-specific response and suppressed IgE in serum. Collectively, this study shows the potential use of probiotics intervention in reducing the allergic response to whey proteins in mice. (c) 2015 Society of Chemical Industry.

Shang, H., Sun, J., and Chen, Y. Q. Clostridium Butyricum CGMCC0313.1 Modulates Lipid Profile, Insulin Resistance and Colon Homeostasis in Obese Mice. PLoS.One. 2016; 11(4):e0154373

ABSTRACT: Obesity is associated with a cluster of metabolic disorders and systemic low-grade inflammation involving multiple organs. Recent findings have suggested that intestine is a key organ altered in response to high fat diet (HFD) feeding. Probiotics mainly lactobacillus strains have earlier been implicated in alleviating metabolic disorders. Here we aimed to examine the effects of a naturally occurring butyrate-producing probiotic clostridium butyricum CGMCC0313.1 (CB0313.1) in limiting the development of HFD-induced obesity. Mice treated with CB0313.1 exhibited reduced lipid accumulation in liver and serum, lower circulating insulin levels and improved glucose tolerance and insulin sensitivity. Furthermore, CB0313.1 administration reversed the HFD-induced colonic inflammation as evidenced by reduced tumor necrosis factor (TNF)-alpha level and increases the interleukin (IL)-10 and IL-22 levels in colon tissue. Additionally to colonic inflammation, CB0313.1 also reduced the colon permeability by upregulating the tight junction (TJ) proteins (claudin-1 and occludin) and contributed to a decreased circulating endotoxin level. In colon content, CB0313.1 administration restored the reduced production of butyrate and other short chain fatty acids (SCFAs) caused by HFD feeding. In adipose tissue, lower transcriptional levels of pro-inflammatory TNF-alpha, IL-6, IL-1beta and monocyte chemotactic protein (MCP)-1 in adipose tissue were observed in CB0313.1-treated mice. Collectively, our data demonstrated that CB0313.1, targeting colon inflammation and permeability, ameliorated HFD-induced obesity, insulin resistance as well as adipose inflammation.

Sharma, B. C. and Singh, J. Probiotics in management of hepatic encephalopathy. Metab Brain Dis. 4-28-2016;

ABSTRACT: Gut microflora leads to production of ammonia and endotoxins which play important role in the pathogenesis of hepatic encephalopathy (HE). There is relationship between HE and absorption of nitrogenous substances from the intestines. Probiotics play a role in treatment of HE by causing alterations in gut flora by decreasing the counts of pathogen bacteria, intestinal mucosal acidification, decrease in production and absorption of ammonia, alterations in permeability of gut, decreased endotoxin levels and changes in production of short chain fatty acids. Role of gut microbiota using prebiotics, probiotics and synbiotics have been evaluated in the management of minimal hepatic encephalopathy (MHE), overt HE and prevention of HE. Many studies

have shown efficacy of probiotics in reduction of blood ammonia levels, treatment of MHE and prevention of HE. However these trials have problems like inclusion of small number of patients, short treatment durations, variability in HE/MHE related outcomes utilized and high bias risk, errors of systematic and random types. Systematic reviews also have shown different results with one systematic review showing clinical benefits whereas another concluded that probiotics do not have any role in treatment of MHE or HE. Also practical questions on optimal dose, ideal combination of organisms, and duration of treatment and persistence of benefits on long term follow-up are still to be clarified. At present, there are no recommendations for use of probiotics in patients with HE.

Sheikhi, A., Shakerian, M., Giti, H., Baghaeifar, M., Jafarzadeh, A., Ghaed, V., Heibor, M. R., Baharifar, N., Dadafarin, Z., and Bashirpour, G. Probiotic Yogurt Culture Bifidobacterium Animalis Subsp. Lactis BB-12 and Lactobacillus Acidophilus LA-5 Modulate the Cytokine Secretion by Peripheral Blood Mononuclear Cells from Patients with Ulcerative Colitis. Drug Res.(Stuttg). 2016; 66(6):300-305.

ABSTRACT: BACKGROUND: There are some evidences for the immunomodulation disorders in the response to intestinal microbiota in inflammatory bowel disease. Yogurt is a fermented milk product made with a starter culture consisting of different probiotics which could be colonized in intestine. However, the role of probiotics in the aetiopathogenesis of ulcerative colitis (UC) has not been clarified. To determine how the immune system responds to these bacteria this study was planned. METHODS: Bifidobacterium lactis BB-12 (B. lactis) and Lactobacillus acidophilus LA-5 (L. acidophilus) were cultivated on MRS broth. PBMCs of 36 UC patients were separated by Ficoll-Hypaque centrifugation and co-cultured with different concentrations of UV killed bacteria in RPMI-1 640 plus 10% FCS for 48/72 h. IL-10, TGF-beta, IFN-gamma and TNF-alpha were measured in supernatant of PBMCs by ELISA. RESULTS: Both bacteria significantly augmented IL-10, TGF-beta, IFN-gamma and TNF-alpha compared to control ($p<0.001$). The secretion levels of IL-10 and TGF-beta by B. lactis- compared to L. acidophilus-stimulated PBMCs were significantly higher ($p<0.05$, $p<0.01$ respectively). The secretion levels of TNF-alpha and IFN-gamma by PBMCs after 72 h were significantly lower compared to 48 h stimulation by B. lactis ($p<0.001$, $p<0.035$ respectively). CONCLUSION: These data show that both probiotics may trigger the pro- and anti-inflammatory immune response of UC patients. It seems that IL-10/TGF-beta uprising by B. lactis could be the reason of TNF-alpha/IFN-gamma reduction. Therefore albeit B. lactis still stimulates the effector Th cells but because of more stimulatory effect on Tregs, it could be a good potential therapeutic candidate for further investigation.

Sheth, R. U., Cabral, V., Chen, S. P., and Wang, H. H. Manipulating Bacterial Communities by in situ Microbiome Engineering. Trends Genet. 2016; 32(4):189-200.

ABSTRACT: Microbial communities inhabit our entire planet and have a crucial role in biogeochemical processes, agriculture, biotechnology, and human health. Here, we argue that 'in situ microbiome engineering' represents a new paradigm of community-scale genetic and microbial engineering. We discuss contemporary applications of this approach to directly add, remove, or modify specific sets of functions and alter community-level properties in terrestrial, aquatic, and host-associated microbial communities. Specifically, we highlight emerging in situ genome engineering approaches as tractable techniques to manipulate microbial communities with high specificity and efficacy. Finally, we describe opportunities for technological innovation

and ways to bridge existing knowledge gaps to accelerate the development of in situ approaches for microbiome manipulations.

Shibahara-Sone, H., Gomi, A., Iino, T., Kano, M., Nonaka, C., Watanabe, O., Miyazaki, K., and Ohkusa, T. Living cells of probiotic Bifidobacterium bifidum YIT 10347 detected on gastric mucosa in humans. Benef.Microbes. 2016; 7(3):319-326.

ABSTRACT: The probiotic strain Bifidobacterium bifidum YIT 10347 has been demonstrated to inhibit Helicobacter pylori activity, prevent injury to the gastric mucosa, and improve general gastric malaise symptoms in H. pylori positive patients. This study aimed to investigate the adhering activity and localisation of B. bifidum YIT 10347 to gastric cells and tissue in vitro, and in human in vivo to clarify the mechanism of its beneficial effects on the stomach. The in vitro study found the adhesion rate of B. bifidum YIT 10347 to human gastric epithelial cells was about 10 times higher than that of lactic acid bacteria and other bifidobacteria. In the human study, 5 H. pylori negative and 12 H. pylori positive subjects ingested milk fermented with B. bifidum YIT 10347. B. bifidum YIT 10347 cells were measured by RT-qPCR for in gastric biopsy samples. Living B. bifidum YIT 10347 cells were detected in the biopsy samples in H. pylori negative subjects (105 cells/g and 104 cells/g at 1 h and 2 h after ingestion, respectively) and H. pylori positive subjects (104 cells/g at 1 h after the ingestion). Moreover, immunostaining analysis of tissue sections found that B. bifidum YIT 10347 cells were located at the interstitial mucin layer of the stomach. These results suggest that cells of probiotic B. bifidum YIT 10347 adhered to the human gastric mucosa in a live state, and that the higher adhering activity of B. bifidum YIT 10347 to the gastric mucosa may be involved in its beneficial effects on the human stomach.

Shin, R., Itoh, Y., Kataoka, M., Iino-Miura, S., Miura, R., Mizutani, T., and Fujisawa, T. Anti-tumor activity of heat-killed Lactobacillus plantarum BF-LP284 on Meth-A tumor cells in BALB/c mice. Int.J.Food Sci.Nutr. 2016; 67(6):641-649.

ABSTRACT: Probiotics exert numerous effects on human well-being. Here, heat-killed Lactobacillus plantarum BF-LP284 (H-Lp) was isolated as a potent immuno-modulator among 15 strains of lactobacilli in terms of TNF-alpha induction ability in peritoneal macrophages. In vitro TNF-alpha and IFN-gamma induction in Peyer's patch (PP) cells was higher when incubated with H-Lp than with live L. plantarum BF-LP284 (L-Lp). Suppression of syngeneic Meth-A tumors in a murine model by oral administration of H-Lp was also greater than that of L-Lp and of controls. H-Lp stimulated IFN-gamma production in spleen cells, which displayed inhibited tumor growth in Winn assays when treated with H-Lp. Moreover, H-Lp increased the ratio of CD3(+)cells among peripheral blood mononuclear cells in Meth-A tumor-bearing mice, suggesting an H-Lp-mediated anti-tumor mechanism whereby immune cells that are activated by H-Lp in PP and acquire anti-tumor activity in the spleen migrate to tumor sites through lymphocyte homing to inhibit tumor growth.

Shino, B., Peedikayil, F. C., Jaiprakash, S. R., Ahmed, Bijapur G., Kottayi, S., and Jose, D. Comparison of Antimicrobial Activity of Chlorhexidine, Coconut Oil, Probiotics, and Ketoconazole on Candida albicans Isolated in Children with Early Childhood Caries: An In Vitro Study. Scientifica.(Cairo.). 2016; 2016:7061587

ABSTRACT: Background. Early childhood caries (ECC) is associated with early colonisation and high levels of cariogenic microorganisms. With C. albicans being one of those, there is a need to determine the effectiveness of various chemotherapeutic agents against it. The study is aimed at isolating Candida species in children with ECC and at studying the antifungal effect of coconut oil, probiotics, Lactobacillus, and 0.2% chlorhexidine on C. albicans in comparison with ketoconazole. Materials and Methods. Samples were collected using sterile cotton swabs, swabbed on the tooth surfaces from children with ECC of 3 to 6 yrs and streaked on Sabouraud dextrose agar (HI Media) plates and incubated in a 5% CO2 enriched atmosphere at 37 degrees C for 24 hours. Candida was isolated and its susceptibility to probiotics, chlorhexidine, ketoconazole, and coconut oil was determined using Disc Diffusion method. Results. The mean zone of inhibition for chlorhexidine was 21.8 mm, whereas for coconut oil it was 16.8 mm, for probiotics it was 13.5 mm, and for ketoconazole it was 22.3 mm. The difference between the groups was not statistically significant (Chi-square value 7.42, P value 0.06). Conclusion. Chlorhexidine and coconut oil have shown significant antifungal activity which is comparable with ketoconazole.

Shukla, A., Gaur, P., and Aggarwal, A. Effect of Probiotics on clinical and immune parameters in Enthesitis-Related-Arthritis category of Juvenile idiopathic arthritis. Clin.Exp.Immunol. 5-30-2016;

ABSTRACT: Gut microflora and dysbiosis as an environmental factor has been linked to the pathogenesis of enthesitis-related-arthritis (JIA-ERA). Thus we did a proof-of-concept study of probiotics to modulate the gut-flora and study the effects on immune and clinical parameters of children having JIA-ERA. Forty- six children with active JIA-ERA were randomized to placebo or probiotic therapy along with NSAIDs for 12-weeks. Patients were assessed using a 6-point composite disease activity index (mJSpADA) based on morning stiffness, joint-count, enthesitis-count, sacroilitis/inflammatory-back-pain, uveitis and ESR/CRP. Frequencies of Th1, Th2, Th17 and T-regulatory cells in blood were measured using flow-cytometry. Serum cytokines IFN-gamma, IL-4, IL-17, IL-10, TNF-alpha and IL-6 were measured by cytokine bead array using flowcytometer. Average-age of 46-children (44-boys) was 15+/-2.5years and duration of disease 3.5+/-3years. There was no significant difference in improvement in mJSpADA between the two groups ($p=0.16$). Serum IL-6 levels showed a decrease ($p<0.05$) in the probiotic-group. Th2 cell frequency ($p<0.05$) and serum IL-10 levels ($p<0.01$) showed an increase in the placebo-group. But again the probiotic-use did not show a significant change in immune parameters when compared to the placebo. Adverse effects among the probiotic and placebo groups were diarrhea (36vs.45%), abdominal pain (9vs.20%), minor infections (4.5vs.20%) and flatulence (23vs.15%) respectively. Thus we can conclude that probiotic-therapy in JIA-ERA children is well tolerated but failed to show any significant immune or clinical effects over NSAID-therapy. This article is protected by copyright. All rights reserved.

Simpson, M. R., Ro, A. D., Grimstad, O., Johnsen, R., Storro, O., and Oien, T. Atopic dermatitis prevention in children following maternal probiotic supplementation does not appear to be mediated by breast milk TSLP or TGF-beta. Clin.Transl.Allergy. 2016; 6:27

ABSTRACT: BACKGROUND: The Probiotics in Prevention of Allergy among Children in Trondheim (ProPACT) study, a randomised, placebo controlled trial, demonstrated that maternal supplementation with probiotic milk reduced the incidence of atopic

dermatitis (AD) in infancy. The mechanisms behind this effect are incompletely understood and breast milk cytokines have been postulated as possible mediating factors. In this study we aimed to assess whether breast milk TLSP and TGF-beta are affected by a maternal probiotic supplementation regime, and their contribution to the preventive effect of this regime on AD in the offspring. METHODS: TSLP and TGF-beta isoforms (TGF-beta1, TGF-beta2 and TGF-beta3) were measured using ELISA and multiplex assays, respectively, in breast milk samples collected at 10 days and 3 months postpartum from women participating in the ProPACT trial (n = 259). The natural indirect and direct effects of maternal probiotics on AD, due to changes in breast milk cytokines, were estimated using causal mediation techniques. RESULTS: Probiotic supplementation tend to lead to high levels of breast milk TSLP at 10 days postpartum (p = 0.062), but this change did not contribute to the prevention of AD according to the mediation analysis. Probiotics had no apparent effect on TSLP at 3 months or TGF-betas at either time points. Thus, these are unlikely to be mediators of the effect of maternal probiotics on AD in offspring. CONCLUSIONS: Whilst maternal probiotic supplementation resulted in higher breast milk concentrations of TLSP at 10 days postpartum, this does not appear to be a mechanism for prevention of AD by maternal probiotics. Trial registration The original trial protocol is registered in ClinicalTrials.gov (identifier NCT00159523).

Singhi, S. C. and Kumar, S. Probiotics in critically ill children. F1000Res. 2016; 5

ABSTRACT: Gut microflora contribute greatly to immune and nutritive functions and act as a physical barrier against pathogenic organisms across the gut mucosa. Critical illness disrupts the balance between host and gut microflora, facilitating colonization, overgrowth, and translocation of pathogens and microbial products across intestinal mucosal barrier and causing systemic inflammatory response syndrome and sepsis. Commonly used probiotics, which have been developed from organisms that form gut microbiota, singly or in combination, can restore gut microflora and offer the benefits similar to those offered by normal gut flora, namely immune enhancement, improved barrier function of the gastrointestinal tract (GIT), and prevention of bacterial translocation. Enteral supplementation of probiotic strains containing either Lactobacillus alone or in combination with Bifidobacterium reduced the incidence and severity of necrotizing enterocolitis and all-cause mortality in preterm infants. Orally administered Lactobacillus casei subspecies rhamnosus, Lactobacillus reuteri, and Lactobacillus rhamnosus were effective in the prevention of late-onset sepsis and GIT colonization by Candida in preterm very low birth weight infants. In critically ill children, probiotics are effective in the prevention and treatment of antibiotic-associated diarrhea. Oral administration of a mix of probiotics for 1 week to children on broad-spectrum antibiotics in a pediatric intensive care unit decreased GIT colonization by Candida, led to a 50% reduction in candiduria, and showed a trend toward decreased incidence of candidemia. However, routine use of probiotics cannot be supported on the basis of current scientific evidence. Safety of probiotics is also a concern; rarely, probiotics may cause bacteremia, fungemia, and sepsis in immunocompromised critically ill children. More studies are needed to answer questions on the effectiveness of a mix versus single-strain probiotics, optimum dosage regimens and duration of treatment, cost effectiveness, and risk-benefit potential for the prevention and treatment of various critical illnesses.

Smith-Norowitz, T. A. and Bluth, M. H. Probiotics and diseases of altered IgE regulation: A short review. J.Immunotoxicol. 2016; 13(2):136-140.

ABSTRACT: The use of probiotics has gained considerable popularity in the marketplace in the US and has been steadily increasing due to consumer interest in potential treatment of various diseases, which may be due to modulation of immune responses. The aim of this review is to present information from representative studies regarding some of the possible applications and clinical effects of probiotic use in diseases of altered immunoglobulin (IgE) regulation (allergic rhinitis (AR), asthma, atopic dermatitis (AD) and food sensitization). Reports in humans are sparse or controversial; there is currently little reliable scientific data that supports the theory that there exists a cause-effect relationship between taking probiotics and alleviation of allergic disease. Unfortunately, these findings are too variable to allow substantial conclusions as to the efficacy and effectiveness of probiotic use in these disease states.

Soderborg, T. K., Borengasser, S. J., Barbour, L. A., and Friedman, J. E. Microbial transmission from mothers with obesity or diabetes to infants: an innovative opportunity to interrupt a vicious cycle. Diabetologia. 2016; 59(5):895-906.

ABSTRACT: Maternal obesity and diabetes dramatically increase the long-term risk for obesity in the next generation, and pregnancy and lactation may be critical periods at which to aim primary prevention to break the obesity cycle. It is becoming increasingly clear that the gut microbiome in newborns and infants plays a significant role in gut health and therefore child development. Alteration of the early infant gut microbiome has been correlated with the development of childhood obesity and autoimmune conditions, including asthma, allergies and, more recently, type 1 diabetes. This is likely to be due to complex interactions between mode of delivery, antibiotic use, maternal diet, components of breastfeeding and a network of regulatory events involving both the innate and adaptive immune systems within the infant host. Each of these factors are critical for informing microbiome development and can affect immune signalling, toxin release and metabolic signals, including short-chain fatty acids and bile acids, that regulate appetite, metabolism and inflammation. In several randomised controlled trials, probiotics have been administered with the aim of targeting the microbiome during pregnancy to improve maternal and infant health but the findings have often been confounded by mode of delivery, antibiotic use, ethnicity, infant sex, maternal health and length of exposure. Understanding how nutritional exposure, including breast milk, affects the assembly and development of both maternal and infant microbial communities may help to identify targeted interventions during pregnancy and in infants born to mothers with obesity or diabetes to slow the transmission of obesity risk to the next generation. The aim of this review is to discuss influences on infant microbiota colonisation and the mechanism(s) underlying how alterations due to maternal obesity and diabetes may lead to increased risk of childhood obesity.

Soukoulis, C., Singh, P., Macnaughtan, W., Parmenter, C., and Fisk, I. D. Compositional and physicochemical factors governing the viability of Lactobacillus rhamnosus GG embedded in starch-protein based edible films. Food Hydrocoll. 2016; 52:876-887.

ABSTRACT: Probiotic incorporation in edible films and coatings has been shown recently to be an efficient strategy for the delivery of probiotics in foods. In the present work, the impact of the compositional, physicochemical and structural properties of binary starch-protein edible films on Lactobacillus rhamnosus GG viability and stability was evaluated. Native rice and corn starch, as well as bovine skin gelatine, sodium caseinate and soy

protein concentrate were used for the fabrication of the probiotic edible films. Starch and protein type both impacted the structural, mechanical, optical and thermal properties of the films, and the process loss of L. rhamnosus GG during evaporation-dehydration was significantly lower in the presence of proteins (0.91-1.07 log CFU/g) compared to solely starch based systems (1.71 log CFU/g). A synergistic action between rice starch and proteins was detected when monitoring the viability of L. rhamnosus GG over four weeks at fridge and room temperature conditions. In particular, a 3- to 7-fold increase in the viability of L. rhamnosus GG was observed in the presence of proteins, with sodium caseinate - rice starch based films offering the most enhanced stability. The film's shelf-life (as calculated using the FAO/WHO (2011) basis of 6 log viable CFU/g) ranged between 27-96 and 15-24 days for systems stored at fridge or room temperature conditions respectively.

Spiller, R., Pelerin, F., Cayzeele, Decherf A., Maudet, C., Housez, B., Cazaubiel, M., and Justen, P. Randomized double blind placebo-controlled trial of Saccharomyces cerevisiae CNCM I-3856 in irritable bowel syndrome: improvement in abdominal pain and bloating in those with predominant constipation. United.European.Gastroenterol.J. 2016; 4(3):353-362.

ABSTRACT: BACKGROUND: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal pain and/or discomfort. Probiotics have been reported to benefit IBS symptoms but the level of benefit remains quite unclear. OBJECTIVE: This study was designed to assess the benefit of Saccharomyces cerevisiae I-3856 on IBS symptoms. METHODS: A randomized, double blind, placebo-controlled trial has been performed in 379 subjects with diagnosed IBS. Subjects were randomly supplemented with the probiotics (1000 mg) or placebo for 12 weeks. Questionnaires (gastrointestinal symptoms, stools, wellbeing, and quality of life) were completed. Primary endpoint was percentage of responders defined as having a 50% decrease in the weekly average "intestinal pain/discomfort score" for at least 4 out of the last 8 weeks of the study. RESULTS: There was no overall benefit of S. cerevisiae I-3856 on IBS symptoms and wellbeing in the study population. Moreover, S. cerevisiae I-3856 was not statistically significant predictor of the responder status of the subjects ($p > 0.05$). Planned subgroup analyses showed significant effect in the IBS-C subjects: improvement of gastrointestinal symptoms was significantly higher in active group, compared to placebo, on abdominal pain/discomfort and bloating throughout the study and at the end of the supplementation. CONCLUSIONS: In this study, S. cerevisiae I-3856 at the dose of 1000 mg per day does not improve intestinal pain and discomfort in general IBS patients. However, it seems to have an effect in the subgroup with constipation which needs further studies to confirm (NCT01613456 in ClinicalTrials.gov registry).

Spinler, J. K., Ross, C. L., and Savidge, T. C. Probiotics as adjunctive therapy for preventing Clostridium difficile infection - What are we waiting for? Anaerobe. 5-13-2016;

ABSTRACT: With the end of the golden era of antibiotic discovery, the emergence of a new post-antibiotic age threatens to thrust global health and modern medicine back to the pre-antibiotic era. Antibiotic overuse has resulted in the natural evolution and selection of multi-drug resistant bacteria. One major public health threat, Clostridium difficile, is now the single leading cause of hospital-acquired bacterial infections and is by far the most deadly enteric pathogen for the U.S. POPULATION: Due to the high morbidity and mortality and increasing incidence that coincides with antibiotic use, non-

traditional therapeutics are ideal alternatives to current treatment methods and also provide an avenue towards prevention. Despite the need for alternative therapies to antibiotics and the safety of most probiotics on the market, researchers are inundated with regulatory issues that hinder the translational science required to push these therapies forward. This review discusses the regulatory challenges of probiotic research, expert opinion regarding the application of probiotics to C. difficile infection and the efficacy of probiotics in preventing this disease.

Staudacher, H. M. and Whelan, K. Altered gastrointestinal microbiota in irritable bowel syndrome and its modification by diet: probiotics, prebiotics and the low FODMAP diet. Proc.Nutr.Soc. 2016; 75(3):306-318.

ABSTRACT: Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by abdominal pain or discomfort with disordered defecation. This review describes the role of the gastrointestinal (GI) microbiota in the pathogenesis of IBS and how dietary strategies to manage symptoms impact on the microbial community. Evidence suggests a dysbiosis of the luminal and mucosal colonic microbiota in IBS, frequently characterised by a reduction in species of Bifidobacteria which has been associated with worse symptom profile. Probiotic supplementation trials suggest intentional modulation of the GI microbiota may be effective in treating IBS. A smaller number of prebiotic supplementation studies have also demonstrated effectiveness in IBS whilst increasing Bifidobacteria. In contrast, a novel method of managing IBS symptoms is the restriction of short-chain fermentable carbohydrates (low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet). Studies consistently demonstrate clinical effectiveness of the low FODMAP diet in patients with IBS. However, one unintentional consequence of this dietary intervention is its impact on the microbiota. This leads to an interesting paradox; namely, increasing luminal Bifidobacteria through probiotic supplementation is associated with a reduction in IBS symptoms while in direct conflict to this, the low FODMAP diet has clinical efficacy but markedly reduces luminal Bifidobacteria concentration. Given the multifactorial aetiology of IBS, the heterogeneity of symptoms and the complex and diverse nature of the microbiome, it is probable that both interventions are effective in patient subgroups. However combination treatment has never been explored and as such, presents an exciting opportunity for optimising clinical management, whilst preventing potentially deleterious effects on the GI microbiota.

Steinert, A., Radulovic, K., and Niess, J. Gastro-intestinal tract: The leading role of mucosal immunity. Swiss.Med.Wkly. 2016; 146:w14293

ABSTRACT: An understanding of mucosal immunity is essential for the comprehension of intestinal diseases that are often caused by a complex interplay between host factors, environmental influences and the intestinal microbiota. Not only improvements in endoscopic techniques, but also advances in high throughput sequencing technologies, have expanded knowledge of how intestinal diseases develop. This review discusses how the host interacts with intestinal microbiota by the direct contact of host receptors with highly conserved structural motifs or molecules of microbes and also by microbe-derived metabolites (produced by the microbe during adaptation to the gut environment), such as short-chain fatty acids, vitamins, bile acids and amino acids. These metabolites are recognised by metabolite-sensing receptors expressed by immune cells to influence functions of macrophages, dendritic cells and T cells, such as migration, conversion and

maintenance of regulatory T cells and regulation of proinflammatory cytokine production, which is essential for the maintenance of intestinal homeostasis and the development of intestinal diseases, such as inflammatory bowel diseases. First interventions in these complex interactions between microbe-derived metabolites and the host immune system for the treatment of gastrointestinal diseases, such as modification of the diet, treatment with antibiotics, application of probiotics and faecal microbiota transplantation, have been introduced into the clinic. Specific targeting of metabolite sensing receptors for the treatment of gastrointestinal diseases is in development. In future, precision medicine approaches that consider individual variability in genes, the microbiota, the environment and lifestyle will become increasingly important for the care of patients with gastrointestinal diseases.

Suchodolski, J. S. and Jergens, A. E. Recent Advances and Understanding of Using Probiotic-Based Interventions to Restore Homeostasis of the Microbiome for the Prevention/Therapy of Bacterial Diseases. Microbiol.Spectr. 2016; 4(2)

ABSTRACT: The importance of the microbiome in health and disease has galvanized interest in using manipulations of the gastrointestinal ecosystem to prevent and/or combat gut bacterial infections and to restore mucosal homeostasis in patients with generalized microbial imbalances (i.e., dysbiosis), including the human inflammatory bowel diseases, Crohn's disease, and ulcerative colitis. Probiotics, prebiotics, or their combination use (i.e., synbiotics) are one mechanism for modifying the microbiota and exerting direct and indirect effects on the host immune responses and metabolomics profiles. These beneficial effects are transferred through various pathways, including the production of antimicrobial peptides, promoting the growth of beneficial microbes and enhancing immunomodulatory functions via various metabolites. While probiotic therapy has been used empirically for decades with mixed success, the recent advances in molecular and mass spectrophotometric techniques for the characterization of the complexity and diversity of the intestinal microbiome has aided in better understanding of host-microbe interactions. It is important to better understand the functional properties of the microbiome, because it is now clear that the microbiota secretes many metabolites that have a direct impact on host immune responses. This information will improve selection of the most appropriate probiotic strains that selectively target intestinal disease processes.

Sun, J., Wang, F., Ling, Z., Yu, X., Chen, W., Li, H., Jin, J., Pang, M., Zhang, H., Yu, J., and Liu, J. Clostridium butyricum attenuates cerebral ischemia/reperfusion injury in diabetic mice via modulation of gut microbiota. Brain Res. 7-1-2016; 1642:180-188.

ABSTRACT: Diabetes is known to exacerbate cerebral ischemia/reperfusion (I/R) injury. Here, we investigated the effects of Clostridium butyricum on cerebral I/R injury in the diabetic mice subjected to 30min of bilateral common carotid arteries occlusion (BCCAO). The cognitive impairment, the blood glucose level, neuronal injury, apoptosis, and expressions of Akt, phospho-Akt (p-Akt), and caspase-3 level were assessed. Meanwhile, the changes of gut microbiota in composition and diversity in the colonic feces were evaluated. Our results showed that diabetic mice subjected to BCCAO exhibited worsened cognitive impairment, cell damage and apoptosis. These were all attenuated by C. butyricum. Moreover, C. butyricum reversed cerebral I/R induced decreases in p-Akt expression and increases in caspase-3 expression, leading to inhibiting neuronal apoptosis. C. butyricum partly restored cerebral I/R induced decreases of fecal

microbiota diversity, changes of fecal microbiota composition. Together, these findings highlight the important role of bacteria in the bidirectional communication of the gut-brain axis and suggest that certain probiotics might prove to be useful therapeutic adjuncts in cerebral I/R injury with diabetes.

Sun, J. and Buys, N. J. Glucose- and glycaemic factor-lowering effects of probiotics on diabetes: a meta-analysis of randomised placebo-controlled trials. Br.J.Nutr. 4-14-2016; 115(7):1167-1177.

ABSTRACT: This meta-analysis examined the effect of probiotics on glucose and glycaemic factors in diabetes and its associated risk factors. All randomised-controlled trials published in English in multiple databases from January 2000 to June 2015 were systematically searched. Only studies that addressed glucose- and glycaemic-related factors as outcome variables were included. The main outcomes of interest in trials were mean changes in glucose, HbA1c, insulin and homoeostasis model assessment-estimated insulin resistance (HOMA-IR). Using the Physiotherapy Evidence Database (PEDro) scale to assess the quality of studies, a total of eleven studies with 614 subjects were included. The pooled mean difference and effect size with a 95% CI were extracted using a random-effect model. It was found that there are statistically significant pooled mean differences between the probiotics and the placebo-controlled groups on the reduction of glucose (-0.52 mmol/l, 95% CI -0.92, -0.11 mmol/l; P=0.01) and HbA1c (-0.32%, 95% CI -0.57, -0.07%; P=0.01). There was no statistically significant pooled mean difference between the probiotics and the placebo-controlled groups on the reduction of insulin (-0.48 microIU/ml, 95% CI -1.34, 0.38 microIU/ml; P=0.27) and HOMA-IR (pooled effect of -0.44, 95% CI -1.57, 0.70; P=0.45). Meta-regression analysis identified that probiotics had significant effects on reduction of glucose, HbA1c, insulin and HOMA-IR in participants with diabetes, but not in participants with other risk factors. The present meta-analysis suggested that probiotics may be used as an important dietary supplement in reducing the glucose metabolic factors associated with diabetes.

Sun, L., Liu, H., Jiang, H., Wei, M., Liang, S., Wang, M., Shi, K., and He, Q. Macrophages Are Involved in Gut Bacterial Translocation and Reversed by Lactobacillus in Experimental Uremia. Dig.Dis.Sci. 2016; 61(6):1534-1544.

ABSTRACT: BACKGROUND: Uremia causes gut microbiome dysbiosis, which is characterized by a reduction in beneficial bacteria. Intestinal bacterial translocation (BT) contributes to microinflammation in uremia, which is associated with adverse outcomes. Whether macrophages are involved in BT remains unclear. AIMS: We investigated the involvement of macrophages in BT and microinflammation in uremic rats and whether Lactobacillus LB can influence macrophage activity. METHODS: Male Sprague-Dawley rats were randomly divided into three groups: sham, uremia, and uremia + probiotic. Macrophages and GFP-labeled tracer bacteria in intestinal and extraintestinal tissues were observed by fluorescence microscopy. The macrophage ultrastructure was examined by transmission electron microscopy. Immunochemistry was used to analyze the expression of cluster of differentiation 11a (CD11a), inducible nitric oxide synthase (iNOS), and intercellular adhesion molecule-1 (ICAM-1). RT-PCR and Western blot were employed to assess the mRNA and protein expression of early growth response gene 1 (EGR1) and toll-like receptor 4 (TLR4). RESULTS: In uremic rats, the colocalization of GFP-labeled tracer bacteria and macrophages was visible in intestinal and extraintestinal tissues. Compared with the sham group, the uremic macrophages showed fewer

cytoplasmic protrusions and pseudopodia. Administration of Lactobacillus LB restored the protrusions and pseudopodia. Compared with the sham group, the uremia group exhibited macrophages with higher staining intensities for CD11a, iNOS, and ICAM-1, and higher mRNA and protein expression of TLR4 and EGR1. CONCLUSIONS: Intestinal macrophages in the uremic rats are polarized toward a proinflammatory phenotype, resulting in microinflammation. Macrophages with impaired phagocytic function are associated with BT. Lactobacillus LB reduces BT by enhancing macrophage phagocytosis.

Sweileh, W. M., Shraim, N. Y., Al-Jabi, S. W., Sawalha, A. F., Rahhal, B., Khayyat, R. A., and Zyoud, S. H. Assessing worldwide research activity on probiotics in pediatrics using Scopus database: 1994-2014. World Allergy Organ J. 2016; 9:25

ABSTRACT: BACKGROUND: A wide variety of probiotic products has been introduced into the market in the past decade. Research trends and activity on probiotics help understand how these products were evolved and their potential future role in medicine. The objective of this study was to assess the research activity on probiotics in pediatrics using bibliometric indicators and network visualization. METHODS: Original and review articles on probiotics in pediatrics published worldwide were retrieved from SciVerse, Scopus (1994-2014) and analyzed. VOSviewer was used for network visualization. RESULTS: The total number of documents published on probiotics in pediatrics was 2817. Research activity on probiotics in pediatrics showed approximately 90- fold increase during the study period. Approximately 22 % of published articles originated from USA and has the greatest share, however, Finland ranked first when data were stratified by population or income. The most productive institution in this field was Turku University in Finland with 82 (2.91 %) articles. Half of the prolific authors were also from Finland. Most of the published research activity appeared in Journal of Pediatric Gastroenterology and Nutrition. Most frequently encountered title terms include nutrition, infant formula, necrotizing enetrocolitis, allergy, and diarrhea. The total number of citations for the retreived documents documents was 70991, and the average citation per article was 25.20. CONCLUSIONS: Interest in probiotic research and its potential benefits in pediatric ailments is relatively recent but significantly increasing. Bibliometric analysis can be used as an indicator of the importance and growth of probiotic use in pediatrics.

Szajewska, H. and Dryl, R. Probiotics for the Management of Infantile Colic. J.Pediatr.Gastroenterol.Nutr. 2016; 63 Suppl 1:S22-S24.

ABSTRACT: PURPOSE OF REVIEW: Evidence suggests that the gut microbiota in subjects with infantile colic differs from the gut microbiota in an unaffected population. In colicky infants, dysbiosis may affect gut motor function and gas production resulting in abdominal pain/colic. If so, it is logical to assume that manipulation of the gut microbiota may play a therapeutic role and also could be a preventive measure in the evolution of these disorders. We aimed to evaluate evidence on the effectiveness of probiotics for treating and preventing infantile colic. RECENT FINDINGS: The administration of Lactobacillusreuteri DSM 17938 is likely to reduce crying time in breastfed infants with infantile colic, but its role in formula-fed infants is less clear. Data summarized in the current review suggest that L reuteri DSM 17938 may be effective in the reduction of crying/colic both in breastfed and formula-fed infants. Other probiotics (single or in combinations) were studied in single trials only. SUMMARY: Given the lack of effective therapy for infantile colic and the good safety profile of L reuteri DSM 17938, this

therapeutic option could be discussed with caregivers. Data on other probiotics, either positive or negative, are too limited to allow one to draw reliable conclusions.

Szajewska, H. What are the indications for using probiotics in children? Arch.Dis.Child. 2016; 101(4):398-403.

ABSTRACT: The health benefits of probiotics have been the subject of extensive research. Still, some questions are being repeatedly asked: should one use or not use probiotics? If yes, how and when should probiotics be used? The purpose of this review is to summarise current evidence on specific probiotics' efficacy and safety to help healthcare professionals make evidence-based decisions on the indications for using specific probiotic strains or combinations in children. To identify relevant data, searches of MEDLINE and the Cochrane Library databases were performed in July 2015 to locate randomised controlled trials or their meta-analyses published in the last five years. The MEDLINE database also was searched for evidence-based clinical practice guidelines, developed by scientific societies. Considering that probiotics have strain-specific effects, the main focus was on data on individual probiotic strains, not on probiotics in general.

Szajewska, H., Konarska, Z., and Kolodziej, M. Probiotic Bacterial and Fungal Strains: Claims with Evidence. Dig.Dis. 2016; 34(3):251-259.

ABSTRACT: BACKGROUND: Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit for the host. This review summarizes current (i.e. published in the last 5 years) key evidence on probiotic efficacy and its safety in adults and children. To identify relevant data, searches of MEDLINE and the Cochrane Library databases were performed in August 2015 to locate randomized controlled trials (RCTs) or their meta-analyses. The focus was on commonly used, well-specified, bacterial and yeast probiotics for the treatment of gastrointestinal disorders. The MEDLINE database was also searched for evidence-based clinical practice guidelines, developed by scientific societies in the same timeframe. Data on safety of probiotics were obtained from a document developed by the US Agency for Healthcare Research and Quality. KEY MESSAGES: A number of relevant RCTs and meta-analyses are available. Saccharomyces boulardii is the most studied yeast probiotic, and Lactobacillus rhamnosus GG is the most studied bacterial probiotic. For both, the best documented fact is their efficacy for the treatment of acute gastroenteritis, especially in children, and for the prevention of antibiotic-associated diarrhea, both in adults and children. There is some evidence to support the use of probiotics to prevent or treat other diseases, such as necrotizing enterocolitis, infantile colic, Helicobacter pylori infection, and irritable bowel syndrome, but further studies are needed to identify which strain(s) is/are the most effective. Data on safety, particularly long-term safety, are limited. The risk of side effects is greater in people who have severe underlying health conditions. CONCLUSIONS: The evidence on bacterial and yeast probiotics has considerably expanded during recent years. Accumulated data allow one to make informed decisions about the effectiveness of probiotics and about how to reduce the use of those without proven efficacy.

Tack, J., Vanuytsel, T., and Corsetti, M. Modern Management of Irritable Bowel Syndrome: More Than Motility. Dig.Dis. 2016; 34(5):566-573.

ABSTRACT: In the treatment of irritable bowel syndrome (IBS), loperamide seems efficacious for diarrhea and ispaghula for constipation, while musculotropic spasmolytics may relieve abdominal pain. Antidepressants were found to be efficacious for abdominal pain, but their tolerance may be problematic and the therapeutic effect varied largely between trials. While meta-analyses suggest efficacy of probiotics as a group, the quality of the trials is often suboptimal and there is large variability. Lubiprostone, a chloride channel activator, and linaclotide, a guanylyl cyclase-C agonist, showed favorable effects on multiple symptoms in IBS with constipation. For IBS with diarrhea (IBS-D), the 5-HT3 receptor antagonist ramosetron showed efficacy in men and women, but is currently only approved in Japan. A multicenter study with the anti-emetic 5-HT3 receptor antagonist ondansetron showed efficacy on stool pattern in IBS-D. The poorly absorbable antibiotic rifaximin and eluxadoline, a mu opioid receptor agonist and delta antagonist, both showed efficacy in phase III trials in IBS-D and were approved by the FDA. Eluxadoline was associated with increased occurrence of sphincter of Oddi spasm and biliary pancreatitis. The non-pharmacological treatment of IBS, with dietary interventions (mainly gluten elimination and low FODMAP (fructose, oligo-, di-, monosaccharides and polyols)) has received a lot of attention lately. While responder rates vary across studies, perhaps based on regional variations in dietary intake of FODMAPs, the dietary approach seems to have acquired recognition as a valid therapeutic alternative. Long-term studies and comparative studies with pharmacotherapy, as well as elucidation of the underlying mechanisms of action, are needed.

Takada, M., Nishida, K., Kataoka-Kato, A., Gondo, Y., Ishikawa, H., Suda, K., Kawai, M., Hoshi, R., Watanabe, O., Igarashi, T., Kuwano, Y., Miyazaki, K., and Rokutan, K. Probiotic Lactobacillus casei strain Shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models. Neurogastroenterol.Motil. 2016; 28(7):1027-1036.

ABSTRACT: BACKGROUND: This study aimed to examine the effects of Lactobacillus casei strain Shirota (LcS) on gut-brain interactions under stressful conditions. METHODS: Three double-blind, placebo-controlled trials were conducted to examine the effects of LcS on psychological and physiological stress responses in healthy medical students under academic examination stress. Subjects received LcS-fermented milk or placebo daily for 8 weeks prior to taking a national standardized examination. Subjective anxiety scores, salivary cortisol levels, and the presence of physical symptoms during the intervention were pooled and analyzed. In the animal study, rats were given feed with or without LcS for 2 weeks, then submitted to water avoidance stress (WAS). Plasma corticosterone concentration and the expression of cFos and corticotropin releasing factor (CRF) in the paraventricular nucleus (PVN) were measured immediately after WAS. In an electrophysiological study, gastric vagal afferent nerve activity was monitored after intragastric administration of LcS to urethane-anesthetized rats. KEY RESULTS: Academic stress-induced increases in salivary cortisol levels and the incidence rate of physical symptoms were significantly suppressed in the LcS group compared with the placebo group. In rats pretreated with LcS, WAS-induced increases in plasma corticosterone were significantly suppressed, and the number of CRF-expressing cells in the PVN was reduced. Intragastric administration of LcS stimulated gastric vagal afferent activity in a dose-dependent manner. CONCLUSIONS & INFERENCES: These findings suggest that LcS may prevent hypersecretion of cortisol and physical symptoms under stressful conditions, possibly through vagal afferent signaling to the brain and reduced stress reactivity in the PVN.

Tamang, J. P., Shin, D. H., Jung, S. J., and Chae, S. W. Functional Properties of Microorganisms in Fermented Foods. Front Microbiol. 2016; 7:578

ABSTRACT: Fermented foods have unique functional properties imparting some health benefits to consumers due to presence of functional microorganisms, which possess probiotics properties, antimicrobial, antioxidant, peptide production, etc. Health benefits of some global fermented foods are synthesis of nutrients, prevention of cardiovascular disease, prevention of cancer, gastrointestinal disorders, allergic reactions, diabetes, among others. The present paper is aimed to review the information on some functional properties of the microorganisms associated with fermented foods and beverages, and their health-promoting benefits to consumers.

Tan, L. T., Chan, K. G., Lee, L. H., and Goh, B. H. Streptomyces Bacteria as Potential Probiotics in Aquaculture. Front Microbiol. 2016; 7:79

ABSTRACT: In response to the increased seafood demand from the ever-going human population, aquaculture has become the fastest growing animal food-producing sector. However, the indiscriminate use of antibiotics as a biological control agents for fish pathogens has led to the emergence of antibiotic resistance bacteria. Probiotics are defined as living microbial supplement that exert beneficial effects on hosts as well as improvement of environmental parameters. Probiotics have been proven to be effective in improving the growth, survival and health status of the aquatic livestock. This review aims to highlight the genus Streptomyces can be a good candidate for probiotics in aquaculture. Studies showed that the feed supplemented with Streptomyces could protect fish and shrimp from pathogens as well as increase the growth of the aquatic organisms. Furthermore, the limitations of Streptomyces as probiotics in aquaculture is also highlighted and solutions are discussed to these limitations.

Tang, Y., Wu, Y., Huang, Z., Dong, W., Deng, Y., Wang, F., Li, M., and Yuan, J. Administration of probiotic mixture DM#1 ameliorated 5-fluorouracil-induced intestinal mucositis and dysbiosis in rats. Nutrition. 5-20-2016;

ABSTRACT: OBJECTIVE: The use of probiotics to alleviate chemotherapy-induced intestinal mucositis is supported by clinical consensus. However, no studies to date, to our knowledge, have systematically analyzed the effects of a probiotic mixture on chemotherapy-induced mucositis or assessed changes in the intestinal microbiota after probiotic treatment. The aim of this study was to report the effects of a probiotic mixture, DM#1, on intestinal mucositis and dysbiosis of rats treated with 5-fluorouracil (5-FU). METHODS: Twenty-eight male Sprague Dawley rats weighing 180 to 220 g were randomly divided into four groups: control, 5-FU, probiotic high (PH), and probiotic low (PL). Except for the control group, all other groups received intraperitoneal injections of 5-FU for 5 d, and the PH and PL groups received DM#1 intragastrically (1 x 109 or 1 x 108 colony-forming units/kg, respectively) for 8 d. One day after the last administration, rats were sacrificed and the ilea were removed for histopathologic assessment and evaluation of permeability, myeloperoxidase activity, levels of cytokines (interleukin [IL]-4, IL-6, tumor necrosis factor [TNF]-alpha), and mRNA of toll-like receptors (TLR; TLR2, TLR4, and TLR9). Additionally, intestinal microbiota profiles were analyzed by polymerase chain reaction (PCR)-denaturing gradient gel electrophoresis and quantitative real-time PCR. RESULTS:

Treatment with DM#1 ameliorated 5-FU-induced intestinal mucosal injury in rats, possibly by reducing proinflammatory cytokine levels and neutrophil infiltration. The increased intestinal permeability caused by 5-FU was ameliorated. These results were closely associated with the reestablishment of intestinal microbial homeostasis and alteration of the TLR2/TLR4 signaling pathway. CONCLUSIONS: Administration of the probiotic mixture DM#1 ameliorated 5-FU-induced intestinal mucositis and dysbiosis in rats.

Tanida, M., Takada, M., Kato-Kataoka, A., Kawai, M., Miyazaki, K., and Shibamoto, T. Intragastric injection of Lactobacillus casei strain Shirota suppressed spleen sympathetic activation by central corticotrophin-releasing factor or peripheral 2-deoxy-d-glucose in anesthetized rats. Neurosci.Lett. 4-21-2016; 619:114-120.

ABSTRACT: Intragastric (IG) administration of probiotic strain Lactobacillus casei Shirota (LcS) decreases the sympathetic nerve outflow of anesthetized rats in a tissue-specific manner. In the present study, we examined the effects of IG administration of LcS on sympathetic activation induced by an intracerebroventricular (ICV) injection of corticotrophin-releasing factor (CRF) and an intravenous (IV) injection of 2-deoxy-d-glucose (2DG) or interleukin (IL)-1beta in urethane-anesthetized rats. The IG administration of LcS differently affected the stimulatory responses of sympathetic nerve outflow to CRF. LcS suppressed the increase in splenic sympathetic nerve activity (Spleen-SNA), induced by central CRF, in a dose-dependent manner; however, it did not alter adrenal sympathetic nervous activity (ASNA). In contrast, LcS did not affect spleen-SNA and ASNA following an IV injection of IL-1beta. On the other hand, IG administration of LcS suppressed the activation of ASNA following an IV injection of 2DG. These findings suggest that the suppression of central CRF-induced sympathetic activation by LcS is tissue-specific. Moreover, it can suppress the 2DG-induced sympathetic activation. Furthermore, we found that stomach-specific vagotomy attenuates the suppressive effect of LcS on CRF-mediated spleen-SNA activation. Thus, the present study suggests that LcS administered to the stomach may act on the afferent vagal nerve and send afferent signals to the brain to regulate efferent SNA induced by sympathetic stimulators.

Tao, J. H., Duan, J. A., Qian, Y. Y., Qian, D. W., and Guo, J. M. Investigation on the interactions between the Chrysanthemum morifolium flowers extract and intestinal bacteria from human and rat. Biomed.Chromatogr. 5-6-2016;

ABSTRACT: Flos Chrysanthemi, dried flower of Chrysanthemum morifolium Ramat, has drawn much attention recently due to its potential beneficial health effects for human. Flos Chrysanthemi products are usually taken orally and metabolized by intestinal microflora. However, investigation on the comprehensive metabolic profile of the Flos Chrysanthemi extract by intestinal flora remains unknown due to its chemical complexity and the limitations of analytical methods. In this paper, a rapid, sensitive and automated analysis method, ultra-performance liquid chromatography/quadrupole time of flight mass spectrometry (UPLC-Q-TOF/MS) including MSE technology and automated data processing MetabolynxTM software, was developed and successfully applied for the biotransformation and metabolic profile of flavonoids in the Flos Chrysanthemi extract by intestinal flora from human and rat. A total of 32 metabolites were detected and tentatively identified in human and rat intestinal bacterial samples. These metabolites indicated that hydrolysis, hydroxylation, acetylation, methylation, hydrogenation and deoxygenation were the major conversion pathways of flavonoids in the Flos Chrysanthemi extract in vitro. Furthermore, the effects of the Flos Chrysanthemi extract

on the growth of different intestinal bacteria were detected using an Emax precision microplate reader. Certain pathogenic bacteria such as Enterobacter, Enterococcus, Clostridium and Bacteroides were significantly inhibited by Flos Chrysanthemi, while commensal probiotics such as Lactobacillus and Bifidobacterium were moderately promoted. Our observation provided further evidence for the importance of intestinal bacteria in the metabolism and potential activity of the Flos Chrysanthemi extract. The results will also be helpful for the further pharmacokinetic study of Flos Chrysanthemi and to unravel how it works in vivo.

Tapiovaara, L., Lehtoranta, L., Poussa, T., Makivuokko, H., Korpela, R., and Pitkaranta, A. Absence of adverse events in healthy individuals using probiotics--analysis of six randomised studies by one study group. Benef.Microbes. 2016; 7(2):161-169.

ABSTRACT: Consumption of live bacteria as probiotic supplements is increasing. There is, however, a lack of information on the safety of ingested probiotics. The main objective of this study was to investigate the adverse events (AEs) of specific probiotics (Lactobacillus rhamnosus GG (LGG) alone or LGG in combination with L. rhamnosus Lc705, Propionibacterium freudenreichii JS, Bifidobacterium lactis BB12, or Bifidobacterium breve 99) studied in six of our study groups' clinical trials, by analysing individual participant data. A secondary objective was to study AEs associated with the consumed probiotic species and mixtures in three specific categories; 'gastrointestinal disorders', 'respiratory, thoracic and mediastinal disorders' and 'infections and infestations'. Six randomised, double-blind, placebo-controlled clinical studies by our study group were included in this AE analysis (study population n=1,909). All AE data were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0. From the 26 CTCAE System Organ Classes, we identified AEs in 20 classes among 1,909 subjects. Probiotic ingestion did not result in statistically significant differences in AEs in different groups, when compared to placebo. A subgroup analysis of gastrointestinal, respiratory, thoracic and mediastinal disorders, infections and infestations, found no differences between the intervention groups or for different probiotic combinations (risk ratio (RR) = 0.97, 95% confidence interval (CI): 0.93-1.02, P=0.30; RR=0.99, 95% CI: 0.97-1.01, P=0.35; RR=0.99, 95% CI: 0.93-1.06, P=0.62, respectively). As a conclusion, ingestion of probiotic supplementations containing LGG alone, or LGG in combination with L. rhamnosus Lc705, P. freudenreichii JS, B. breve 99, or B. lactis BB12 did not seem to cause AEs in young and elderly subjects in this analysis.

Tapiovaara, L., Kumpu, M., Makivuokko, H., Waris, M., Korpela, R., Pitkaranta, A., and Winther, B. Human rhinovirus in experimental infection after peroral Lactobacillus rhamnosus GG consumption, a pilot study. Int.Forum Allergy Rhinol. 2016; 6(8):848-853.

ABSTRACT: BACKGROUND: Data has emerged on possible beneficial effects of probiotics in respiratory tract viral infections, but it is unclear if the promising positive effects evidenced are due to a reduced viral load during infections. The aims of this work were to investigate the effect of peroral probiotic Lactobacillus rhamnosus GG (American Type Culture Collection [ATCC], Accession No. 53103) consumption on human rhinovirus (HRV) load in nasopharyngeal lavage samples in experimental HRV infection, and to correlate viral load to clinical symptoms. METHODS: Intranasal HRV A39 inoculation was performed on 59 adults, who had consumed juice enriched with live or heat-inactivated L. rhamnosus GG or control juice for 3 weeks prior to inoculation in a randomized, controlled, pilot trial setting. Nasopharyngeal lavage samples and symptom data were

analyzed on day 0 before inoculation, and on days 2 and 5. Samples were subjected to quantitative HRV detection by polymerase chain reaction (PCR). RESULTS: Before inoculation 9 of 59 (15%) samples presented with another HRV strain than the studied A39. There was a tendency toward the lowest HRV loads in the L. rhamnosus GG groups and the highest in placebo group (log10 copies/mL, 95% confidence interval [CI], 6.20 [5.18 to 7.40] in live, 6.30 [4.91 to 7.08] in inactivated L. rhamnosus GG, and 7.25 [5.81 to 7.52] in placebo group, p = 0.57 in day 2) in the wild-type excluded population. The HRV load positively correlated with the symptom scores on days 2 and 5 (correlation coefficient 0.61 [p < 0.001] and 0.28 [p = 0.034], respectively). CONCLUSION: Results did not show statistical differences in viral loads in subjects using L. rhamnosus GG when compared to placebo. HRV load positively correlated with the total symptom scores.

Terayama, Y., Matsuura, T., Uchida, M., Narama, I., and Ozaki, K. Probiotic (yogurt) containing Lactobacillus gasseri OLL2716 is effective for preventing Candida albicans-induced mucosal inflammation and proliferation in the forestomach of diabetic rats. Histol.Histopathol. 2016; 31(6):689-697.

ABSTRACT: Oral and esophageal candidiasis sometimes leads to mucosal hyperplasia, and progresses to carcinoma. We have produced an animal model for hyperplastic mucosal candidiasis in the forestomach that has a proliferative lesion of the squamous epithelium with chronic inflammation and C. albicans infection, some of which advanced to squamous cell carcinoma. There are many reports of the antibacterial effects of probiotics, but consensus about their antifungal effect has not been reached. In the present study, we investigate whether probiotic (yogurt) containing Lactobacillus gasseri OLL2716 (LG21 yogurt) can prevent proliferative and inflammatory changes caused by C. albicans in this mucosal candidiasis animal model. Diabetes was induced in 8-week-old WBN/Kob rats by intravenous administration of alloxan. One group of diabetic rats received a saline containing C. albicans and LG21 yogurt orally (DC+LG21 group) for 30 weeks, and another group received only C. albicans (DC group) for 30 weeks. They were sacrificed at 40 weeks of age, and analyzed histopathologically. In the DC+LG21 group, squamous hyperplasia at the greater curvature was significantly milder, and the Ki-67 positive index was significantly lower compared with the DC group. Suppurative inflammation with C. albicans also tended to be suppressed at the greater curvature. These findings suggest that probiotic (yogurt) containing Lactobacillus gasseri OLL2716 can suppress squamous hyperplastic change and inflammation associated with C. albicans infection in the forestomach.

Thakur, B. K., Saha, P., Banik, G., Saha, D. R., Grover, S., Batish, V. K., and Das, S. Live and heat-killed probiotic Lactobacillus casei Lbs2 protects from experimental colitis through Toll-like receptor 2-dependent induction of T-regulatory response. Int.Immunopharmacol. 2016; 36:39-50.

ABSTRACT: Inflammatory bowel disease (IBD) is a group of inflammatory disorders of the intestine caused by dysregulated T-cell mediated immune response against commensal microflora. Probiotics are reported as therapeutically effective against IBD. However, variable efficacy of the live probiotic strains, difference in survival and persistence in the gut between the strains and the lack of insight into the mechanisms of probiotic action limit optimal therapeutic efficacy. Our aims were to evaluate the lactobacillus strains isolated from the North Indian population for the generation of regulatory cells and cytokines in the intestine, to study their effects on pro-inflammatory mediators in the

mouse model of inflammatory bowel disease and to explore the underlying mechanisms of their actions. Among the selected lactobacillus strains, Lactobacillus casei Lbs2 (MTCC5953) significantly suppressed lipopolysaccharide-induced pro-inflammatory cytokine (TNF-alpha, IL-6) secretion. Both live and heat-killed Lbs2 polarized Th0 cells to T-regulatory (Treg) cells in vitro, increased the frequency of FoxP3(+) Treg cells in the mesenteric lymph nodes (MLNs) and alleviated macroscopic and histopathological features of colitis in probiotic-fed mice. Moreover, the levels of IL-12, TNF-alpha and IL-17A were suppressed, while IL-10 and TGF-beta levels were augmented in the colonic tissues of Lbs2-treated mice. The induced Treg (iTreg) cells secreted IL-10 and TGF-beta and exerted suppressive effects on the proliferation of effector T-cells. Adoptive transfer of iTreg cells ameliorated the disease manifestations of murine colitis and suppressed the levels of TNF-alpha and IL-17A. Finally, Lbs2 effects were mediated by Toll-like receptor 2 (TLR2) activation on the dendritic cells. This study identified live and heat-killed Lbs2 as putative therapeutic candidates against IBD and highlighted their Toll-like receptor 2-dependent immunomodulatory and regulatory function.

Toh, J. Y., Yip, G., Han, W. M., Fok, D., Low, Y. L., Lee, Y. S., Rebello, S. A., Saw, S. M., Kwek, K., Godfrey, K. M., Chong, Y. S., and Chong, M. F. Infant Feeding Practices in a Multi-Ethnic Asian Cohort: The GUSTO Study. Nutrients. 2016; 8(5)

ABSTRACT: The optimal introduction of complementary foods provides infants with nutritionally balanced diets and establishes healthy eating habits. The documentation of infant feeding practices in multi-ethnic Asian populations is limited. In a Singapore cohort study (GUSTO), 842 mother-infant dyads were interviewed regarding their feeding practices when the infants were aged 9 and 12 months. In the first year, 20.5% of infants were given dietary supplements, while 5.7% took probiotics and 15.7% homeopathic preparations. At age 9 months, 45.8% of infants had seasonings added to their foods, increasing to 56.3% at 12 months. At age 12 months, 32.7% of infants were given blended food, although 92.3% had begun some form of self-feeding. Additionally, 87.4% of infants were fed milk via a bottle, while a third of them had food items added into their bottles. At both time points, more than a third of infants were provided sweetened drinks via the bottle. Infants of Indian ethnicity were more likely to be given dietary supplements, have oil and seasonings added to their foods and consumed sweetened drinks from the bottle ($p < 0.001$). These findings provide a better understanding of variations in infant feeding practices, so that healthcare professionals can offer more targeted and culturally-appropriate advice.

Tomicic, Z., Zupan, J., Matos, T., and Raspor, P. Probiotic yeast Saccharomyces boulardii (nom. nud.) modulates adhesive properties of Candida glabrata. Med.Mycol. 6-1-2016;

ABSTRACT: Following the widespread use of immunosuppressive therapy together with broad-spectrum antimycotic therapy, the frequency of mucosal and systemic infections caused by the pathogenic yeast Candida glabrata has increased in the past decades. Due to the resistance of C. glabrata to existing azole drugs, it is very important to look for new strategies helping the treatment of such fungal diseases. In this study, we investigated the effect of the probiotic yeast Saccharomyces boulardii (nom. nud.) on C. glabrata adhesion at different temperatures, pH values, and in the presence of fluconazole, itraconazole and amphotericin B. We also studied the adhesion of C. glabrata co-culture with Candida krusei, Saccharomyces cerevisiae, two bacterial probiotics Lactobacillus rhamnosus and Lactobacillus casei The method used to assess adhesion was crystal violet staining. Our results showed that despite the nonadhesiveness

of S. boulardii cells, this probiotic significantly affected the adherence ability of C. glabrata This effect was highly dependent on C. glabrata strain and was either antagonistic or synergistic. Regarding the extrinsic factors, temperature did not indicate any significant influence on this S. boulardii modulatory effect, while at high pH and at increased concentrations of antimycotics, S. boulardii did not manage to repress the adhesion of C. glabrata strains. The experiments of C. glabrata co-cultures with other species showed that the adhesiveness of two separate cultures could not be used to predict the adhesiveness of their co-culture.

Turck, D., Braegger, C. P., Colombo, C., Declercq, D., Morton, A., Pancheva, R., Robberecht, E., Stern, M., Strandvik, B., Wolfe, S., Schneider, S. M., and Wilschanski, M. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin.Nutr. 2016; 35(3):557-577.

ABSTRACT: BACKGROUND: Malnutrition is both a frequent feature and a comorbidity of cystic fibrosis (CF), with nutritional status strongly associated with pulmonary function and survival. Nutritional management is therefore standard of care in CF patients. ESPEN, ESPGHAN and ECFS recommended guidelines to cover nutritional management of patients with CF. METHODS: The guidelines were developed by an international multidisciplinary working group in accordance with officially accepted standards. The GRADE system was used for determining grades of evidence and strength of recommendation. Statements were discussed, submitted to Delphi rounds, reviewed by ESPGHAN and ECFS and accepted in an online survey among ESPEN members. RESULTS: The Working Group recommends that initiation of nutritional management should begin as early as possible after diagnosis, with subsequent regular follow up and patient/family education. Exclusive breast feeding is recommended but if not possible a regular formula is to be used. Energy intake should be adapted to achieve normal weight and height for age. When indicated, pancreatic enzyme and fat soluble vitamin treatment should be introduced early and monitored regularly. Pancreatic sufficient patients should have an annual assessment including fecal pancreatic elastase measurement. Sodium supplementation is recommended and a urinary sodium:creatinine ratio should be measured, corresponding to the fractional excretion of sodium. If iron deficiency is suspected, the underlying inflammation should be addressed. Glucose tolerance testing should be introduced at 10 years of age. Bone mineral density examination should be performed from age 8-10 years. Oral nutritional supplements followed by polymeric enteral tube feeding are recommended when growth or nutritional status is impaired. Zinc supplementation may be considered according to the clinical situation. Further studies are required before essential fatty acids, anti-osteoporotic agents, growth hormone, appetite stimulants and probiotics can be recommended. CONCLUSION: Nutritional care and support should be an integral part of management of CF. Obtaining a normal growth pattern in children and maintaining an adequate nutritional status in adults are major goals of multidisciplinary cystic fibrosis centers.

Turner, P., Pol, S., Soeng, S., Sar, P., Neou, L., Chea, P., Day, N. P., Cooper, B. S., and Turner, C. High Prevalence of Antimicrobial-resistant Gram-negative Colonization in Hospitalized Cambodian Infants. Pediatr.Infect.Dis.J. 2016; 35(8):856-861.

ABSTRACT: BACKGROUND: Antimicrobial-resistant Gram-negative infections are a significant cause of mortality in young infants. We aimed to determine characteristics of, and risk factors for, colonization and invasive infection caused by 3rd generation

cephalosporin (3GC) or carbapenem-resistant organisms in outborn infants admitted to a neonatal unit (NU) in Cambodia. METHODS: During the first year of operation, patients admitted to the Angkor Hospital for Children NU, Siem Reap, Cambodia, underwent rectal swabbing on admission and twice weekly until discharge. Swabs were taken also from 7 environmental sites. Swabs were cultured to identify 3GC or carbapenem-resistant Acinetobacter sp., Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa. RESULTS: The study included 333 infants with a median age at NU admission of 10 days (range, 0-43). Colonization by >/=1 3GC-resistant organism was detected in 85.9% (286/333). Admission swabs were collected in 289 infants: 61.9% were colonized by a 3GC-resistant organism at the time of admission, and a further 23.2% were colonized during hospitalization, at a median of 4 days [95% confidence interval: 3-5]. Probiotic treatment (hazard ratio: 0.58; 95% confidence interval: 0.35-0.98) was associated with delayed colonization. Colonization by a carbapenem-resistant organism occurred in 25 (7.5%) infants. Six infants had NU-associated K. pneumoniae bacteremia; phenotypically identical colonizing strains were found in 3 infants. Environmental colonization occurred early. CONCLUSIONS: Colonization by antimicrobial-resistant Gram-negative organisms occurred early in hospitalized Cambodian infants and was associated with subsequent invasive infection. Trials of potential interventions such as probiotics are needed.

Tytgat, H. L., Douillard, F. P., Reunanen, J., Rasinkangas, P., Hendrickx, A. P., Laine, P. K., Paulin, L., Satokari, R., and de Vos, W. M. Lactobacillus rhamnosus GG Outcompetes Enterococcus faecium by Mucus-Binding Pili - Evidence for a Novel Probiotic Mechanism on a Distance. Appl.Environ.Microbiol. 7-15-2016;

ABSTRACT: Vancomycin-resistant enterococci (VRE) have become a major nosocomial threat. Enterococcus faecium is of special concern as it can easily acquire new antibiotic resistances and is an excellent colonizer of the human intestinal tract. Several clinical studies have explored the potential to use beneficial bacteria to weed out opportunistic pathogens. Especially the widely studied Lactobacillus rhamnosus GG has been applied successfully in the context of VRE infections. Here, we provide new insight into the molecular mechanism underlying the effects of this model probiotic on VRE decolonization. Both clinical VRE isolates and L. rhamnosus GG express pili on their cell wall, which are the key modulators of their highly efficient colonization of the intestinal mucosa. We found that one of the VRE pili clusters shares considerable sequence similarity to the SpaCBA-SrtC1 pilus cluster of L. rhamnosus GG. Remarkable immunological and functional similarities were discovered between the mucus-binding pili of L. rhamnosus GG and those of the clinical E. faecium strain E1165, which was characterized at the genome level. Moreover, E. faecium strain E1165 bound efficiently to mucus and this could be prevented by the presence of the mucus-binding SpaC protein or antibodies against L. rhamnosus GG or SpaC. These results present experimental support for a novel probiotic mechanism, in which the mucus-binding pili of L. rhamnosus GG prevent host binding of a potential pathogen. Hence, we provide a molecular basis for the further exploitation of L. rhamnosus GG and its pilins for prophylaxis and treatment of VRE infections. IMPORTANCE: Concern about the vancomycin-resistant Enterococcus faecium causing nosocomial infections is globally rising. The arsenal of antibiotic strategies to treat these infections is nearly exhausted and hence new treatment strategies are urgently needed. Here we provide molecular evidence to underpin the reports on the successful clinical application of Lactobacillus rhamnosus GG in VRE decolonization strategies. Our results provide support for a new molecular mechanism, in which probiotics can perform competitive exclusion and possibly immune interaction. Moreover, we spur the further exploration of the potential of

intact L. rhamnosus GG and purified SpaC pilin as prophylactic and curative agents of the VRE carrier state.

Upadhaya, S. D., Hossiendoust, A., and Kim, I. H. Probiotics in Salmonella-challenged Hy-Line brown layers. Poult.Sci. 8-1-2016; 95(8):1894-1897.

ABSTRACT: A total of 192 Hy-Line Brown 40-week-old Salmonella-free layers were randomly assigned to 4 dietary treatments in a 5-wk experiment to test the efficacy of probiotics on egg production and quality, excreta and intestinal microbiota of laying birds challenged with Salmonella gallinarum. Dietary treatment comprised of (1) NC: ; basal diet, negative control, (2) PC: ; basal diet + oral S. gallinarum administration, positive control, (3) T1: ; basal diet + 0.1% Bacillus subtilis RX7 1 x 10(9) cfu/g + S. gallinarum administration and (4) T2: ; basal diet + 0.1% Bacillus methylotrophicus C14 1 x 10(9) cfu/g + S. gallinarum administration. All birds (n = 144) except NC were orally challenged with 1 ml suspension of 10(8) cfu/mL S. gallinarum KVCC BA 0700722 once at d 28 after the initiation of experiment. The egg production improved in post Salmonella-challenged birds whereas egg equality was improved during pre-challenge in probiotic supplemented birds compared to NC and PC. The Salmonella counts in the excreta were lower ($P < 0.05$) in T1 and T2 than PC at the end of the experiment whereas the Lactobacillus counts in the excreta were higher ($P < 0.05$) in T1 compared with NC. The Escherichia coli counts in excreta were numerically lower in T1 and T2 than PC. In the small and large intestine, there was slight increase in Lactobacillus counts in T2 compared with PC. The Salmonella counts in small and large intestine tended to be lower in T1 and T2 as compared with PC. However, Salmonella counts in challenged birds not supplemented with probiotics were significantly higher than non-challenged birds.

Upadrasta, A. and Madempudi, R. S. Probiotics and blood pressure: current insights. Integr.Blood Press Control. 2016; 9:33-42.

ABSTRACT: Gut microbiota play a significant role in host metabolic processes, and recent metagenomic surveys have revealed that they are involved in host immune modulation and influence host development and physiology (organ development). Initially, probiotics are identified as potential therapeutics to treat gastrointestinal disorders and to revitalize the disturbed gut ecosystem. Currently, studies are exploring the potential for expanded uses of probiotics for improving the health conditions in metabolic disorders that increase the risk of developing cardiovascular diseases such as hypertension. Further investigations are required to evaluate targeted and effective use of the wide variety of probiotic strains in various metabolic disorders to improve the overall health status of the host. This review addresses the causes of hypertension and the hypotensive effect of probiotics, with a focus on their mechanistic action.

Uranga, J. A., Lopez-Miranda, V., Lombo, F., and Abalo, R. Food, nutrients and nutraceuticals affecting the course of inflammatory bowel disease. Pharmacol.Rep. 2016; 68(4):816-826.

ABSTRACT: Inflammatory bowel diseases (ulcerative colitis; Crohn's disease) are debilitating relapsing inflammatory disorders affecting the gastrointestinal tract, with deleterious effect on quality of life, and increasing incidence and prevalence. Mucosal inflammation, due to altered microbiota, increased intestinal permeability and immune system dysfunction underlies the symptoms and may be caused in susceptible individuals

by different factors (or a combination of them), including dietary habits and components. In this review we describe the influence of the Western diet, obesity, and different nutraceuticals/functional foods (bioactive peptides, phytochemicals, omega 3-polyunsaturated fatty acids, vitamin D, probiotics and prebiotics) on the course of IBD, and provide some hints that could be useful for nutritional guidance. Hopefully, research will soon offer enough reliable data to slow down the spread of the disease and to make diet a cornerstone in IBD therapy.

Urbaniak, C. and Reid, G. The potential influence of the microbiota and probiotics on women during long spaceflights. Womens Health (Lond). 2016; 12(2):193-198.

ABSTRACT: Humans have been exploring space for almost 55 years but space travel comes with many psychological and physiological changes that astronauts have to adapt to, both during and post flight missions. Now, with the reality of such missions lasting years, maintaining proper health of the flight crew is a high priority. While conditions such as nausea, bone loss, renal calculi and depression have been recognized, and approaches to medical and surgical care in space considered, the influence of the microbiota could be of added significance in maintaining astronaut health. While probiotics have long been part of the Russian cosmonaut diet, their use for specific health concerns of women has not been assessed. In this article, we explore the ways in which the microbiome may influence the health of female astronauts during long space flights, and present a rationale for the use of probiotics.

Urbanska, A. M., Bhathena, J., Cherif, S., and Prakash, S. Orally delivered microencapsulated probiotic formulation favorably impacts polyp formation in APC (Min/+) model of intestinal carcinogenesis. Artif.Cells Nanomed.Biotechnol. 2016; 44(1):1-11.

ABSTRACT: The development of intestinal polyps in an orthotopic colorectal mouse model, receiving a probiotic yogurt formulation containing microencapsulated live Lactobacillus acidophilus cells was investigated. The expression of various immunohistochemical markers namely CD8, Mac-1, Ki-67, and cleaved caspase-3, was evaluated. Results suggest that the probiotic formulation decreases overall intestinal inflammation. Mice receiving the probiotic formulation were found to develop almost two-fold fewer tumors in the small intestines. In the large intestine, however, there was no significant difference observed among polyp numbers. The formulation appears to have potential application in the prevention of various GI pathological conditions.

Urbanska, M., Gieruszczak-Bialek, D., and Szajewska, H. Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for diarrhoeal diseases in children. Aliment.Pharmacol.Ther. 2016; 43(10):1025-1034.

ABSTRACT: BACKGROUND: Not all probiotics are equal. AIM: To investigate the efficacy of Lactobacillus reuteri DSM 17938 (L. reuteri) in the management of various types of diarrhoeal diseases in children. METHODS: Medline, Embase, the Cochrane Library, trial registries and reference lists of included studies were searched in January 2016, with no language restriction, for randomised controlled trials (RCTs). RESULTS: Eight RCTs (n = 1229) met the inclusion criteria. In treatment trials, L. reuteri administration reduced the duration of diarrhoea (three RCTs, n = 256, mean difference, MD -24.82 h, 95% CI -38.8 to -10.8) and increased the cure rate on day 1 and day 2. However, heterogeneity and wide

confidence intervals call for caution in interpreting results. In preventive trials carried out in hospitalised children, based on the findings from two RCTs (n = 290), there was no significant reduction in the risk of nosocomial diarrhoea, rotavirus diarrhoea or diarrhoea of any origin with L. reuteri administration. Based on one RCT (n = 97), there was no effect of L. reuteri on the risk of antibiotic-associated diarrhoea. However, the evidence is limited because the overall frequency of diarrhoea was surprisingly low. In preventive studies carried out in apparently healthy children, L. reuteri reduced diarrhoeal outcomes in one RCT; the evidence from another trial was less convincing. CONCLUSIONS: In therapeutic settings, L. reuteri administration reduces the duration of diarrhoea and increases the chance of cure. In preventive settings, L. reuteri has the potential to reduce the risk of community-acquired diarrhoea in otherwise healthy children.

Urmann, K., rshavsky-Graham, S., Walter, J. G., Scheper, T., and Segal, E. Whole-cell detection of live lactobacillus acidophilus on aptamer-decorated porous silicon biosensors. Analyst. 7-6-2016;

ABSTRACT: This work describes the design of optical aptamer-based porous silicon (PSi) biosensors for the direct capture of Lactobacillus acidophilus. Aptamers are oligonucleotides (single-stranded DNA or RNA) that can bind their targets with high affinity and specificity, making them excellent recognition elements for biosensing applications. Herein, aptamer Hemag1P, which specifically targets the important probiotic L. acidophilus, was utilized for direct bacteria capture onto oxidized PSi Fabry-Perot thin films. Monitoring changes in the reflectivity spectrum (using reflective interferometric Fourier transform spectroscopy) allows for bacteria detection in a label-free, simple and rapid manner. The performance of the biosensor was optimized by tuning the PSi nanostructure, its optical properties, as well as the immobilization density of the aptamer. We demonstrate the high selectivity and specificity of this simple "direct-capture" biosensing scheme and show its ability to distinguish between live and dead bacteria. The resulting biosensor presents a robust and rapid method for the specific detection of live L. acidophilus at concentrations relevant for probiotic products and as low as 106 cells per mL. Rapid monitoring of probiotic bacteria is crucial for quality, purity and safety control as the use of probiotics in functional foods and pharmaceuticals is becoming increasingly popular.

Vaghef-Mehrabany, E., Homayouni-Rad, A., Alipour, B., Sharif, S. K., Vaghef-Mehrabany, L., and ipour-Ajiry, S. Effects of Probiotic Supplementation on Oxidative Stress Indices in Women with Rheumatoid Arthritis: A Randomized Double-Blind Clinical Trial. J.Am.Coll.Nutr. 2016; 35(4):291-299.

ABSTRACT: OBJECTIVE: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that causes great pain and disability and increasing oxidative stress in patients. The objective of the present study was to evaluate the effects of probiotics-live microorganisms with many health benefits, including antioxidant properties-on oxidative stress indices of patients with RA. This study is a secondary analysis from a previously published study Methods: In a randomized double-blind placebo-controlled clinical trial, 46 patients with RA were assigned to one of two groups; patients in the probiotic group received a daily capsule containing 10(8) colony forming units (CFUs) of Lactobacillus casei 01 (L. casei 01), while those in the placebo group took identical capsules containing maltodextrin, for 8 weeks. In the baseline and at the end of the study, anxiety,

physical activity levels, and dietary intakes were assessed. Anthropometric parameters, serum malondialdehyde (MDA), total antioxidant capacity (TAC), erythrocyte superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activities were measured. RESULTS: There was no significant difference between the two groups for demographic characteristics, anthropometric parameters, physical activity, anxiety levels, or dietary intakes, throughout the course of the study. No significant within- and between-group differences were observed for MDA, TAC, or CAT. SOD activity decreased only in the probiotic group and GPx activity decreased in both study groups ($p < 0.05$); however, no significant between-group difference was found for these enzymes activities at the end of the study ($p > 0.05$). CONCLUSION: No significant effect of L. casei 01 supplementation was observed on the oxidative status of patients with RA, compared to placebo.

Valdes-Varela, L., Hernandez-Barranco, A. M., Ruas-Madiedo, P., and Gueimonde, M. Effect of Bifidobacterium upon Clostridium difficile Growth and Toxicity When Co-cultured in Different Prebiotic Substrates. Front Microbiol. 2016; 7:738

ABSTRACT: The intestinal overgrowth of Clostridium difficile, often after disturbance of the gut microbiota by antibiotic treatment, leads to C. difficile infection (CDI) which manifestation ranges from mild diarrhea to life-threatening conditions. The increasing CDI incidence, not only in compromised subjects but also in traditionally considered low-risk populations, together with the frequent relapses of the disease, has attracted the interest for prevention/therapeutic options. Among these, probiotics, prebiotics, or synbiotics constitute a promising approach. In this study we determined the potential of selected Bifidobacterium strains for the inhibition of C. difficile growth and toxicity in different carbon sources. We conducted co-cultures of the toxigenic strain C. difficile LMG21717 with four Bifidobacterium strains (Bifidobacterium longum IPLA20022, Bifidobacterium breve IPLA20006, Bifidobacterium bifidum IPLA20015, and Bifidobacterium animalis subsp. lactis Bb12) in the presence of various prebiotic substrates (Inulin, Synergy, and Actilight) or glucose, and compared the results with those obtained for the corresponding mono-cultures. C. difficile and bifidobacteria levels were quantified by qPCR; the pH and the production of short chain fatty acids was also determined. Moreover, supernatants of the cultures were collected to evaluate their toxicity using a recently developed model. Results showed that co-culture with B. longum IPLA20022 and B. breve IPLA20006 in the presence of short-chain fructooligosaccharides, but not of Inulin, as carbon source significantly reduced the growth of the pathogen. With the sole exception of B. animalis Bb12, whose growth was enhanced, the presence of C. difficile did not show major effects upon the growth of the bifidobacteria. In accordance with the growth data, B. longum and B. breve were the strains showing higher reduction in the toxicity of the co-culture supernatants.

Valdes-Varela, L., onso-Guervos, M., Garcia-Suarez, O., Gueimonde, M., and Ruas-Madiedo, P. Screening of Bifidobacteria and Lactobacilli Able to Antagonize the Cytotoxic Effect of Clostridium difficile upon Intestinal Epithelial HT29 Monolayer. Front Microbiol. 2016; 7:577

ABSTRACT: Clostridium difficile is an opportunistic pathogen inhabiting the human gut, often being the aetiological agent of infections after a microbiota dysbiosis following, for example, an antibiotic treatment. C. difficile infections (CDI) constitute a growing health problem with increasing rates of morbidity and mortality at groups of risk, such as elderly and hospitalized patients, but also in populations traditionally considered low-risk. This

could be related to the occurrence of virulent strains which, among other factors, have high-level of resistance to fluoroquinolones, more efficient sporulation and markedly high toxin production. Several novel intervention strategies against CDI are currently under study, such as the use of probiotics to counteract the growth and/or toxigenic activity of C. difficile. In this work, we have analyzed the capability of twenty Bifidobacterium and Lactobacillus strains, from human intestinal origin, to counteract the toxic effect of C. difficile LMG21717 upon the human intestinal epithelial cell line HT29. For this purpose, we incubated the bacteria together with toxigenic supernatants obtained from C. difficile. After this co-incubation new supernatants were collected in order to quantify the remnant A and B toxins, as well as to determine their residual toxic effect upon HT29 monolayers. To this end, the real time cell analyser (RTCA) model, recently developed in our group to monitor C. difficile toxic effect, was used. Results obtained showed that strains of Bifidobacterium longum and B. breve were able to reduce the toxic effect of the pathogen upon HT29, the RTCA normalized cell-index values being inversely correlated with the amount of remnant toxin in the supernatant. The strain B. longum IPLA20022 showed the highest ability to counteract the cytotoxic effect of C. difficile acting directly against the toxin, also having the highest capability for removing the toxins from the clostridial toxigenic supernatant. Image analysis showed that this strain prevents HT29 cell rounding; this was achieved by preserving the F-actin microstructure and tight-junctions between adjacent cells, thus keeping the typical epithelium-like morphology. Besides, preliminary evidence showed that the viability of B. longum IPLA20022 is needed to exert the protective effect and that secreted factors seems to have anti-toxin activity.

Van Beek, A. A., Hoogerland, J. A., Belzer, C., De, Vos P., de Vos, W. M., Savelkoul, H. F., and Leenen, P. J. Interaction of mouse splenocytes and macrophages with bacterial strains in vitro: the effect of age in the immune response. Benef.Microbes. 2016; 7(2):275-287.

ABSTRACT: Probiotics influence the immune system, both at the local and systemic level. Recent findings suggest the relation between microbiota and the immune system alters with age. Our objective was to address direct effects of six bacterial strains on immune cells from young and aged mice: Lactobacillus plantarum WCFS1, Lactobacillus casei BL23, Lactococcus lactis MG1363, Bifidobacterium breve ATCC15700, Bifidobacterium infantis ATCC15697, and Akkermansia muciniphila ATCC BAA-835. We used splenocytes and naive or interferon-gamma-stimulated bone marrow-derived macrophages (BMDM) as responder populations. All tested bacterial strains induced phenotypic and cytokine responses in splenocytes and BMDM. Based on magnitude of the cellular inflammatory response and cytokine profiles, two subgroups of bacteria were identified, i.e. L. plantarum and L. casei versus B. breve, B. infantis, and A. muciniphila. The latter group of bacteria induced high levels of cytokines produced under inflammatory conditions, including tumour necrosis factor (TNF), interleukin (IL)-6 and IL-10. Responses to L. lactis showed features of both subgroups. In addition, we compared responses by splenocytes and BMDM derived from young mice to those of aged mice, and found that splenocytes and BMDM derived from aged mice had an increased IL-10 production and dysregulated IL-6 and TNF production compared to young immune cells. Overall, our study shows differential inflammatory responses to distinct bacterial strains, and profound age-dependent effects. These findings, moreover, support the view that immune environment importantly influences bacterial immune effects.

Vandenplas, Y. and Salvatore, S. Infant Formula with Partially Hydrolyzed Proteins in Functional Gastrointestinal Disorders. Nestle.Nutr.Inst.Workshop Ser. 2016; 86:29-37.

ABSTRACT: Over 50% of all infants present with one or more functional gastrointestinal disorders (FGIDs) during the first months of life. The literature on the effect of partially hydrolyzed formula (pHF) in the management of FGIDs was reviewed. There is insufficient evidence to recommend pHFs in regurgitation, although one study suggests that a thickened pHF may be more effective than antiregurgitation formulas with intact protein. No randomized clinical trials on pHFs in infants with colicky symptoms have been published. pHFs, fortified with pre- and/or probiotics, with high levels of sn-2 palmitate in the fat blend or without palm oil provide some benefit in functional constipation. However, there are no studies evaluating the efficacy of pHF as single intervention in constipated infants. CONCLUSION: Overall, pHF may offer some useful alternative to intact protein in the dietary management of common FGIDs, although the evidence is very scarce. Well-designed, randomized trials are needed to allow to recommend the use of pHF in infants with FGIDs.

Vanholder, R. C., Eloot, S., and Glorieux, G. L. Future Avenues to Decrease Uremic Toxin Concentration. Am.J.Kidney Dis. 2016; 67(4):664-676.

ABSTRACT: In this article, we review approaches for decreasing uremic solute concentrations in chronic kidney disease and in particular, in end-stage renal disease (ESRD). The rationale to do so is the straightforward relation between concentration and biological (toxic) effect for most toxins. The first section is devoted to extracorporeal strategies (kidney replacement therapy). In the context of high-flux hemodialysis and hemodiafiltration, we discuss increasing dialyzer blood and dialysate flows, frequent and/or extended dialysis, adsorption, bioartificial kidney, and changing physical conditions within the dialyzer (especially for protein-bound toxins). The next section focuses on the intestinal generation of uremic toxins, which in return is stimulated by uremic conditions. Therapeutic options are probiotics, prebiotics, synbiotics, and intestinal sorbents. Current data are conflicting, and these issues need further study before useful therapeutic concepts are developed. The following section is devoted to preservation of (residual) kidney function. Although many therapeutic options may overlap with therapies provided before ESRD, we focus on specific aspects of ESRD treatment, such as the risks of too-strict blood pressure and glycemic regulation and hemodynamic changes during dialysis. Finally, some recommendations are given on how research might be organized with regard to uremic toxins and their effects, removal, and impact on outcomes of uremic patients.

Vastano, V., Pagano, A., Fusco, A., Merola, G., Sacco, M., and Donnarumma, G. The Lactobacillus plantarum Eno A1 Enolase Is Involved in Immunostimulation of Caco-2 Cells and in Biofilm Development. Adv.Exp.Med.Biol. 2016; 897:33-44.

ABSTRACT: The role of probiotics in prevention and treatment of a variety of diseases is now well assessed. The presence of adhesive molecules on the cell surface of probiotics has been related to the ability to confer health benefit to the host. We have previously shown that the enolase EnoA1 of Lactobacillus plantarum, one of the most predominant species in the gut microbiota of healthy individuals, is cell surface-expressed and is involved in binding with human fibronectin and plasminogen. By means of comparative analysis between L. plantarum LM3 (wild type) and its isogenic LM3-CC1 (DeltaenoA1)

mutant strain, here we show that EnoA1 affects the ability of this bacterium to modulate immune response as determined by analysis of expression of immune system molecules in Caco-2 cells. Indeed, we observed induction of TLR2 expression in cells exposed to L. plantarum LM3, while no induction was detectable in cells exposed to LM3-CC1. This difference was much less consistent when expression of TLR4 was determined in cells exposed to the two strains. Pro-inflammatory (IL-6) and anti-inflammatory cytokines (IL-10, TGF-beta), and the antimicrobial peptide HBD-2 were induced in Caco-2 cells exposed to L. plantarum LM3, while lower levels of induction were detected in cells exposed to LM3-CC1. We also analyzed the ability to develop biofilm of the two strains, and observed a decrease of about 65 % in the development of mature biofilm in LM3-CC1 compared to the wild type.

Vey Neufeld, K. A., Luczynski, P., Dinan, T. G., and Cryan, J. F. Reframing the Teenage Wasteland: Adolescent Microbiota-Gut-Brain Axis. Can.J.Psychiatry. 2016; 61(4):214-221.

ABSTRACT: Human adolescence is arguably one of the most challenging periods of development. The young adult is exposed to a variety of stressors and environmental stimuli on a backdrop of significant physiological change and development, which is especially apparent in the brain. It is therefore unsurprising that many psychiatric disorders are first observable during this time. The human intestine is inhabited by trillions of microorganisms, and evidence from both preclinical and clinical research focusing on the established microbiota-gut-brain axis suggests that the etiology and pathophysiology of psychiatric disorders may be influenced by intestinal dysbiosis. Provocatively, many if not all of the challenges faced by the developing teen have a documented impact on these intestinal commensal microbiota. In this review, we briefly summarize what is known about the developing adolescent brain and intestinal microbiota, discuss recent research investigating the microbiota-gut-brain axis during puberty, and propose that pre- and probiotics may prove useful in both the prevention and treatment of psychiatric disorders specifically benefitting the young adult.

Vey Neufeld, K. A., Luczynski, P., Seira, Oriach C., Dinan, T. G., and Cryan, J. F. What's bugging your teen?-The microbiota and adolescent mental health. Neurosci.Biobehav.Rev. 6-7-2016;

ABSTRACT: Human adolescence is a time of enormous developmental change, second only to infancy and early childhood in terms of brain shaping and growth. It is also a period in life when the young adult is faced with distinct environmental challenges and stressors. Interestingly, we now know that these external sources of stress all have an impact on the intestinal microbiota. Given that there is now a significant body of knowledge indicating a role for the microbiota-gut-brain axis in development and function of the brain, and potentially the emergence of psychiatric illnesses, we need to draw our attention to the intestinal microbiota in the adolescent. As psychiatric illnesses frequently first manifest during the teenage years it may be that the intestinal bacteria are playing an as yet unidentified role in disease pathogenesis. Identifying a role for the microbiota in psychiatric illnesses opens up an exciting opportunity for therapeutic advances via bacterial manipulation. This could prove to be a beneficial and novel avenue for treatment of mental illnesses in the developing teen.

Videhult, F. K. and West, C. E. Nutrition, gut microbiota and child health outcomes. Curr.Opin.Clin.Nutr.Metab Care. 2016; 19(3):208-213.

ABSTRACT: PURPOSE OF REVIEW: Diet is one of the main drivers of the composition and function of the gut microbiota. The scope of this review is to summarize recent studies assessing the role of gut microbiota in clinical pediatric conditions and to review studies using nutritional approaches to favorably modify the gut microbiota to improve health outcomes in children. RECENT FINDINGS: New studies underscore that breastfeeding and infant diet impact the gut microbiome and metagenome. A comprehensive study using metagenomic shotgun sequencing, suggests that the cessation of breastfeeding rather than the introduction of solid foods, drives the functional maturation of the infant gut microbiome toward an adult-like state. There is further support for the view that a disturbed early gut microbiota is implicated in allergic and autoimmune diseases. New studies using prebiotics, probiotics, and synbiotics in various pediatric disorders have yielded promising results, yet the evidence for specific guidelines on their use is still low. SUMMARY: Intestinal dysbiosis is associated with several pediatric disorders but a cause-effect relationship remains to be clearly demonstrated in most conditions. Future studies using new systems biology approaches are anticipated to provide further insight into the functional capacities of the gut microbiome and its establishment in childhood. This may then lay the ground for improved treatment and prevention strategies targeting the gut microbiota.

Vlainic, J., Suran, J., Vlainic, T., and Vukorep, A. L. Probiotics as an adjuvant therapy in major depressive disorder. Curr.Neuropharmacol. 5-26-2016;

ABSTRACT: Major depressive disorder is a common, debilitating psychiatric disorder, which originates from the interaction of susceptibility genes and noxious environmental events, in particular stressful events. It has been shown that dysregulation of hypothalamus-pituitary-adrenal (HPA) axis, imbalance between anti- and pro-inflammatory cytokines, depletion of neurotransmitters (serotonin, norepinephrine and/or dopamine) in the central nervous system, altered glutamatergic and GABAergic transmission have an important role in the pathogenesis of depression. Due to pletiphora of biological events included in the pathophysiology of depression a large number of antidepressant drugs exerting distinct pharmacological effects have been developed. Nevertheless, clinical needs are still not solved. Relatively new research strategies advanced the understanding of psychiatric illness and their connections with disturbances in gastrointestinal tract. The existence of bidirectional communication between the brain and the gut has been proven, and an increasing body of evidence supports the hypothesis that cognitive and emotional processes are influenced through the brain-gut axis. On the other hand, microbiome may influence brain function and even behavior giving to the specific microorganisms a psychobiotic potential. In this review we discuss the possibilities of classical antidepressant drug treatment being supported with the psychobiotics/probiotic bacteria in patients suffering from major depressive disorder.

Vlasova, A. N., Shao, L., Kandasamy, S., Fischer, D. D., Rauf, A., Langel, S. N., Chattha, K. S., Kumar, A., Huang, H. C., Rajashekara, G., and Saif, L. J. Escherichia coli Nissle 1917 protects gnotobiotic pigs against human rotavirus by modulating pDC and NK-cell responses. Eur.J.Immunol. 7-26-2016;

ABSTRACT: Lactobacillus rhamnosus GG (LGG), a gram-positive lactic acid bacterium, is one of the most widely used probiotics; while fewer gram-negative probiotics including Escherichia coli Nissle 1917 (EcN) are characterized. A mechanistic understanding of their individual and interactive effects on human rotavirus (HRV) and immunity is lacking. In this study, noncolonized, EcN-, LGG- and EcN+LGG-colonized neonatal gnotobiotic (Gn) pigs were challenged with HRV. EcN colonization is associated with a greater protection against HRV, and induces the highest frequencies of plasmacytoid dendritic cells (pDCs), significantly increased natural killer (NK)-cell function and decreased frequencies of apoptotic and TLR4+ mononuclear cells (MNCs). Consistent with the highest NK-cell activity, splenic CD172+ MNCs (DC enriched fraction) of EcN-colonized pigs produced the highest levels of IL-12 in vitro. LGG colonization has little effect on the above parameters, which are intermediate in EcN+LGG-colonized pigs, suggesting that probiotics modulate each other's effects. Additionally, in vitro EcN-treated splenic or intestinal MNCs produce higher levels of innate, immunoregulatory and immunostimulatory cytokines, IFN-alpha, IL-12 and IL-10, compared to MNCs of pigs treated with LGG. These results indicate that the EcN-mediated greater protection against HRV is associated with potent stimulation of the innate immune system and activation of the DC-IL-12-NK immune axis. This article is protected by copyright. All rights reserved.

Vlasova, A. N., Kandasamy, S., Chattha, K. S., Rajashekara, G., and Saif, L. J. Comparison of probiotic lactobacilli and bifidobacteria effects, immune responses and rotavirus vaccines and infection in different host species. Vet.Immunol.Immunopathol. 2016; 172:72-84.

ABSTRACT: Different probiotic strains of Lactobacillus and Bifidobacterium genera possess significant and widely acknowledged health-promoting and immunomodulatory properties. They also provide an affordable means for prevention and treatment of various infectious, allergic and inflammatory conditions as demonstrated in numerous human and animal studies. Despite the ample evidence of protective effects of these probiotics against rotavirus (RV) infection and disease, the precise immune mechanisms of this protection remain largely undefined, because of limited mechanistic research possible in humans and investigated in the majority of animal models. Additionally, while most human clinical probiotic trials are well-standardized using the same strains, uniform dosages, regimens of the probiotic treatments and similar host age, animal studies often lack standardization, have variable experimental designs, and non-uniform and sometime limited selection of experimental variables or observational parameters. This review presents selected data on different probiotic strains of lactobacilli and bifidobacteria and summarizes the knowledge of their immunomodulatory properties and the associated protection against RV disease in diverse host species including neonates.

Vongbhavit, K. and Underwood, M. A. Prevention of Necrotizing Enterocolitis Through Manipulation of the Intestinal Microbiota of the Premature Infant. Clin.Ther. 2016; 38(4):716-732.

ABSTRACT: PURPOSE: In spite of four decades of research, necrotizing enterocolitis (NEC) remains the most common gastrointestinal complication in premature infants with high mortality and long-term morbidity. The composition of the intestinal microbiota of the premature infant differs dramatically from that of the healthy term infant and appears to

be an important risk factor for NEC. METHODS: We review the evidence of an association between intestinal dysbiosis and NEC and summarize published English language clinical trials and cohort studies involving attempts to manipulate the intestinal microbiota in premature infants. FINDINGS: Promising NEC prevention strategies that alter the intestinal microbiota include probiotics, prebiotics, synbiotics, lacteroferrin, and human milk feeding. IMPLICATIONS: Shaping the intestinal microbiota of the premature infant through human milk feeding and dietary supplements decreases the risk of NEC. Further studies to identify the ideal microbial composition and the most effective combination of supplements are indicated.

Wang, B. G., Wu, Y., Qiu, L., Shah, N. P., Xu, F., and Wei, H. Integration of genomic and proteomic data to identify candidate genes in HT-29 cells after incubation with Bifidobacterium bifidum ATCC 29521. J.Dairy Sci. 6-29-2016;

ABSTRACT: As the predominant group inhabiting the human gastrointestinal tract, bifidobacteria play a vital role in human nutrition, therapeutics, and health by shaping and maintaining the gut ecosystem, reducing blood cholesterol, and promoting the supply of nutrients. The interaction between bacterial cells and human intestinal epithelial cell lines has been studied for decades in an attempt to understand the mechanisms of action. These studies, however, have been limited by lack of genomic and proteomic database to aid in achieving comprehensive understanding of these mechanisms at molecular levels. Microarray data (GSE: 74119) coupled with isobaric tags for relative and absolute quantitation (iTRAQ) were performed to detect differentially expressed genes and proteins in HT-29 cells after incubation with Bifidobacterium bifidum. Real-time quantitative PCR, gene ontology, and Kyoto Encyclopedia of Genes and Genomes analyses were further conducted for mRNA validation, functional annotation, and pathway identification, respectively. According to the results of microarray, 1,717 differentially expressed genes, including 1,693 upregulated and 24 downregulated genes, were selected and classified by the gene ontology database. The iTRAQ analysis identified 43 differentially expressed proteins, where 29 proteins were upregulated and 14 proteins were downregulated. Eighty-two candidate genes showing consistent differences with microarray and iTRAQ were further validated in HT-29 and Caco-2 cells by real-time quantitative PCR. Nine of the top genes showing interesting results with high confidence were further investigated in vivo in mice intestine samples. Integration of genomic and proteomic data provides an approach to identify candidate genes that are more likely to function in ubiquitin-mediated proteolysis, positive regulation of apoptosis, membrane proteins, and transferase catalysis. These findings might contribute to our understanding of molecular mechanisms regulating the interaction between probiotics and intestinal epithelial cell lines.

Wang, F., Zhang, C., and Zeng, Q. Gut microbiota and immunopathogenesis of diabetes mellitus type 1 and 2. Front Biosci.(Landmark.Ed). 2016; 21:900-906.

ABSTRACT: Diabetes mellitus (DM) is a major increasing global health burden in the aging population. Understanding the etiology of DM is beneficial for its prevention as well as treatment. In light of the metagenome hypothesis, defined as the overall bacterial genome, gut microbes have attracted increasing attention in the pathogenesis of DM. Many studies have found that gut microbes are involved in the immunopathogenesis of DM. Probiotics strengthen the host's intestinal barrier and modulate the immune system, and have therefore been investigated in DM management. Recent epigenetic findings

in context of genes associated with inflammation suggest a possible way in which gut microbiota participate in the immunopathogenesis of DM. In this review, we discuss the role of gut microbiota in the immunopathogenesis of DM.

Wang, H., Lee, I. S., Braun, C., and Enck, P. Effect of probiotics on central nervous system functions in animals and humans - a systematic review. J.Neurogastroenterol.Motil. 7-13-2016;

ABSTRACT: To systematically review the effects of probiotics on central nervous system function in animals and humans, to summarize effective interventions (species of probiotic, dose, duration), and to analyze the possibility of translating preclinical studies. Literature searches were conducted in Pubmed, Medline, Embase, and the Cochrane Library. Only randomized controlled trials were included. In total, 38 studies were included: 25 in animals and 15 in humans (2 study was conducted in both). Most studies used Bifidobacterium (eg, B. longum, B. breve, and B. infantis) and Lactobacillus (eg, L. helveticus, and L. rhamnosus), with doses between 109 and 1010 colony-forming units for 2 weeks in animals and 4 weeks in humans. These probiotics showed efficacy in improving psychiatric disorder-related behaviors including anxiety, depression, autism spectrum disorder (ASD), obsessive-compulsive disorder, and memory abilities, including spatial and non-spatial memory. Because many of the basic science studies showed some efficacy of probiotics on central nervous system function, this background may guide and promote further preclinical and clinical studies. Translating animal studies to human studies has obvious limitations but also suggests possibilities. Here, we provide several suggestions for the translation of animal studies. More experimental designs with both behavioral and neuroimaging measures in healthy volunteers and patients are needed in the future.

Wang, H., Gao, K., Wen, K., Allen, I. C., Li, G., Zhang, W., Kocher, J., Yang, X., Giri-Rachman, E., Li, G. H., Clark-Deener, S., and Yuan, L. Lactobacillus rhamnosus GG modulates innate signaling pathway and cytokine responses to rotavirus vaccine in intestinal mononuclear cells of gnotobiotic pigs transplanted with human gut microbiota. BMC.Microbiol. 2016; 16(1):109

ABSTRACT: BACKGROUND: A better understanding of mechanisms underlying dose-effects of probiotics in their applications as treatments of intestinal infectious or inflammatory diseases and as vaccine adjuvant is needed. In this study, we evaluated the modulatory effects of Lactobacillus rhamnosus GG (LGG) on transplanted human gut microbiota (HGM) and on small intestinal immune cell signaling pathways in gnotobiotic pigs vaccinated with an oral attenuated human rotavirus (AttHRV) vaccine. RESULTS: Neonatal HGM transplanted pigs were given two doses of AttHRV on 5 and 15 days of age and were divided into three groups: none-LGG (AttHRV), 9-doses LGG (AttHRV + LGG9X), and 14-doses LGG (AttHRV + LGG14X) (n = 3-4). At post-AttHRV-inoculation day 28, all pigs were euthanized and intestinal contents and ileal tissue and mononuclear cells (MNC) were collected. AttHRV + LGG14X pigs had significantly increased LGG titers in the large intestinal contents and shifted structure of the microbiota as indicated by the formation of a cluster that is separated from the cluster formed by the AttHRV and AttHRV + LGG9X pigs. The increase in LGG titers concurred with significantly increased ileal HRV-specific IFN-gamma producing T cell responses to the AttHRV vaccine reported in our previous publication, suggesting pro-Th1 adjuvant effects of the LGG. Both 9- and 14-doses LGG fed pig groups had significantly higher

IkBalpha level and p-p38/p38 ratio, while significantly lower p-ERK/ERK ratio than the AttHRV pigs, suggesting activation of regulatory signals during immune activation. However, 9-doses, but not 14-doses LGG fed pigs had enhanced IL-6, IL-10, TNF-alpha, TLR9 mRNA levels, and p38 MAPK and ERK expressions in ileal MNC. Increased TLR9 mRNA was in parallel with higher mRNA levels of cytokines, p-NF-kB and higher p-p38/p38 ratio in MNC of the AttHRV + LGG9X pigs. CONCLUSIONS: The relationship between modulation of gut microbiota and regulation of host immunity by different doses of probiotics is complex. LGG exerted divergent dose-dependent effects on the intestinal immune cell signaling pathway responses, with 9-doses LGG being more effective in activating the innate immunostimulating TLR9 signaling pathway than 14-doses in the HGM pigs vaccinated with AttHRV.

Wang, J., Han, M., Zhang, G., Qiao, S., Li, D., and Ma, X. The Signal Pathway of Antibiotic Alternatives on Intestinal Microbiota and Immune Function. Curr.Protein Pept.Sci. 5-26-2016;

ABSTRACT: Antibiotics are one of the most important discoveries in the 20th century and have been widely used for treating animal diseases in the 21st century. However, antibiotic resistance among bacterial pathogens and widespread concerns regarding their use in animals has received great attention all over the world. Great attention has focused on scientific breakthroughs of the alternatives to antibiotics. Various materials such as enzymes, prebiotics, probiotics, minerals, antimicrobial peptides, acidifiers, plants and plant extracts have been tested as possible antibiotics alternatives. Owing to their effects on intestinal microbiota and immune function, research efforts have been conducted on the application of these feed supplements. This review highlights promising research results about the alternatives to antibiotics in animal husbandry that are expected to beneficially limit the adverse effects of antibiotics and ensure the safety of animal-derived foods and the environment.

Wang, J., Huang, S., Fu, N., Jeantet, R., and Chen, X. D. Thermal Aggregation of Calcium-Fortified Skim Milk Enhances Probiotic Protection during Convective Droplet Drying. J.Agric.Food Chem. 8-3-2016; 64(30):6003-6010.

ABSTRACT: Probiotic bacteria have been reported to confer benefits on hosts when delivered in an adequate dose. Spray-drying is expected to produce dried and microencapsulated probiotic products due to its low production cost and high energy efficiency. The bottleneck in probiotic application addresses the thermal and dehydration-related inactivation of bacteria during process. A protective drying matrix was designed by modifying skim milk with the principle of calcium-induced protein thermal aggregation. The well-defined single-droplet drying technique was used to monitor the droplet-particle conversion and the protective effect of this modified Ca-aggregated milk on Lactobacillus rhamnosus GG. The Ca-aggregated milk exhibited a higher drying efficiency and superior protection on L. rhamnosus GG during thermal convective drying. The mechanism was explained by the aggregation in milk, causing the lower binding of water in the serum phase and, conversely, local concentrated milk aggregates involved in bacteria entrapment in the course of drying. This work may open new avenues for the development of probiotic products with high bacterial viability and calcium enrichment.

Wang, J., Sun, C., Liu, C., Yang, Y., and Lu, W. Comparison of vaginal microbial community structure in healthy and endometritis dairy cows by PCR-DGGE and real-time PCR. Anaerobe. 2016; 38:1-6.

ABSTRACT: The normal vaginal microflora provides protection against infections of the reproductive tract. Previous studies have focused on the isolation and screening of probiotic strains from the vagina of cows; however, the vaginal microflora of postpartum cows is poorly characterized. The present study was conducted to evaluate and characterize the vaginal microflora of healthy postpartum cows in relation to postpartum cows with endometritis by using PCR followed by denaturing gradient gel electrophoresis (PCR-DGGE) and Real-time PCR. The study population comprised 5 healthy cows and 5 cows with endometritis. The results indicated that the vaginal bacterial microflora of healthy postpartum cows was dominated by Lactobacillus sakei subsp. and Weissella koreensis, while there were no dominant bacterial species in the vaginal microflora of postpartum cows with endometritis. Common microorganisms such as Bacteroides spp., Fusobacterium spp., Enterococcus spp., Prevotella spp., Clostridium perfringens strains, and Escherichia coli were detected in both groups of cows by Real-time PCR. The bacterial diversity in the vagina of cows with endometritis was significantly higher than that in healthy cows. The results indicated that the vaginal microflora of cows with endometritis was more diverse and lacked dominant bacterial species as compared to that of the healthy cows, suggesting that disruption of the normal vaginal microflora may contribute to the onset of endometritis. This microbial community analysis provided information that might be used to develop probiotics to treat endometritis in cows; however, further investigation is needed.

Wang, W., Cao, J., Yang, F., Wang, X., Zheng, S., Sharshov, K., and Li, L. High-throughput sequencing reveals the core gut microbiome of Bar-headed goose (Anser indicus) in different wintering areas in Tibet. Microbiologyopen. 2016; 5(2):287-295.

ABSTRACT: Elucidating the spatial dynamic and core gut microbiome related to wild bar-headed goose is of crucial importance for probiotics development that may meet the demands of bar-headed goose artificial breeding industries and accelerate the domestication of this species. However, the core microbial communities in the wild bar-headed geese remain totally unknown. Here, for the first time, we present a comprehensive survey of bar-headed geese gut microbial communities by Illumina high-throughput sequencing technology using nine individuals from three distinct wintering locations in Tibet. A total of 236,676 sequences were analyzed, and 607 OTUs were identified. We show that the gut microbial communities of bar-headed geese have representatives of 14 phyla and are dominated by Firmicutes, Proteobacteria, Actinobacteria, and Bacteroidetes. The additive abundance of these four most dominant phyla was above 96% across all the samples. At the genus level, the sequences represented 150 genera. A set of 19 genera were present in all samples and considered as core gut microbiome. The top seven most abundant core genera were distributed in that four dominant phyla. Among them, four genera (Lactococcus, Bacillus, Solibacillus, and Streptococcus) belonged to Firmicutes, while for other three phyla, each containing one genus, such as Proteobacteria (genus Pseudomonas), Actinobacteria (genus Arthrobacter), and Bacteroidetes (genus Bacteroides). This broad survey represents the most in-depth assessment, to date, of the gut microbes that associated with bar-headed geese. These data create a baseline for future bar-headed goose microbiology research, and make an original contribution to probiotics development for bar-headed goose artificial breeding industries.

Wang, X., Farnell, Y. Z., Peebles, E. D., Kiess, A. S., Wamsley, K. G., and Zhai, W. Effects of prebiotics, probiotics, and their combination on growth performance, small intestine morphology, and resident Lactobacillus of male broilers. Poult.Sci. 6-1-2016; 95(6):1332-1340.

ABSTRACT: Effects of commercial antimicrobials and the individual and combinational use of commercial prebiotics and probiotics in feed from d zero to 41 on the growth performance, small intestine size, jejunal morphology, and ileal resident bacteria population of broiler chickens were determined. A total of 1,040 one-day-old male Ross x Ross 708 broilers were randomly distributed to 80 floor pens (5 treatments, 16 replications per treatment, 13 chicks per pen). Five dietary treatments were employed: 1) a corn soybean-meal basal diet (served as a negative control diet, NC); 2) a basal diet supplemented with a commercial prebiotic product (Pre); 3) a basal diet supplemented with a probiotic product containing Bacillus subtilis spores (Pro); 4) a basal diet supplemented with both prebiotic and probiotic products (Pre + Pro); and 5) a basal diet supplemented with commercial antimicrobials (served as a positive control diet, PC). At d 14, Pre diets improved the relative level of Lactobacillus in ileal mucosa as compared to NC, Pro, or PC diets (P = 0.045) without improving broiler BW. Broilers fed PC diets exhibited the highest BW gain from d 15 to 27, the lowest duodenum, jejunum, and ileum relative weights as percentage of BW at d 27, and the highest breast weight at d 42 (P = 0.026, 0.035, 0.002, 0.025, and 0.035, respectively). Broilers fed Pro or Pre + Pro diets exhibited higher BW gain from d 28 to 41 (P = 0.005) and higher overall BW gain from d zero to 41 (P = 0.039) than those fed other diets. Dietary treatments did not affect jejunal morphology or ileal resident Escherichia coli level at any age. From our results, including spores of Bacillus subtilis in feed may stimulate growth at a later age and may facilitate broilers in reaching their target weight sooner. Therefore, probiotics are recommended as potential alternatives to antimicrobials in chicken diets, especially in grower and finisher feed.

Wang, Y., Li, X., Ge, T., Xiao, Y., Liao, Y., Cui, Y., Zhang, Y., Ho, W., Yu, G., and Zhang, T. Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016; 95(31):e4509

ABSTRACT: BACKGROUND: Respiratory tract infections (RTIs) represent one of the main health problems in children. Probiotics are viable bacteria that colonize the intestine and affect the host intestinal microbial balance. Accumulating evidence suggests that probiotic consumption may decrease the incidence of or modify RTIs. The authors systematically reviewed data from randomized controlled trials (RCTs) to investigate the effect of probiotic consumption on RTIs in children. METHODS: MEDLINE/PubMed, Embase, Cochrane Library, and Web of Science were systematically searched for RCTs regarding the effect of probiotics on RTIs in children. The outcomes included number of children experienced with at least 1 RTI episode, duration of illness episodes, days of illness per subject, and school/day care absenteeism due to infection. A random-effects model was used to calculate pooled relative risks, or mean difference (MD) with the corresponding 95% confidence interval (CI). RESULTS: A total of 23 trials involving 6269 children were eligible for inclusion in the systematic review. None of the trials showed a high risk of bias. The quality of the evidence of outcomes was moderate. The age range of subjects was from newborn to 18 years. The results of meta-analysis showed that

probiotic consumption significantly decreased the number of subjects having at least 1 RTI episode (17 RCTs, 4513 children, relative risk 0.89, 95% CI 0.82-0.96, P = 0.004). Children supplemented with probiotics had fewer numbers of days of RTIs per person compared with children who had taken a placebo (6 RCTs, 2067 children, MD -0.16, 95% CI -0.29 to 0.02, P = 0.03), and had fewer numbers of days absent from day care/school (8 RCTs, 1499 children, MD -0.94, 95% CI -1.72 to -0.15, P = 0.02). However, there was no statistically significant difference of illness episode duration between probiotic intervention group and placebo group (9 RCTs, 2817 children, MD -0.60, 95% CI -1.49 to 0.30, P = 0.19). CONCLUSION: Based on the available data and taking into account the safety profile of RCTs, probiotic consumption appears to be a feasible way to decrease the incidence of RTIs in children.

Wang, Y. B., Du, W., Fu, A. K., Zhang, X. P., Huang, Y., Lee, K. H., Yu, K., Li, W. F., and Li, Y. L. Intestinal microbiota and oral administration of Enterococcus faecium associated with the growth performance of new-born piglets. Benef.Microbes. 4-19-2016; 1-10.

ABSTRACT: The oral administration of Enterococcus faecium EF1 to new-born suckling and weaning piglets along with their growth performances and intestinal microbiota was investigated in this study. Twenty-four new-born piglets were initially divided into 2 groups. The probiotics group received 2 ml of 10% sterilised skimmed milk by oral gavage supplemented with 6x108 cfu/ml viable E. faecium EF1 at the first, the third and the fifth day after birth, while the control group received 2 ml of 10% sterilised skimmed milk without probiotics at the same time. Results showed that oral administration of E. faecium EF1 was associated with a remarkable increase on the body weight of piglets for both suckling and weaning periods, by 30.73% (P<0.01) and 320.84% (P<0.01), and also decreased the diarrhoea rate, by 43.21% (P<0.05) and 71.42% (P<0.05), respectively. In addition, 454-pyrosequencing analysis revealed that there was no significant difference in the intestinal microbial diversity of the suckling piglets between the two groups; nevertheless, when compared to the control group, the relative abundance of Firmicutes in the probiotics group was substantially augmented, while the relative abundance of Proteobacteria, Bacteroidetes and Fusobacteria diminished. However, results indicated that oral administration of E. faecium EF1 did not have any influence on the relative abundance of Firmicutes in weaning piglets rather than increasing the relative abundance of Bacteroidetes and decreasing the relative abundance of Proteobacteria. Furthermore, at the level of the Firmicutes phylum, the relative abundance of Lactobacillales in the probiotic group increased significantly. These findings suggest that oral administration of E. faecium EF1 to new-born piglets could improve the growth performance and intestinal microbiota of piglets for both suckling and weaning periods.

Wang, Y. H., Yao, N., Wei, K. K., Jiang, L., Hanif, S., Wang, Z. X., and Pei, C. X. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. Eur.J.Clin.Nutr. 6-22-2016;

ABSTRACT: A systematic review and meta-analysis were designed to evaluate the efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer. We searched the Cochrane Library, PubMed, EMBASE and Web of Science up to November 2015. We also hand searched the citation lists of included studies and previously identified systematic reviews to identify

further relevant trials. Odds ratio (OR) was used to compare efficacy, and the pooled OR was estimated using a random effects model; heterogeneity was assessed with Cochran's Q and the Higgins' I2-test. Two reviewers assessed trial quality and extracted data independently. Analysis and bias for each included study were performed using Review Manager 5.2. Nine randomized and placebo-controlled studies (N=1265 participants) were included for assessing efficacy, of which seven were about radiotherapy and two about chemotherapy. Probiotic groups were compared with control groups with respect to the the incidence of diarrhea, OR=0.47 (95% confidence interval 0.28-0.76; P=0.002). Eleven studies, including 1612 people (873 consuming probiotics and 739 not consuming probiotics), were used for the analysis of safety of probiotics. Of the 11 studies, seven studies had no adverse events (AEs) caused by probiotics, whereas four studies reported varying degrees of AEs in their treatment. Probiotics may have a beneficial effect in prevention of chemoradiotherapy-induced diarrhea generally, especially for Grade2 diarrhea. Probiotics may rarely cause AEs.European Journal of Clinical Nutrition advance online publication, 22 June 2016; doi:10.1038/ejcn.2016.102.

Wang, Z., Wang, L., Chen, Z., Ma, X., Yang, X., Zhang, J., and Jiang, Z. In Vitro Evaluation of Swine-Derived Lactobacillus reuteri: Probiotic Properties and Effects on Intestinal Porcine Epithelial Cells Challenged with Enterotoxigenic Escherichia coli K88. J.Microbiol.Biotechnol. 6-28-2016; 26(6):1018-1025.

ABSTRACT: Probiotics are considered as the best effective alternatives to antibiotics. The aim of this study was to characterize the probiotic potential of lactobacilli for use in swine farming by using in vitro evaluation methods. A total of 106 lactic acid bacterial isolates, originating from porcine feces, were first screened for the capacity to survive stresses considered important for putative probiotic strains. Sixteen isolates showed notable acid and bile resistance, antibacterial activity, and adherence to intestinal porcine epithelial cells (IPEC-1). One isolate, LR1, identified as Lactobacillus reuteri, was selected for extensive study of its probiotic and functional properties in IPEC-1 cell models. L. reuteri LR1 exhibited good adhesion to IPEC-1 cells and could inhibit the adhesion of enterotoxigenic Escherichia coli (ETEC) to IPEC-1 cells. L. reuteri LR1 could also modulate transcript and protein expression of cytokines involved in inflammation in IPEC-1 cells; the Lactobacillus strain inhibited the ETEC-induced expression of proinflammatory transcripts (IL-6 and TNF-alpha) and protein (IL-6), and increased the level of anti-inflammatory cytokine (IL-10). Measurement of the permeation of FD-4 showed that L. reuteri LR1 could maintain barrier integrity in monolayer IPEC-1 cells exposed to ETEC. Immunolocalization experiments showed L. reuteri LR1 could also prevent ETEC-induced tight junction ZO-1 disruption. Together, these results indicate that L. reuteri LR1 exhibits desirable probiotic properties and could be a potential probiotic for use in swine production.

Ward, T., Nichols, M., and Nutter, J. Can Probiotics Improve Your Surgical Outcomes? Plast.Surg.Nurs. 2016; 36(2):74-77.

ABSTRACT: Despite ongoing advances in medical technology, postoperative infections and infectious complications continue to be a significant cause of morbidity and mortality. Surgical trauma and prophylactic antibiotics disrupt the balance of the intestinal microbiota and barrier function of the gut, potentiating an enhanced inflammatory response and further immune system depression. With the increasing costs of health care and emergence of multidrug-resistant bacteria, alternative approaches

must be explored. Many clinical studies have demonstrated that the use of probiotics, prebiotics, or a combination of both (synbiotics) as a part of innovative strategies can improve outcomes of elective abdominal and gastrointestinal surgical procedures. It has been demonstrated that probiotics play a role in gut barrier improvement and immunomodulation. However, it is evident that additional research is needed including larger, multicenter, randomized controlled trials to validate the safety and efficacy of their use in surgical patients. The purpose of this article is to discuss background of probiotic use in abdominal/gastrointestinal surgery, risk and benefits, clinical relevance for health care providers, and further implications for research.

Warner, B. B. and Tarr, P. I. Necrotizing enterocolitis and preterm infant gut bacteria. Semin.Fetal Neonatal Med. 6-22-2016;

ABSTRACT: Necrotizing enterocolitis remains an intractable consequence of preterm birth. Gut microbial communities, especially bacterial communities, have long been suspected to play a role in the development of necrotizing enterocolitis. Direct-from-stool nucleic acid sequencing technology now offers insights into the make-up of these communities. Data are now converging on the roles of Gram-negative bacteria as causative agents, despite the dynamic nature of bacterial populations, the varying technologies and sampling strategies, and the overall small sample sizes in these case-control studies. Bacteria that confer protection from necrotizing enterocolitis have not been identified across studies. The beneficial effect of probiotics is not apparent in infants with birth weights <1000 g (these infants are at greatest risk of, and have the highest case fatality rate from, necrotizing enterocolitis). Further work should be directed to the modulating gut microbes, or the products they produce, to prevent this devastating complication of preterm birth.

Waserman, S. Doctor, can we prevent food allergy and eczema in our baby? Curr.Opin.Allergy Clin.Immunol. 2016; 16(3):265-271.

ABSTRACT: PURPOSE OF REVIEW: The purpose is to review evidence from recent clinical trials that focus on early life interventions to prevent the onset of eczema and food allergy. RECENT FINDINGS: There is evidence that skin barrier defects may be a risk factor for the development of eczema and may increase the risk of early onset food sensitization and allergy. The measurement of transepidermal water loss as a marker of skin barrier defect may be a simple, noninvasive measurement that may predict who is at risk of eczema, however, the protective effects of daily moisturizer application in high-risk infants remains unclear.Although there is increased attention on the role of intestinal microbiota and its influence on sensitization, there is limited evidence to support the preventive effects of probiotics on allergic diseases.Recent clinical trials have provided much needed evidence supporting the early introduction of peanut in the primary and secondary prevention of peanut allergy in high-risk children. There still remain unanswered questions and challenges regarding protocols and implementation of current recommendations. SUMMARY: Although progress has been considerable, the fact is that there are no simple strategies to prevent the development of eczema and food allergy in infants. Physicians must remain informed of the dynamic evidence in allergy prevention to make responsible, informed recommendations to families.

Weinberg, Z. G., Chen, Y., Volchinski, V., Sela, S., Ogunade, I. M., and Adesogan, A. An in vitro model to study interactions between Escherichia coli and lactic acid bacterial inoculants for silage in rumen fluid. Lett.Appl.Microbiol. 2016; 63(1):60-65.

ABSTRACT: Previous studies have shown that silages treated with lactic acid bacteria (LAB) inoculants enhance ruminants' performance. The objective of the current experiments was to develop an in vitro model to study interactions between LAB silage inoculants and inoculated silages and Escherichia coli (EC) in rumen fluid (RF). Our hypothesis was that some inoculants inhibit EC in RF. For that purpose buffered RF was incubated under anaerobic conditions at 39 degrees C with commercial strains of LAB silage inoculants or with laboratory corn and wheat silages treated with these LAB, an EC strain and with various ruminant feed ingredients. The EC strain was originally isolated from cattle manure and tagged with a plasmid expressing the green fluorescence protein and kanamycin and streptomycin resistance. Results indicate that the LAB or the treated silages did not suppress EC numbers in the RF. When the pH of the RF decreased below 5.0 the EC disappeared. We conclude that both LAB inoculants for silage and EC survived in RF for several days; however, the inoculants and silages treated with such inoculants did not inhibit EC in RF in vitro. SIGNIFICANCE AND IMPACT OF THE STUDY: Forage crops, silage and hay are initial stages of the food chain for humans. Cattle harbours and sheds enterobacteria regularly, some strains of which are pathogens. These can contaminate forage crops through field fertilization with cattle manure. The objective of this study was to develop an in vitro model to test whether lactic acid bacteria, which are used in silage inoculants, alone or in treated silages can inhibit Escherichia coli in rumen fluid. This study presents safety aspects and it is also part of a broad research effort aimed at finding out how LAB silage inoculants and inoculated silages enhance ruminant performance or exert probiotic effects in ruminants.

Weizman, Z., bu-Abed, J., and Binsztok, M. Lactobacillus reuteri DSM 17938 for the Management of Functional Abdominal Pain in Childhood: A Randomized, Double-Blind, Placebo-Controlled Trial. J.Pediatr. 2016; 174:160-164.

ABSTRACT: OBJECTIVE: To determine whether administration of Lactobacillus reuteri DSM 17938 is beneficial in functional abdominal pain (FAP) of childhood. STUDY DESIGN: A total of 101 children, aged 6-15 years, who fulfilled the Rome III criteria for FAP were enrolled in a randomized double-blind, placebo-controlled trial, and were randomly assigned to receive either L reuteri DSM 17938 or placebo for 4 weeks, with further follow-up of additional 4 weeks. Response to therapy was based on a self-reported daily questionnaire monitoring frequency and intensity of abdominal pain, using the faces scoring system by Hicks. RESULTS: L reuteri (n = 47) was significantly superior to placebo (n = 46) in relieving frequency (1.9 +/- 0.8 vs 3.6 +/- 1.7 episodes/wk, P < .02) and intensity (4.3 +/- 2.2 vs 7.2 +/- 3.1 Hicks score/wk, P < .01) of abdominal pain following 4 weeks of supplementation. There was no difference in school absenteeism rate or other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention and bloating, favoring L reuteri. CONCLUSIONS: L reuteri DSM 17938, compared with placebo, significantly reduced the frequency and intensity of FAP in children. TRIAL REGISTRATION: ClicalTrials.gov: NCT01180556.

West, C. E. Probiotics for allergy prevention. Benef.Microbes. 2016; 7(2):171-179.

ABSTRACT: Probiotics, given either as a supplement or in infant foods, have been evaluated in randomised controlled trials for allergy prevention. Here, the aim is to give an overview of the results from these primary prevention studies and to discuss current strategies. In most studies, single strains or a mixture of strains of lactic acid bacteria and bifidobacteria have been used--prenatally, postnatally or perinatally. Several meta-analyses have reported a moderate benefit of probiotics for eczema prevention, and the most consistent effect has been observed with a combined perinatal intervention in infants at high risk of allergic disease due to familial predisposition. In a recent meta-analysis, the use of multi-strain probiotics appeared to be most effective for eczema prevention. No preventive effect has been shown for other allergic manifestations. As long-term follow-up data on later onset allergic conditions (asthma and allergic rhinitis) are available only from a few of the initiated studies, reports from ongoing follow-up studies that are adequately powered to examine long-term outcomes are anticipated to provide more insight. Arguably, the differences in many aspects of study design and the use of different probiotic strains and combinations have made direct comparison difficult. To date, expert bodies do not generally recommend probiotics for allergy prevention, although the World Allergy Organization (WAO) in their recently developed guidelines suggests considering using probiotics in pregnant women, during breastfeeding and/or to the infant if at high risk of developing allergic disease (based on heredity). However, in concordance with other expert bodies, the WAO guideline panel stressed the low level of evidence and the need for adequately powered randomised controlled trials and a more standardised approach before clinical recommendations on specific strains, dosages and timing can be given.

West, C. E., Jenmalm, M. C., Kozyrskyj, A. L., and Prescott, S. L. Probiotics for treatment and primary prevention of allergic diseases and asthma: looking back and moving forward. Expert.Rev.Clin.Immunol. 2016; 12(6):625-639.

ABSTRACT: Microbial ecosystems cover the surface of the human body and it is becoming increasingly clear that our modern environment has profound effects on microbial composition and diversity. A dysbiotic gut microbiota has been associated with allergic diseases and asthma in cross-sectional and observational studies. In an attempt to restore this dysbiosis, probiotics have been evaluated in randomized controlled trials. Here, we review treatment and primary prevention studies, recent meta-analyses, and discuss the current understanding of the role of probiotics in this context. Many meta-analyses have shown a moderate benefit of probiotics for eczema prevention, whereas there is less evidence of a benefit for other allergic manifestations. Because of very low quality evidence and heterogeneity between studies, specific advice on the most effective regimens cannot yet be given - not even for eczema prevention. To be able to adopt results into specific recommendations, international expert organizations stress the need for well-designed studies.

Williams, B., Landay, A., and Presti, R. M. Microbiome alterations in HIV infection a review. Cell Microbiol. 2016; 18(5):645-651.

ABSTRACT: Recent developments in molecular techniques have allowed researchers to identify previously uncultured organisms, which has propelled a vast expansion of our knowledge regarding our commensal microbiota. Interest in the microbiome specific to HIV grew from earlier findings suggesting that bacterial translocation from the intestines is the cause of persistent immune activation despite effective viral suppression with

antiretroviral therapy (ART). Studies of SIV infected primates have demonstrated that Proteobacteria preferentially translocate and that mucosal immunity can be restored with probiotics. Pathogenic SIV infection results in a massive expansion of the virome, whereas non-pathogenic SIV infection does not. Human HIV infected cohorts have been shown to have microbiota distinctive from that of HIV negative controls and efforts to restore the intestinal microbiome via probiotics have often had positive results on host markers. The microbiota of the genital tract may play a significant role in acquisition and transmission of HIV. Modification of commensal microbial communities likely represents an important therapeutic adjunct to treatment of HIV. Here we review the literature regarding human microbiome in HIV infection.

Wischmeyer, P. E., McDonald, D., and Knight, R. Role of the microbiome, probiotics, and 'dysbiosis therapy' in critical illness. Curr.Opin.Crit Care. 2016; 22(4):347-353.

ABSTRACT: PURPOSE OF REVIEW: Loss of 'health-promoting' microbes and overgrowth of pathogenic bacteria (dysbiosis) in ICU is believed to contribute to nosocomial infections, sepsis, and organ failure (multiple organ dysfunction syndrome). This review discusses new understanding of ICU dysbiosis, new data for probiotics and fecal transplantation in ICU, and new data characterizing the ICU microbiome. RECENT FINDINGS: ICU dysbiosis results from many factors, including ubiquitous antibiotic use and overuse. Despite advances in antibiotic therapy, infections and mortality from often multidrug-resistant organisms (i.e., Clostridium difficile) are increasing. This raises the question of whether restoration of a healthy microbiome via probiotics or other 'dysbiosis therapies' would be an optimal alternative, or parallel treatment option, to antibiotics. Recent clinical data demonstrate probiotics can reduce ICU infections and probiotics or fecal microbial transplant (FMT) can treat Clostridium difficile. This contributes to recommendations that probiotics should be considered to prevent infection in ICU. Unfortunately, significant clinical variability limits the strength of current recommendations and further large clinical trials of probiotics and FMT are needed. Before larger trials of 'dysbiosis therapy' can be thoughtfully undertaken, further characterization of ICU dysbiosis is needed. To addressing this, we conducted an initial analysis demonstrating a rapid and marked change from a 'healthy' microbiome to an often pathogen-dominant microbiota (dysbiosis) in a broad ICU population. SUMMARY: A growing body of evidence suggests critical illness and ubiquitous antibiotic use leads to ICU dysbiosis that is associated with increased ICU infection, sepsis, and multiple organ dysfunction syndrome. Probiotics and FMT show promise as ICU therapies for infection. We hope future-targeted therapies using microbiome signatures can be developed to correct 'illness-promoting' dysbiosis to restore a healthy microbiome post-ICU to improve patient outcomes.

Woloszynek, S., Pastor, S., Mell, J. C., Nandi, N., Sokhansanj, B., and Rosen, G. L. Engineering Human Microbiota: Influencing Cellular and Community Dynamics for Therapeutic Applications. Int.Rev.Cell Mol.Biol. 2016; 324:67-124.

ABSTRACT: The complex relationship between microbiota, human physiology, and environmental perturbations has become a major research focus, particularly with the arrival of culture-free and high-throughput approaches for studying the microbiome. Early enthusiasm has come from results that are largely correlative, but the correlative phase of microbiome research has assisted in defining the key questions of how these microbiota interact with their host. An emerging repertoire for engineering the microbiome places current research on a more experimentally grounded footing. We

present a detailed look at the interplay between microbiota and host and how these interactions can be exploited. A particular emphasis is placed on unstable microbial communities, or dysbiosis, and strategies to reestablish stability in these microbial ecosystems. These include manipulation of intermicrobial communication, development of designer probiotics, fecal microbiota transplantation, and synthetic biology.

Wong, M. H., Mo, W. Y., Choi, W. M., Cheng, Z., and Man, Y. B. Recycle food wastes into high quality fish feeds for safe and quality fish production. Environ.Pollut. 6-25-2016;

ABSTRACT: The amount of food waste generated from modern societies is increasing, which has imposed a tremendous pressure on its treatment and disposal. Food waste should be treated as a valuable resource rather than waste, and turning it into fish feeds would be a viable alternative. This paper attempts to review the feasibility of using food waste to formulate feed pellets to culture a few freshwater fish species, such as grass carp, grey mullet, and tilapia, under polyculture mode (growing different species in the same pond). These species occupy different ecological niches, with different feeding modes (i.e., herbivorous, filter feeding, etc.), and therefore all the nutrients derived from the food waste could be efficiently recycled within the ecosystem. The problems facing environmental pollution and fish contamination; the past and present situation of inland fish culture (focusing on South China); upgrade of food waste based feed pellets by adding enzymes, vitamin-mineral premix, probiotics (yeast), prebiotics, and Chinese medicinal herbs into feeds; and potential health risks of fish cultivated by food waste based pellets are discussed, citing some local examples. It can be concluded that appropriate portions of different types of food waste could satisfy basic nutritional requirements of lower trophic level fish species such as grass carp and tilapia. Upgrading the fish pellets by adding different supplements mentioned above could further elevated the quality of feeds, leading to higher growth rates, and enhanced immunity of fish. Health risk assessments based on the major environmental contaminants (mercury, PAHs and DDTs) in fish flesh showed that fish fed food waste based pellets are safer for consumption, when compared with those fed commercial feed pellets.

Woodman, Z. Can one size fit all? Approach to bacterial vaginosis in sub-Saharan Africa. Ann.Clin.Microbiol.Antimicrob. 2016; 15:16

ABSTRACT: Bacterial vaginosis (BV) is the most common vaginal disorder affecting women of reproductive age and is associated with increased risk of sexually transmitted infections such as human immunodeficiency syndrome (HIV-1). Sub-Saharan Africa has the highest BV and HIV-1 burden and yet very few studies have focused on understanding the aetiology of BV and its association with HIV in this region. It has been suggested that we need to accurately diagnose and treat BV to lower the risk of HIV infection globally. However, effective diagnosis requires knowledge of what constitutes a "healthy" cervicovaginal microbiome and current studies indicate that Lactobacillus crispatus might not be the only commensal protective against BV: healthy women from different countries and ethnicities harbour alternative commensals. Microbiotas associated with BV have also shown global variation, further complicating effective diagnosis via culture-based assays as some species are difficult to grow. Antibiotics and probiotics have been suggested to be key in controlling BV infection, but the efficacy of this treatment might rely on reconstituting endogenous commensals while targeting a specific species of BV-associated bacteria (BVAB). Alternatively, therapy could inhibit essential BV bacterial growth factors e.g. sialidases or provide anti-microbial compounds

e.g. lactic acid associated with a healthy cervicovaginal microbiome. But without global investigation into the mechanism of BV pathogenesis and its association with HIV, selection of such compounds could be limited to Caucasian women from certain regions. To confirm this suggestion and guide future therapy we require standardised diagnostic assays and research methodologies. This review will focus on research papers that describe the global variation of BV aetiology and how this influences the identification of determinants of BV pathogenesis and potential probiotic and antimicrobial therapy.

Wu, B. B., Yang, Y., Xu, X., and Wang, W. P. Effects of Bifidobacterium supplementation on intestinal microbiota composition and the immune response in healthy infants. World J.Pediatr. 2016; 12(2):177-182.

ABSTRACT: BACKGROUND: Intestinal microbiotas are thought to be the most important source of maturational stimuli to the development of the immune system. However, few studies have focused on the development of T helper (Th) 1 immune response and antibody response to vaccinations in healthy infants, especially in a large cohort. Through this randomized, double-blind control trial, we investigated the effects of Bifidobacterium longum BB536 (BB536) supplementation on intestinal microbiota composition and the immune response in term infants. METHODS: In total, 300 healthy newborns were recruited, randomized and fed formula either supplemented with BB536 or with no supplementation. Stool samples were analyzed at months 2, 4 and 11. The representative cytokine for Th1 [interferon-gamma (IFN-gamma)] and Th2 [interleukin-4 (IL-4)] secretion cells were measured using enzyme-linked immunospot assay at 4 and 7 months of age. The antibody response to vaccines was measured at months 7 and 11. RESULTS: A total of 264 infants completed the study. The amount of bifidobacteria and the bifidobacteria/ Enterobacteriaceae ratio (B/E) were significantly higher in the BB536 supplementation group at months 2 and 4. The number of IFN-gamma secretion cells and the ratio of IFN-gamma/IL-4 secretion cells were increased in the BB536 supplementation group at 7 months. Moreover, the higher value of B/E in the early stages seems to be related to the increased Th1 response. No difference was observed between groups in the antibody response after vaccination. CONCLUSION: BB536 has positive effects on establishing a healthy intestinal microbiota early in life, and it also plays an important role in improving the Th1 immune response.

Wu, X., Ren, J., and Li, J. [Maintenance of intestinal barrier function in patients with chronic critical illness]. Zhonghua Wei Chang Wai Ke.Za Zhi. 2016; 19(7):740-742.

ABSTRACT: The syndrome known as chronic critical illness (CCI) is defined as that critically ill patients survive their initial acute illness but go on to experience persistent organ failures necessitating prolonged intensive care. Intestinal barrier is the physical barrier that separates the internal and external environments and prevents the invasion of pathogenic antigens. Due to its pathogenesis, many CCI patients have injured intestinal barrier. Gut is the motor organ of stress responses, and gut-associated infections may initiate multiple organ dysfunction. In this way, it is important to maintain intestinal barrier of such patients. Apart from treatment for underlying diseases, resuscitation aiming at improving tissue perfusion, appropriate nutritional support, protection of normal intestinal flora, and provision of probiotics can maintain intestinal barrier of CCI patients. The maintenance and support of barrier function requires attention.

Xie, Q., Pan, M., Huang, R., Tian, X., Tao, X., Shah, N. P., Wei, H., and Wan, C. Short communication: Modulation of the small intestinal microbial community composition over short-term or long-term administration with Lactobacillus plantarum ZDY2013. J.Dairy Sci. 6-16-2016;

ABSTRACT: The small intestinal (SI) microbiota has an essential role in the maintenance of human health. However, data about the indigenous bacteria in SI as affected by probiotics are limited. In our study, the short-term and long-term effects of a probiotic candidate, Lactobacillus plantarum ZDY2013, on the SI microbiota of C57BL/6J mice were investigated by the Illumina HiSeq (Novogene Bioinformatics Technology Co., Ltd., Tianjin, China) platform targeting the V4 region of the 16S rDNA. A total of 858,011 sequences in 15 samples were read. The alpha diversity analysis revealed that oral administration with L. plantarum ZDY2013 for 3 wk led to a significant increase in the richness and diversity of the SI bacterial community. Principal coordinate analysis and unweighted pair-group method with arithmetic means analysis showed a clear alteration in the SI microbiota composition after 3 wk of L. plantarum ZDY2013 treatment, although these changes were not found 6 wk after ceasing L. plantarum ZDY2013 administration. Species annotation showed that the dominant phyla in SI microbiota were Firmicutes, Bacteroidetes, Proteobacteria, and Verrucomicrobia. Interestingly, operational taxonomic unit cluster analysis showed that administration with L. plantarum ZDY2013 for 3 wk significantly increased the abundance of Proteobacteria, but decreased that of Bacteroidetes. Linear discriminant analysis coupled with effect size identified 18 bacterial taxa (e.g., Ruminococcus spp. and Clostridium spp.) that overgrew in the SI microbiota of the mice administered with L. plantarum ZDY2013 for 3 wk, and most of them belonged to the phyla Bacteroidetes and Proteobacteria. However, only one bacterial taxon (e.g., Nocardioides spp.) was over-represented in the SI microbiota of mice 6 wk after L. plantarum ZDY2013 administration. Overall, this study shows that oral administration with probiotic results in an important but transient alteration in the microbiota of SI.

Xiong, J., Dai, W., and Li, C. Advances, challenges, and directions in shrimp disease control: the guidelines from an ecological perspective. Appl.Microbiol.Biotechnol. 2016; 100(16):6947-6954.

ABSTRACT: High-density aquaculture has led to increasing occurrences of diseases in shrimp. Thus, it is imperative to establish effective and quantitative strategies for preventing and predicting these diseases. Water quality indices and investigations of specific pathogen abundance provide only a qualitative evaluation of the risk of shrimp disease and can be inaccurate. To address these shortcomings, we introduced intestinal indicative assemblages as independent variables with which to quantitatively predict incidences of shrimp disease. Given the ignorance regarding the niches differences in the shrimp intestine throughout its developmental stages, the use of probiotics in aquaculture has had limited success. Therefore, we propose the exploration of effective probiotic bacteria from shrimp intestinal flora and the establishment of therapeutic strategies dependent on shrimp age. Following ecological selection principles, we hypothesize that the larval stage provides the best opportunity to establish a desired gut microbiota through preemptive colonization of the treated rearing water with known probiotics. To employ this strategy, however, substantial barriers must be overcome.

Xu, J., Zhong, F., Zhang, Y., Zhang, J., Huo, S., Lin, H., Wang, L., Cui, D., and Li, X. Construction of Bacillus subtilis strain engineered for expression of porcine beta-defensin-2/cecropin P1 fusion antimicrobial peptides and its growth-promoting effect and antimicrobial activity. Asian-Australas.J.Anim Sci. 6-30-2016;

ABSTRACT: Probiotics and antimicrobial peptides (AMPs) in animal gastrointestinal tract play the crucial roles in microbiota maintenance, immune regulation and pathogen defending. Generating probiotics strain engineered for expressing AMPs should be beneficial for animal growth and production. Here, we generated B. subtilis strain engineered for expressing porcine beta-defensin-2 (pBD-2) and cecropin P1 (CP1) fusion antimicrobial peptide using their codon-optimized genes mediated by pMK4 prokaryotic expression vector. Results showed that the B. subtilis strain could efficiently express pBD-2/CP1 fusion antimicrobial peptide, without significantly influencing the growth of engineered B. subtilis by itself-produced fusion peptide. Both expressed pBD-2/CP1 fusion peptide and their individual peptides recovered from parental fusion peptide by enterokinase digestion possessed the antimicrobial activities to a variety of the bacteria, including gram-negative bacteria (E. coli, Salmonella typhimurium and Haemophilus parasuis) and gram-positive bacteria (Staphylococcus aureus). Supplementing the engineered B. subtilis to the pig feed could significantly promote the growth and the resistance to experimental colibacillosis in weaned piglets. This study laid the foundation for further investigation on its application in swine industry.

Xu, L., Wang, Y., Wang, Y., Fu, J., Sun, M., Mao, Z., and Vandenplas, Y. A double-blinded randomized trial on growth and feeding tolerance with Saccharomyces boulardii CNCM I-745 in formula-fed preterm infants. J.Pediatr.(Rio J.). 2016; 92(3):296-301.

ABSTRACT: OBJECTIVE: The use of probiotics is increasingly popular in preterm neonates, as they may prevent necrotizing enterocolitis sepsis and improve growth and feeding tolerance. There is only limited literature on Saccharomyces boulardii CNCM I-745 (S. boulardii) in preterm infants. METHOD: A prospective, randomized, case-controlled trial with the probiotic S. boulardii (50mg/kg twice daily) was conducted in newborns with a gestational age of 30-37 weeks and a birth weight between 1500 and 2500g. RESULTS: 125 neonates were enrolled; 63 in the treatment and 62 in the control group. Weight gain (16.14+/-1.96 vs. 10.73+/-1.77g/kg/day, p<0.05) and formula intake at maximal enteral feeding (128.4+/-6.7 vs. 112.3+/-7.2mL/kg/day, p<0.05) were significantly higher in the intervention group. Once enteral feeding was started, the time needed to reach full enteral feeding was significantly shorter in the probiotic group (0.4+/-0.1 vs. 1.7+/-0.5 days, p<0.05). There was no significant difference in sepsis. Necrotizing enterocolitis did not occur. No adverse effects related to S. boulardii were observed. CONCLUSION: Prophylactic supplementation of S. boulardii at a dose of 50mg/kg twice a day improved weight gain, improved feeding tolerance, and had no adverse effects in preterm infants >30 weeks old.

Xu, L. Z., Yang, L. T., Qiu, S. Q., Yang, G., Luo, X. Q., Miao, B. P., Geng, X. R., Liu, Z. Q., Liu, J., Wen, Z., Wang, S., Zhang, H. P., Li, J., Liu, Z. G., Li, H. B., and Yang, P. C. Combination of specific allergen and probiotics induces specific regulatory B cells and enhances specific immunotherapy effect on allergic rhinitis. Oncotarget. 7-29-2016;

ABSTRACT: The therapeutic efficacy of allergen specific immunotherapy (SIT) on allergic diseases is to be improved. Probiotics can regulate immune response. This study aims to

promote the effect of SIT on allergic rhinitis (AR) by co-administration with Clostridium butyricum (Cb). In this study, patients with AR sensitized to mite allergens were enrolled to this study, and treated with SIT or/and Cb. The therapeutic efficacy was evaluated by the total nasal symptom scores (NSS), medication scores, serum specific IgE levels and T helper (Th)2 cytokine levels. The improvement of immune regulation in the AR patients was assessed by immunologic approaches. The results showed that treating AR patients with SIT alone markedly reduced NSS and medication scores; but did not alter the serum specific IgE, Th2 cytokines and skin prick test (SPT) index. The clinical symptoms on AR in SIT group relapsed one month after stopping SIT. Co-administration of Cb significantly enhanced the efficacy of SIT on AR as shown by suppression of NSS, medication scores, serum specific IgE, Th2 cytokines and SPT index; the regulatory B cell frequency was also markedly increased. Such an effect on AR was maintained throughout the observation period even after stopping the treatment. Butyrate blocked the activation of histone deacetylase-1, the downstream activities of epsilon chain promoter activation, and the IgE production in the antigen specific B cells. On the other hand, butyrate induced the IL-10 expression in B cells with a premise of the B cell receptor activation by specific antigens. In conclusion, administration with Cb can markedly enhance the efficacy of SIT on AR.

Yacoub, R., Kaji, D., Patel, S. N., Simoes, P. K., Busayavalasa, D., Nadkarni, G. N., He, J. C., Coca, S. G., and Uribarri, J. Association between probiotic and yogurt consumption and kidney disease: insights from NHANES. Nutr.J. 2016; 15:10

ABSTRACT: BACKGROUND: Data from experimental animals suggest that probiotic supplements may retard CKD progression. However, the relationship between probiotic use, frequent yogurt consumption (as a natural probiotic source), and kidney parameters have not been evaluated in humans. FINDINGS: We utilized NHANES data, and analyzed the association of probiotic alone (1999-2012) and yogurt/probiotic (2003-2006) use with albuminuria and eGFR after adjustment for demographic and clinical parameters. Frequent yogurt consumption was defined as thrice or more weekly over the year prior to the interview. Frequent yogurt/probiotic consumers had lower adjusted odds of developing combined outcome (albuminuria and/or eGFR < 60 ml/min/1.73 m(2)) compared to infrequent consumers (OR = 0.76; 95 % CI = 0.61-0.94). When evaluated separately, frequent consumers had lower odds of albuminuria and nonsignificant trend towards decreased odds of low eGFR compared to infrequent consumers. In the probiotic cohort, probiotic consumers were found to have a lower adjusted odds of albuminuria compared to nonusers (OR = 0.59; 95 % CI = 0.37-0.94). CONCLUSION: Frequent yogurt and/or probiotics use is associated with decreased odds of proteinuric kidney disease. These hypothesis-generating results warrant further translational studies to further delineate the relationship between yogurt/probiotics with kidney dysfunction, as well as microbiome and dysbiosis as potential mediators.

Yadav, V., Varum, F., Bravo, R., Furrer, E., Bojic, D., and Basit, A. W. Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets. Transl.Res. 5-6-2016;

ABSTRACT: Ulcerative colitis and Crohn's disease are the 2 major phenotypes of inflammatory bowel disease (IBD), which are influenced by a complex interplay of immunological and genetic elements, though the precise etiology still remains unknown. With IBD developing into a globally prevailing disease, there is a need to explore new targets and a thorough understanding of the pathophysiological differences between

the healthy and diseased gut could unearth new therapeutic opportunities. In this review, we provide an overview of the major aspects of IBD pathogenesis and thereafter present a comprehensive analysis of the gut pathophysiology leading to a discussion on some of the most promising targets and biologic therapies currently being explored. These include various gut proteins (CXCL-10, GATA-3, NKG2D, CD98, microRNAs), immune cells recruited to the gut (mast cells, eosinophils, toll-like receptors 2, 4), dysregulated proinflammatory cytokines (interleukin-6, -13, -18, -21), and commensal microbiota (probiotics and fecal microbiota transplantation). We also evaluate some of the emerging nonconventional therapies being explored in IBD treatment focusing on the latest developments in stem cell research, oral targeting of the gut-associated lymphoid tissue, novel anti-inflammatory signaling pathway targeting, adenosine deaminase inhibition, and the beneficial effects of antioxidant and nutraceutical therapies. In addition, we highlight the growth of biologics and their targets in IBD by providing information on the preclinical and clinical development of over 60 biopharmaceuticals representing the state of the art in ulcerative colitis and Crohn's disease drug development.

Yamamoto, M. and Matsumoto, S. Gut microbiota and colorectal cancer. Genes Environ. 2016; 38:11

ABSTRACT: The mucosal immune system is unique to the gastrointestinal mucosa, in which a large number of immune cells are located and exert multiple functions. Meanwhile, ~100 trillion microorganisms are thought to co-inhabit in the gastrointestinal tract. Furthermore, immune cells and gut microbiota have a mutual influence and the maintenance of this symbiotic relationship results in gut homeostasis. A recent study suggested that a disturbance of gut microbiota-so called "dysbiosis"-is related to various diseases, such as inflammatory bowel disease (IBD) and colitis-associated cancer (CAC). In this review, we discuss the relationship between gut microbiota and the mucosal immune system with regard to the development of IBD and CAC. In addition, we elucidate the possibility of probiotics in treatment against these diseases.

Yan, K. and Garcia-Tsao, G. Novel prevention strategies for bacterial infections in cirrhosis. Expert.Opin.Pharmacother. 2016; 17(5):689-701.

ABSTRACT: INTRODUCTION: Bacterial infections are a serious complication of cirrhosis, as they can lead to decompensation, multiple organ failure, and/or death. Preventing infections is therefore very relevant. Because gut bacterial translocation is their main pathogenic mechanism, prevention of infections is mostly based on the use of orally administered poorly absorbed antibiotics such as norfloxacin (selective intestinal decontamination). However, antibiotic prophylaxis leads to antibiotic resistance, limiting therapy and increasing morbidity and mortality. Prevention of bacterial infections in cirrhosis should therefore move away from antibiotics. AREAS COVERED: This review focuses on various potentially novel methods to prevent infections in cirrhosis focusing on non-antibiotic strategies. The use of probiotics, nonselective intestinal decontamination with rifaximin, prokinetics and beta-blockers or fecal microbiota transplant as means of targeting altered gut microbiota, bile acids and FXR agonists are all potential alternatives to selective intestinal decontamination. Prokinetics and beta-blockers can improve intestinal motility, while bile acids and FXR agonists help by improving the intestinal barrier. Finally, granulocyte colony stimulating factor (G-CSF) and statins are emerging therapeutic strategies that may improve immune dysfunction in cirrhosis. EXPERT

OPINION: Evidence for these strategies has been restricted to animal studies and proof-of concept studies but we expect this to change in coming years.

Yang, D., Yu, X., Wu, Y., Chen, X., Wei, H., Shah, N. P., and Xu, F. Enhancing flora balance in the gastrointestinal tract of mice by lactic acid bacteria from Chinese sourdough and enzyme activities metabolism of protein, fat, and carbohydrate by the flora. J.Dairy Sci. 7-20-2016;

ABSTRACT: In this study, we investigated the effect of administration of 5 strains of lactic acid bacteria (LAB) isolated from traditional Chinese sourdough on the flora balance of gastrointestinal tract of mice. We specifically measured Enterococcus, Enterobacter, Bacteroides, and Lactobacillus by plate count and real-time PCR methods, and alpha-glucosidase, lactate dehydrogenase, esterase, and aminopeptidase activities as indicative of metabolism of sugar, fat, and protein from LAB isolated from feces of mice in vitro. The results showed that administration of Lactobacillus acidophilus LAC0201 and Lactobacillus fermentum LFE0302 lowered the uric acid index of serum. Lactobacillus acidophilus LAC0201, L. fermentum LFE0302, as well as Lactobacillus curvatus LCU0401 administration resulted in a reduction in the opportunistic pathogens (i.e., Enterococcus and Enterobacter), meanwhile, administration of L. fermentum LFE0302 and Lactobacillus sp. ULA0104 resulted in an increase in the counts of Lactobacillus. Lactobacillus fermentum LFE0302 administration increased starch digestion of intestinal flora after 4 wk of feeding and also resulted in increased alpha-glucosidase activity in the intestinal flora after 3 wk of feeding. We found a similar trend in esterase activity after administration of L. acidophilus LAC0201 for 3 wk. Hence, our study suggested that LAB from Chinese sourdough might be used as potential probiotics to strengthen the flora balance in gastrointestinal tract and positively change the metabolism of nutrients through bacterial enzyme activities.

Yang, G. Y., Zhu, Y. H., Zhang, W., Zhou, D., Zhai, C. C., and Wang, J. F. Influence of orally fed a select mixture of Bacillus probiotics on intestinal T-cell migration in weaned MUC4 resistant pigs following Escherichia coli challenge. Vet.Res. 2016; 47(1):71

ABSTRACT: Efficient strategies for treating enteritis caused by F4(+) enterotoxigenic Escherichia coli (ETEC)/verocytotoxigenic Escherichia coli (VTEC)/enteropathogenic E. coli (EPEC) in mucin 4 resistant (MUC4 RR; supposed to be F4ab/ac receptor-negative [F4ab/acR(-)]) pigs remain elusive. A low (3.9 x 10(8) CFU/day) or high (7.8 x 10(8) CFU/day) dose of Bacillus licheniformis and Bacillus subtilis spore mixture (BLS-mix) was orally administered to MUC4 RR piglets for 1 week before F4(+) ETEC/VTEC/EPEC challenge. Orally fed BLS-mix upregulated the expression of TLR4, NOD2, iNOS, IL-8, and IL-22 mRNAs in the small intestine of pigs challenged with E. coli. Expression of chemokine CCL28 and its receptor CCR10 mRNAs was upregulated in the jejunum of pigs pretreated with high-dose BLS-mix. Low-dose BLS-mix pretreatment induced an increase in the proportion of peripheral blood CD4(-)CD8(-) T-cell subpopulations and high-dose BLS-mix induced the expansion of CD4(-)CD8(-) T cells in the inflamed intestine. Immunostaining revealed that considerable IL-7Ralpha-expressing cells accumulated at the lamina propria of the inflamed intestines after E. coli challenge, even in pigs pretreated with either low- or high-dose BLS-mix, although Western blot analysis of IL-7Ralpha expression in the intestinal mucosa did not show any change. Our data indicate that oral administration of the probiotic BLS-mix partially ameliorates E. coli-induced enteritis through facilitating upregulation of intestinal IL-22 and IkappaBalpha expression, and

preventing loss of intestinal epithelial barrier integrity via elevating ZO-1 expression. However, IL-22 also elicits an inflammatory response in inflamed intestines as a result of infection with enteropathogenic bacteria.

Yao, G., Gao, P., and Zhang, W. Complete genome sequence of probiotic Bacillus coagulans HM-08: A potential lactic acid producer. J.Biotechnol. 6-20-2016; 228:71-72.

ABSTRACT: Bacillus coagulans HM-08 is a commercialized probiotic strain in China. Its genome contains a 3.62Mb circular chromosome with an average GC content of 46.3%. In silico analysis revealed the presence of one xyl operon as well as several other genes that are correlated to xylose utilization. The genetic information provided here may help to expand its future biotechnology potential in lactic acid production.

Yasueda, A., Mizushima, T., Nezu, R., Sumi, R., Tanaka, M., Nishimura, J., Kai, Y., Hirota, M., Osawa, H., Nakajima, K., Mori, M., and Ito, T. The effect of Clostridium butyricum MIYAIRI on the prevention of pouchitis and alteration of the microbiota profile in patients with ulcerative colitis. Surg.Today. 2016; 46(8):939-949.

ABSTRACT: PURPOSE: Ulcerative colitis (UC) is a chronic, relapsing, and refractory disorder of the intestine. Total proctocolectomy with ileal pouch anal anastomosis (IPAA) is the preferred and standard surgical procedure for patients' refractory to medical therapy. Pouchitis is one of the most common long-term complications after IPAA. In the present study, the safety and efficacy of Clostridium butyricum MIYAIRI (CBM) as a probiotic were examined. METHODS: A randomized and placebo-controlled study was performed. Seventeen patients were recruited from 2007 to 2013. Nine tablets of MIYA-BM((R)) or placebo were orally administered once daily. The cumulative pouchitis-free survival, pouch condition (using the modified pouch disease activity index), and blood parameters were evaluated. A fecal sample analysis was also performed. RESULTS: Subjects were randomly allocated to receive MIYA-BM or placebo (9 and 8 subjects, respectively). One subject in the MIYA-BM group and four subjects in the placebo group developed pouchitis. No side effects occurred in either group. Characteristic intestinal flora was observed in each group. CONCLUSIONS: Our results suggest that probiotic therapy with CBM achieved favorable results with minimal side effects and might be a useful complementary therapy for the prevention of pouchitis in patients with UC who have undergone IPAA.

Yee, C. S. and Rachid, R. The Heterogeneity of Oral Immunotherapy Clinical Trials: Implications and Future Directions. Curr.Allergy Asthma Rep. 2016; 16(4):25

ABSTRACT: Food allergy is a potentially life-threatening disease which affects up to 8% of children and 2-3% of adults. Increasing food allergy prevalence poses a major public health concern. Induction of desensitization to food allergens through oral immunotherapy (OIT) is an expanding area of study encompassing peanut, egg, milk, and other food allergens. OIT consists of administering incremental doses of food allergen to food-allergic patients, to induce a state of desensitization. Safety, tolerability, and efficacy all remain ongoing concerns. Clinical trials for oral immunotherapy have encompassed many variations, including differences in dosage sizes and frequency, duration of build-up, type of allergen used, patient characteristics, and adjuvant therapies. Consequently, studies have also shown variation in rates of adverse effects,

and successful desensitization. Here, we provide an overview of the key studies and discuss the implications of this heterogeneity. While desensitization is successful in the majority of patients, only a minority appear to develop sustained unresponsiveness even after years of therapy. Much larger and longitudinal studies using more homogenous protocols are needed in order to evaluate the clinical applicability of OIT, its long-term effectiveness, and effect on quality of life. The role of adjunctive therapies, including omalizumab and probiotics, requires further evaluation.

Yeung, T. W., Ucok, E. F., Tiani, K. A., McClements, D. J., and Sela, D. A. Microencapsulation in Alginate and Chitosan Microgels to Enhance Viability of Bifidobacterium longum for Oral Delivery. Front Microbiol. 2016; 7:494

ABSTRACT: Probiotic microorganisms are incorporated into a wide variety of foods, supplements, and pharmaceuticals to promote human health and wellness. However, maintaining bacterial cell viability during storage and gastrointestinal transit remains a challenge. Encapsulation of bifidobacteria within food-grade hydrogel particles potentially mitigates their sensitivity to environmental stresses. In this study, Bifidobacterium longum subspecies and strains were encapsulated in core-shell microgels consisting of an alginate core and a microgel shell. Encapsulated obligate anaerobes Bifidobacterium longum subsp. infantis and Bifidobacterium longum subsp. longum exhibited differences in viability in a strain-dependent manner, without a discernable relationship to subspecies lineage. This includes viability under aerobic storage conditions and modeled gastrointestinal tract conditions. Coating alginate microgels with chitosan did not improve viability compared to cells encapsulated in alginate microgels alone, suggesting that modifying the surface charge alone does not enhance delivery. Thus hydrogel beads have great potential for improving the stability and efficacy of bifidobacterial probiotics in various nutritional interventions.

Yeung, T. W., rroyo-Maya, I. J., McClements, D. J., and Sela, D. A. Microencapsulation of probiotics in hydrogel particles: enhancing Lactococcus lactis subsp. cremoris LM0230 viability using calcium alginate beads. Food Funct. 4-20-2016; 7(4):1797-1804.

ABSTRACT: Probiotics are beneficial microbes often added to food products to enhance the health and wellness of consumers. A major limitation to producing efficacious functional foods containing probiotic cells is their tendency to lose viability during storage and gastrointestinal transit. In this study, the impact of encapsulating probiotics within food-grade hydrogel particles to mitigate sensitivity to environmental stresses was examined. Confocal fluorescence microscopy confirmed that Lactococcus lactis were trapped within calcium alginate beads formed by dripping a probiotic-alginate mixture into a calcium solution. Encapsulation improved the viability of the probiotics during aerobic storage: after seven days, less than a two-log reduction was observed in encapsulated cells stored at room temperature, demonstrating that a high concentration of cells survived relative to non-encapsulated bacteria. These hydrogel beads may have applications for improving the stability and efficacy of probiotics in functional foods.

Yeung, T. W., rroyo-Maya, I. J., McClements, D. J., and Sela, D. A. Correction: Microencapsulation of probiotics in hydrogel particles: enhancing Lactococcus lactis

subsp. cremoris LM0230 viability using calcium alginate beads. Food Funct. 6-15-2016; 7(6):2909

ABSTRACT: Correction for 'Microencapsulation of probiotics in hydrogel particles: enhancing Lactococcus lactis subsp. cremoris LM0230 viability using calcium alginate beads' by Timothy W. Yeung et al., Food Funct., 2016, 7, 1797-1804.

Yi, S. H., Jernigan, J. A., and McDonald, L. C. Prevalence of probiotic use among inpatients: A descriptive study of 145 U.S. hospitals. Am.J.Infect.Control. 5-1-2016; 44(5):548-553.

ABSTRACT: BACKGROUND: To inform clinical guidance, public health efforts, and research directions, probiotic use in U.S. health care needs to be better understood. This work aimed to assess the prevalence of inpatient probiotic use in a sample of U.S. hospitals. METHODS: Probiotic use among patients discharged in 2012 was estimated using the MarketScan Hospital Drug Database. In addition, the annual trend in probiotic use (2006-2012) was assessed among a subset of hospitals. RESULTS: Among 145 hospitals with 1,976,167 discharges in 2012, probiotics were used in 51,723 (2.6%) of hospitalizations occurring in 139 (96%) hospitals. Patients receiving probiotics were 9 times more likely to receive antimicrobials (P < .0001) and 21 times more likely to have a Clostridium difficile infection diagnosis (P < .0001). The most common probiotic formulations were Saccharomyces boulardii (32% of patients receiving probiotics), Lactobacillus acidophilus and Lactobacillus bulgaricus (30%), L acidophilus (28%), and Lactobacillus rhamnosus (11%). Probiotic use increased from 1.0% of 1,090,373 discharges in 2006 to 2.9% of 1,006,051 discharges in 2012 (P < .0001). CONCLUSIONS: In this sample of U.S. hospitals, a sizable and growing number of inpatients received probiotics as part of their care despite inadequate evidence to support their use in this population. Additional research is needed to guide probiotic use in the hospital setting.

Younan, S., Sakita, G. Z., Albuquerque, T. R., Keller, R., and Bremer-Neto, H. Chromium(VI) bioremediation by probiotics. J.Sci.Food Agric. 2016; 96(12):3977-3982.

ABSTRACT: Chromium is a common mineral in the earth's crust and can be released into the environment from anthropogenic sources. Intake of hexavalent chromium (Cr(VI)) through drinking water and food causes toxic effects, leading to serious diseases, and is a commonly reported environmental problem. Microorganisms can mitigate or prevent the toxic effects caused by heavy metals in addition to having effective resistance mechanisms to prevent cell damage and bind to these metals, sequestering them from the cell surface and removing them from the body. Species of Lactobacillus, Streptococcus, Bacillus and Bifidobacterium present in the human mouth and gut and in fermented foods have the ability to bind and detoxify some of these substances. This review address the primary topics related to Cr(VI) poisoning in animals and humans and the use of probiotics as a way to mitigate or prevent the toxic effects caused by Cr(VI). Further advances in the genetic knowledge of such microorganisms may lead to discoveries which will clarify the most active microorganisms that act as bioprotectants in bodies exposed to Cr(VI) and are an affordable option for people and animals intoxicated by the oral route. (c) 2016 Society of Chemical Industry.

Yu, A. Q. and Li, L. The Potential Role of Probiotics in Cancer Prevention and Treatment. Nutr.Cancer. 2016; 68(4):535-544.

ABSTRACT: The human gut microbiota has a significant effect on many aspects of human physiology such as metabolism, nutrient absorption, and immune function. Imbalance of the microbiota has been implicated in many disorders including inflammatory bowel disease, obesity, asthma, psychiatric illnesses, and cancers. As a kind of functional foods, probiotics have been shown to play a protective role against cancer development in animal models. Clinical application of probiotics indicated that some probiotic strains could diminish the incidence of postoperative inflammation in cancer patients. Chemotherapy or radiotherapy-related diarrhea was relieved in patients who were administered oral probiotics. The present review summarizes the up-to-date studies on probiotic effects and the underlying mechanisms related to cancer. At present, it is commonly accepted that most commercial probiotic products are generally safe and can improve the health of the host. By modulating intestinal microbiota and immune response, some strains of probiotics can be used as an adjuvant for cancer prevention or/and treatment.

Yuan, Y., Sun, Z. M., Zhang, Y., Liang, F. F., and He, X. X. [Influence of gut microecology on the pathogenesis and treatment of nonalcoholic fatty liver disease]. Zhonghua Gan Zang.Bing.Za Zhi. 5-20-2016; 24(5):375-379.

ABSTRACT: OBJECTIVE: To establish a rat model of nonalcoholic fatty liver disease (NAFLD) using high-fat diet, and to dynamically observe the influence of the changes in gut microbiota on the development and progression of NAFLD in rats during and after modeling. METHODS: Sprague-Dawley rats were given high-fat diet to establish the model of NAFLD, and these rats were randomly divided into high-fat group, antibiotic pretreatment group, antibiotic treatment group, restricted diet group, and control group. The rats were sacrificed in different feeding periods, and 16sRNA fluorescent quantitative PCR was used to analyze the changes in ileocecal microbiota in rats. The liver pathological scores were determined, and enzymatic colorimetry was used to measure blood lipid level in serum and liver homogenate. The sample mean t-test was used for comparison between groups. RESULTS: Compared with the high-fat group, the restricted diet group showed the most significant improvements in quality of life and biochemical parameters. In the restricted diet group, the number of probiotics (Bifidobacterium and Lactobacillus) at the end of the ileum gradually increased and tended to increase over the time of intervention, and the most significant difference between this group and the high-fat group occurred at the 10th week (Bifidobacterium: 0.91+/-0.23 vs 0.28+/-0.12, $P < 0.05$; Lactobacillus: 0.78+/-0.04 vs 0.21+/-0.03, $P < 0.05$), while the number of enterococci decreased. There were no significant differences in enteric bacilli between groups (all $P > 0.05$). At the 10th week, the liver pathological scores in the control group, antibiotic treatment group, and restricted diet group were 1.13+/-1.74, 4.86+/-0.86, and 2.94+/-1.91, respectively, significantly lower than 7.09+/-2.03 in the high fat group (all $P < 0.05$). CONCLUSION: Diet structure change and antibiotic intervention can adjust gut microecology, alleviate the lesions of NAFLD, and thus provide new strategies for the prevention and treatment of NAFLD from the perspective of microecology.

Zacche, M. M. and Giarenis, I. Therapies in early development for the treatment of urinary tract inflammation. Expert.Opin.Investig.Drugs. 2016; 25(5):531-540.

ABSTRACT: INTRODUCTION: Urinary tract inflammation is a very common clinical condition. It is caused by several pathogens and antibiotic treatment is the mainstay of

therapy. Increasing antimicrobial resistance and high recurrence rates represent a challenge. Consequently, there is an unmet need for new therapeutic options. AREAS COVERED: The authors discuss the rationale of emerging management strategies and current experimentation. Furthermore, they focus on both acute and recurrent urinary tract infections (UTIs) and examine a range of therapeutics, including new antibiotics, vaccines, mannosides, hyaluronic acid, probiotics, immunomodulant agents and novel compounds derived from nanotechnology. EXPERT OPINION: Basic science studies have elucidated the pathogenesis of UTIs and built up the ground for the development of new therapies. Evidence is mainly derived from animal studies on murine models of bacterial cystitis. However, clinical trials are scanty and cannot provide us with robust evidence. Hetereogeneity and virulence of uropathogens pose a threat that scientists and clinicians are struggling to overcome.

Zamani, B., Golkar, H. R., Farshbaf, S., Emadi-Baygi, M., Tajabadi-Ebrahimi, M., Jafari, P., Akhavan, R., Taghizadeh, M., Memarzadeh, M. R., and Asemi, Z. Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Int.J.Rheum.Dis. 5-2-2016;

ABSTRACT: OBJECTIVE: This study was performed to determine the effects of probiotic supplementation on clinical and metabolic status of patients with rheumatoid arthritis (RA). METHODS: Sixty patients with RA aged 25-70 years were assigned into two groups to receive either probiotic capsules (n = 30) or placebo (n = 30) in this randomized, double-blind, placebo-controlled trial. The patients in the probiotic group received a daily capsule that contained three viable and freeze-dried strains: Lactobacillus acidophilus (2 x 109 colony-forming units [CFU]/g), Lactobacillus casei (2 x 109 CFU/g) and Bifidobacterium bifidum (2 x 109 CFU/g) for 8 weeks. The placebo group took capsules filled with cellulose for the same time period. Fasting blood samples were taken at the beginning and the end of the study to quantify related markers. RESULTS: After 8 weeks of intervention, compared with the placebo, probiotic supplementation resulted in improved Disease Activity Score of 28 joints (DAS-28) (-0.3 +/- 0.4 vs. -0.1 +/- 0.4, P = 0.01). In addition, a significant decrease in serum insulin levels (-2.0 +/- 4.3 vs. +0.5 +/- 4.9 mulU/mL, P = 0.03), homeostatic model assessment-B cell function (HOMA-B) (-7.5 +/- 18.0 vs. +4.3 +/- 25.0, P = 0.03) and serum high-sensitivity C-reactive protein (hs-CRP) concentrations (-6.66 +/- 2.56 vs. +3.07 +/- 5.53 mg/L, P < 0.001) following the supplementation of probiotics compared with the placebo. Subjects who received probiotic capsules experienced borderline statistically significant improvement in total- (P = 0.09) and low-density lipoprotein-cholesterol levels (P = 0.07) compared with the placebo. CONCLUSION: Overall, the results of this study indicated that taking probiotic supplements for 8 weeks among patients with RA had beneficial effects on DAS-28, insulin levels, HOMA-B and hs-CRP levels.

Zamberi, N. R., Abu, N., Mohamed, N. E., Nordin, N., Keong, Y. S., Beh, B. K., Zakaria, Z. A., Nik Abdul Rahman, N. M., and Alitheen, N. B. The Antimetastatic and Antiangiogenesis Effects of Kefir Water on Murine Breast Cancer Cells. Integr.Cancer Ther. 5-26-2016;

ABSTRACT: BACKGROUND: Kefir is a unique cultured product that contains beneficial probiotics. Kefir culture from other parts of the world exhibits numerous beneficial qualities such as anti-inflammatory, immunomodulation, and anticancer effects. Nevertheless, kefir cultures from different parts of the world exert different effects because of variation in culture conditions and media. Breast cancer is the leading

cancer in women, and metastasis is the major cause of death associated with breast cancer. The antimetastatic and antiangiogenic effects of kefir water made from kefir grains cultured in Malaysia were studied in 4T1 breast cancer cells. METHODS: 4T1 cancer cells were treated with kefir water in vitro to assess its antimigration and anti-invasion effects. BALB/c mice were injected with 4T1 cancer cells and treated orally with kefir water for 28 days. RESULTS: Kefir water was cytotoxic toward 4T1 cells at IC50 (half-maximal inhibitory concentration) of 12.5 and 8.33 mg/mL for 48 and 72 hours, respectively. A significant reduction in tumor size and weight (0.9132 +/- 0.219 g) and a substantial increase in helper T cells (5-fold) and cytotoxic T cells (7-fold) were observed in the kefir water-treated group. Proinflammatory and proangiogenic markers were significantly reduced in the kefir water-treated group. CONCLUSIONS: Kefir water inhibited tumor proliferation in vitro and in vivo mainly through cancer cell apoptosis, immunomodulation by stimulating T helper cells and cytotoxic T cells, and anti-inflammatory, antimetastatic, and antiangiogenesis effects. This study brought out the potential of the probiotic beverage kefir water in cancer treatment.

Zarate, G., Palacios, J. M., Villena, J., and Zuniga-Hansen, M. E. Inhibition of enteropathogens adhesion to human enterocyte-like HT-29 cells by a dairy strain of Propionibacterium acidipropionici. Benef.Microbes. 2016; 7(3):431-441.

ABSTRACT: Adhesion to the host intestinal mucosa is considered relevant for orally delivered probiotics as it prolongs their persistence in the gut and their health promoting effects. Classical propionibacteria are microorganisms of interest due to their role as dairy starters as well as for their functions as probiotics. Propionibacterium acidipropionici Q4, is a dairy strain isolated from a Swiss-type cheese made in Argentina that displays probiotic potential. In the present work we assessed the ability of this strain to adhere to the human enterocyte-like HT-29 cell line and to counteract the adhesion of two common human enteropathogens, such as Escherichia coli C3 and Salmonella Enteritidis 90/390. The results were compared with those obtained with the well-known probiotic Lactobacillus rhamnosus GG. P. acidipropionici Q4 showed a high adhesion capacity, even higher than the reference strain L. rhamnosus GG (42.3+/-4.4% and 36.2+/-2.3%, respectively), whereas adhesion of enteropathogens was significantly lower (25.2+/-2.2% for E. coli and 21.0+/-3.4% for S. Enteritidis). Propionibacteria as well as lactobacilli were able to inhibit by exclusion and competition the adherence of E. coli C3 and S. Enteritidis 90/390 whereas only L. rhamnosus GG displaced S. Enteritidis from HT-29 intestinal cells. Inhibition of pathogens by propionibacteria was not exerted by antimicrobials or coaggregation but was mainly due to exclusion by cell surface components, such as proteins and carbohydrates. The relevance of cell surface proteins (CSP) for preventing pathogens infection was confirmed by their concentration dependent effect observed for both pathogens: 100 microg/ml of CSP inhibited E. coli attachment almost as untreated propionibacteria, whereas it partially inhibited the attachment of S. Enteritidis. Results suggest that P. acidipropionici Q4 could be considered for the development of propionibacteria containing functional foods helpful in counteracting enteropathogen infection.

Zarlok, K. [Lactobacillus fermentum CECT5. Wiad.Lek. 2016; 69(2 pt 2):271-275.

ABSTRACT: Probiotics are an intensively growing part of the pharmaceutical and nutrition industries. Along with the intensive development of sales volumes and product offers, more and more scientific publications on this subject are available (at the time of writing

this article there are available almost 14 thousand publications in PubMed library). Scientists are trying to find new uses and new sources for this crucial group of nutrients or potential drugs. At the beginning of the XXI century it was discovered that the source of probiotics doesn't need to be only gastrointestinal tract (as previously thought), since they were obtained from breast milk which for many years were considered to be sterile. Probiotics from breast milk are an interesting group which could find application in mastitis, immunity support, infection prevention, infant colics and oral health. Main representative of this group is a strain of lactic acid bacteria Lactobacillus fermentum CECT5716.

Zeber-Lubecka, N., Kulecka, M., Ambrozkiewicz, F., Paziewska, A., Lechowicz, M., Konopka, E., Majewska, U., Borszewska-Kornacka, M., Mikula, M., Cukrowska, B., and Ostrowski, J. Effect of Saccharomyces boulardii and Mode of Delivery on the Early Development of the Gut Microbial Community in Preterm Infants. PLoS.One. 2016; 11(2):e0150306

ABSTRACT: BACKGROUND: Recent advances in culture-independent approaches have enabled insights into the diversity, complexity, and individual variability of gut microbial communities. OBJECTIVES: To examine the effect of oral administration of Saccharomyces (S.) boulardii and mode of delivery on the intestinal microbial community in preterm infants. STUDY DESIGN: Stool samples were collected from preterm newborns randomly divided into two groups: a probiotic-receiving group (n = 18) or a placebo group (n = 21). Samples were collected before probiotic intake (day 0), and after 2 and 6 weeks of supplementation. The composition of colonizing bacteria was assessed by 16S ribosomal RNA (rRNA) gene sequencing of fecal samples using the Ion 16S Metagenomics Kit and the Ion Torrent Personal Genome Machine platform. RESULTS: A total of 11932257 reads were generated, and were clustered into 459, 187, and 176 operational taxonomic units at 0 days, 2 weeks, and 6 weeks, respectively. Of the 17 identified phyla, Firmicutes Actinobacteria, Proteobacteria, and Bacteroidetes were universal. The microbial community differed at day 0 compared with at 2 weeks and 6 weeks. There was a tendency for increased bacterial diversity at 2 weeks and 6 weeks compared with day 0, and infants with a gestational age of 31 weeks or higher presented increased bacterial diversity prior to S. boulardii administration. Firmicutes and Proteobacteria remained stable during the observation period, whereas Actinobacteria and Bacteroidetes increased in abundance, the latter particularly more sharply in vaginally delivered infants. CONCLUSION: While the mode of delivery may influence the development of a microbial community, this study had not enough power to detect statistical differences between cohorts supplemented with probiotics, and in a consequence, to speculate on S. boulardii effect on gut microbiome composition in preterm newborns.

Zenda, T., Araki, I., Nakamiya, O., Tokuumi, Y., Shimada, Y., Komai, K., and Taniuchi, Y. Achilles tendinitis as a rare extraintestinal manifestation of ulcerative colitis. Clin.J.Gastroenterol. 2016; 9(3):129-133.

ABSTRACT: Patients with inflammatory bowel disease often have extraintestinal manifestations (EIMs) involving almost all organ systems, but little has been reported on Achilles tendinitis. Herein, we present a unique case of Achilles tendinitis, which manifested shortly after initiation of mesalazine therapy for ulcerative colitis. A 26-year-old Japanese woman with bloody diarrhea and abdominal cramps lasting for 7 days was referred to our hospital. The Lichtiger clinical activity index (CAI) score was 9 at the

first visit. Based on the clinical symptoms and examination results, she was diagnosed with ulcerative pancolitis in the active phase, and treatment with mesalazine (2.4 g/day) and probiotics was initiated. Her symptoms resolved within 7 days of treatment (CAI 3). However, she then developed bilateral Achilles tendinitis without any apparent cause. The Achilles tendinitis subsided with conservative management within 2 weeks, despite continuation of mesalazine therapy. This case instructively suggests that Achilles tendinitis should be noted as an EIM of ulcerative colitis.

Zeng, J. and Wang, C. T. Ventilation-associated pneumonia and probiotics: many clues do not make evidence. Response to comments by Colombo and Codazzi. Intensive Care Med. 7-28-2016.

No abstract currently available.

Zeng, J., Wang, C. T., Zhang, F. S., Qi, F., Wang, S. F., Ma, S., Wu, T. J., Tian, H., Tian, Z. T., Zhang, S. L., Qu, Y., Liu, L. Y., Li, Y. Z., Cui, S., Zhao, H. L., Du, Q. S., Ma, Z., Li, C. H., Li, Y., Si, M., Chu, Y. F., Meng, M., Ren, H. S., Zhang, J. C., Jiang, J. J., Ding, M., and Wang, Y. P. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. Intensive Care Med. 2016; 42(6):1018-1028.

ABSTRACT: PURPOSE: To evaluate the potential preventive effect of probiotics on ventilator-associated pneumonia (VAP). METHODS: This was an open-label, randomized, controlled multicenter trial involving 235 critically ill adult patients who were expected to receive mechanical ventilation for >/=48 h. The patients were randomized to receive (1) a probiotics capsule containing live Bacillus subtilis and Enterococcus faecalis (Medilac-S) 0.5 g three times daily through a nasogastric feeding tube plus standard preventive strategies or (2) standard preventive strategies alone, for a maximum of 14 days. The development of VAP was evaluated daily, and throat swabs and gastric aspirate were cultured at baseline and once or twice weekly thereafter. RESULTS: The incidence of microbiologically confirmed VAP in the probiotics group was significantly lower than that in the control patients (36.4 vs. 50.4 %, respectively; P = 0.031). The mean time to develop VAP was significantly longer in the probiotics group than in the control group (10.4 vs. 7.5 days, respectively; P = 0.022). The proportion of patients with acquisition of gastric colonization of potentially pathogenic microorganisms (PPMOs) was lower in the probiotics group (24 %) than the control group (44 %) (P = 0.004). However, the proportion of patients with eradication PPMO colonization on both sites of the oropharynx and stomach were not significantly different between the two groups. The administration of probiotics did not result in any improvement in the incidence of clinically suspected VAP, antimicrobial consumption, duration of mechanical ventilation, mortality and length of hospital stay. CONCLUSION: Therapy with the probiotic bacteria B. Subtilis and E. faecalis are an effective and safe means for preventing VAP and the acquisition of PPMO colonization in the stomach.

Zhai, Q., Tian, F., Zhao, J., Zhang, H., Narbad, A., and Chen, W. Oral Administration of Probiotics Inhibits Absorption of the Heavy Metal Cadmium by Protecting the Intestinal Barrier. Appl.Environ.Microbiol. 7-15-2016; 82(14):4429-4440.

ABSTRACT: The heavy metal cadmium (Cd) is an environmental pollutant that causes adverse health effects in humans and animals. Our previous work demonstrated that oral

administration of probiotics can significantly inhibit Cd absorption in the intestines of mice, but further evidence is needed to gain insights into the related protection mode. The goal of this study was to evaluate whether probiotics can inhibit Cd absorption through routes other than the Cd binding, with a focus on gut barrier protection. In the in vitro assay, both the intervention and therapy treatments of Lactobacillus plantarum CCFM8610 alleviated Cd-induced cytotoxicity in the human intestinal cell line HT-29 and protected the disruption of tight junctions in the cell monolayers. In a mouse model, probiotics with either good Cd-binding or antioxidative ability increased fecal Cd levels and decreased Cd accumulation in the tissue of Cd-exposed mice. Compared with the Cd-only group, cotreatment with probiotics also reversed the disruption of tight junctions, alleviated inflammation, and decreased the intestinal permeability of mice. L. plantarum CCFM8610, a strain with both good Cd binding and antioxidative abilities, exhibited significantly better protection than the other two strains. These results suggest that along with initial intestinal Cd sequestration, probiotics can inhibit Cd absorption by protecting the intestinal barrier, and the protection is related to the alleviation of Cd-induced oxidative stress. A probiotic with both good Cd-binding and antioxidative capacities can be used as a daily supplement for the prevention of oral Cd exposure. IMPORTANCE: The heavy metal cadmium (Cd) is an environmental pollutant that causes adverse health effects in humans and animals. For the general population, food and drinking water are the main sources of Cd exposure due to the biomagnification of Cd within the food chain; therefore, the intestinal tract is the first organ that is susceptible to Cd contamination. Moreover, Cd exposure causes the disruption of the intestinal barrier and further induces the amplification of Cd absorption. The present study confirms that, along with initial intestinal Cd sequestration, oral administration of probiotics can inhibit Cd absorption by protecting the intestinal barrier. A probiotic with both good Cd-binding and antioxidative capacities can be used as a daily supplement for the prevention of oral Cd exposure.

Zhang, F., Jiang, M., Wan, C., Chen, X., Chen, X., Tao, X., Shah, N. P., and Wei, H. Screening probiotic strains for safety: Evaluation of virulence and antimicrobial susceptibility of enterococci from healthy Chinese infants. J.Dairy Sci. 2016; 99(6):4282-4290.

ABSTRACT: The aim of this study was to evaluate the safety of enterococci isolated from Chinese infants and screen out potential probiotic candidates. One hundred eight strains were isolated from feces of 34 healthy infants, and 38 strains of Enterococcus spp. were categorized as follows: E. faecalis (22), E. faecium (10), E. hirae (3), E. durans (2), and E. casseliflavus (1). Of these, 72.7% of E. faecalis came from infants delivered by cesarean and 62.5% of E. faecium from infants delivered vaginally. For safety evaluation of strains, we determined presence of virulence genes; production of hemolysin, gelatinase, and biofilm; and antimicrobial susceptibility of enterococci. Six out of 14 virulence genes were detected with a distribution of gelE (26.3%), cylA (39.4%), esp (15.8%), efaA (63.2%), asa1 (50.0%), and ace (50.0%). In phenotype analysis, 36.8% of the strains exhibited positive hemolytic activity and 17.5% were positive for production of gelatinase. Results of antimicrobial susceptibility showed that different percentages of the strains were resistant to ciprofloxacin (5.2%), vancomycin (7.8%), rifampicin (10.5%), erythromycin (52.6%), and gentamycin (52.6%); remarkably, none of the strains were resistant to ampicillin or chloramphenicol. In total, 10 strains, including 6 E. faecium, which are free of virulence determinants and sensitive to common antimicrobial agents (e.g., ampicillin and vancomycin), were further assessed for their probiotic properties. All strains survived well in simulated gastric fluid and intestinal tract, with maximum reductions of 0.600 and 0.887 log cfu/mL, respectively. Six strains of E. faecium could resist 0.3 to 1.0% bile salt, of which

E. faecium WEFA23 presented the highest growth (75.06%) at 1.0% bile salt. All strains showed bile salt hydrolase activity on glycodeoxycholic acid, but only 3 of E. faecium showed activity on taurodeoxycholic acid. These results deliver useful information on the safety of enterococci in infants in China, and provide a protocol to screen probiotics for absence of virulence and antimicrobial susceptibility of enterococci.

Zhang, L., Zhang, L., Zhan, X., Zeng, X., Zhou, L., Cao, G., Chen, A., and Yang, C. Effects of dietary supplementation of probiotic, Clostridium butyricum, on growth performance, immune response, intestinal barrier function, and digestive enzyme activity in broiler chickens challenged with Escherichia coli K88. J.Anim Sci.Biotechnol. 2016; 7:3

ABSTRACT: BACKGROUND: Colibacillosis caused by enterotoxigenic Escherichia coli (E. coli) results in economic losses in the poultry industry. Antibiotics are usually used to control colibacillosis, however, E. coli has varying degrees of resistance to different antibiotics. Therefore the use of probiotics is becoming accepted as an alternative to antibiotics. In this study, we evaluated the effects of Clostridium butyricum (C. butyricum) on growth performance, immune response, intestinal barrier function, and digestive enzyme activity in broiler chickens challenged with Escherichia coli (E. coli) K88. METHODS: The chickens were randomly divided into four treatment groups for 28 days. Negative control treatment (NC) consisted of birds fed a basal diet without E. coli K88 challenge and positive control treatment (PC) consisted of birds fed a basal diet and challenged with E. coli K88. C. butyricum probiotic treatment (CB) consisted of birds fed a diet containing 2 x 10(7) cfu C. butyricum/kg of diet and challenged with E. coli K88. Colistin sulfate antibiotic treatment (CS) consisted of birds fed a diet containing 20 mg colistin sulfate/kg of diet and challenged with E. coli K88. RESULTS: The body weight (BW) and average day gain (ADG) in the broilers of CB group were higher ($P < 0.05$) than the broilers in the PC group overall except the ADG in the 14-21 d post-challenge. The birds in CB treatment had higher ($P < 0.05$) concentration of tumor necrosis factor-alpha (TNF-alpha) at 3 and 7 d post-challenge, and higher ($P < 0.05$) concentration of interleukin-4 (IL-4) at 14 d post-challenge than those in the PC treatment group. The concentration of serum endotoxin in CB birds was lower ($P < 0.05$) at 21 d post-challenge, and the concentrations of serum diamine oxidase in CB birds were lower ($P < 0.05$) at 14 and 21 d post-challenge than in PC birds. Birds in CB treatment group had higher ($P < 0.05$) jejunum villi height than those in PC, NC, or CS treatment at 7, 14, and 21 d post-challenge. In comparison to PC birds, the CB birds had lower ($P < 0.05$) jejunum crypt depth during the whole experiment. The birds in CB or CS treatment group had higher ($P < 0.05$) activities of amylase and protease at 3, 7, and 14 d post-challenge, and higher ($P < 0.05$) activity of lipase at 3, 7 d post-challenge than PC birds. CONCLUSIONS: In all, these results indicate that dietary supplementation with C. butyricum promotes immune response, improves intestinal barrier function, and digestive enzyme activities in broiler chickens challenged with E. coli K88. There is no significant difference between the C. butyricum probiotic treatment and the colistin sulfate antibiotic treatment. Therefore, the C. butyricum probiotic may be an alternative to antibiotic for broiler chickens.

Zhang, Q., Wu, Y., and Fei, X. Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Medicina (Kaunas.). 2016; 52(1):28-34.

ABSTRACT: OBJECTIVE: Our aim was to investigate the effects of probiotics on glucose metabolism in patients with type 2 diabetes mellitus using a meta-analysis of randomized,

controlled trials. MATERIALS AND METHODS: Online databases Embase, Web of Science, and PubMed were searched until August 2014 to identify eligible articles. Finally, 7 trials were included. RESULTS: Probiotic consumption significantly changed fasting plasma glucose (FPG) by -15.92mg/dL (95% confidence interval [CI], -29.75 to -2.09) and glycosylated hemoglobin (HbA1c) by -0.54% (95% CI, -0.82 to -0.25) compared with control groups. Subgroup analysis was conducted to trials with non-yogurts control. Meta-analysis of trials with multiple species of probiotics found a significant reduction in FPG (weighted mean difference [WMD]: -35.41mg/dL, 95% CI: -51.98 to -18.89). The duration of intervention for >/=8 weeks resulted in a significant reduction in FPG (WMD: -20.34mg/dL, 95% CI: -35.92 to -4.76). Subgroup analysis of trials with species of probiotics did not result in a significant meta-analysis effect. Furthermore, the duration of intervention <8 weeks did not result in a significant reduction in FPG. The results also showed that probiotic therapy significantly decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration (WMD: -1.08, 95% CI: -1.88 to -0.28; and WMD: -1.35mIU/L, 95% CI: -2.38 to -0.31, respectively). CONCLUSIONS: The present meta-analysis suggests that consuming probiotics may improve glucose metabolism by a modest degree, with a potentially greater effect when the duration of intervention is >/=8 weeks, or multiple species of probiotics are consumed.

Zhang, T., Xie, J., Zhang, M., Fu, N., and Zhang, Y. Effect of a potential probiotics Lactococcus garvieae B301 on the growth performance, immune parameters and caecum microflora of broiler chickens. J.Anim Physiol Anim Nutr.(Berl). 2016; 100(3):413-421.

ABSTRACT: In this study, a novel Lactococcus garvieae B301 was isolated from the intestinal tract of a healthy piglet. L. garvieae B301 was tolerant to acid pH, simulated gastric and small intestinal transit juices, indicating that it was capable of surviving in the gastrointestinal tract. L. garvieae B301 was safe and beneficial to broilers, as broiler chickens supplemented with L. garvieae B301 had lower diarrhoea incidence and mortality than the Control. Moreover, supplementation of broiler diets with L. garvieae B301 resulted in an increase in body weight and the number of caecum lactic acid bacteria and Bifidobacterium spp., and decrease in feed-to-gain ratio and the number of caecum coliforms. It also had a positive effect on the thymus index and bursa of Fabricius index and enhanced serum levels of immune globulins. All these results showed that L. garvieae B301 could enhance the growth performance of broiler chickens and improve their health. Thus, L. garvieae B301 could be a promising feed additive for broiler chickens.

Zhang, W., Guo, R., Yang, Y., Ding, J., and Zhang, Y. Long-term effect of heavy-metal pollution on diversity of gastrointestinal microbial community of Bufo raddei. Toxicol.Lett. 9-6-2016; 258:192-197.

ABSTRACT: Gastrointestinal (GI) microbiota plays a very important role in maintaining its host's health. However, the effects of environmental contamination on the GI microbiota homeostasis of amphibians have not yet been reported. The present study reveals the long-term effect of natural heavy-metal pollution on the GI microbial community diversity and structural changes of Bufo raddei (B. raddei). Basing on the 16S rRNA sequencing method, the GI microbiota of B. raddei from a heavily heavy-metal-polluted area (Baiyin, (BY)) and a relatively unpolluted area (Liujiaxia, (LJX)) were profiled. The results showed that heavy-metal pollution had caused significant shifts in the composition of the GI microbiota both at the phylum and genus levels. Specifically, Bacteroidetes dominated

in the GI tract of B. raddei from BY, while Tenericutes was much more common in those from LJX. The ratio of Firmicutes/Bacteroidetes and the proportion of probiotics in the GI microbiota of B. raddei from BY were reduced compared to those from LJX, as well. Heavy-metal pollution also induced in a reduction of species diversity and decreased proportion of unique operational taxonomic units in the GI tract. In short, our results demonstrate that long-term heavy-metal exposure re-shaped the composition and decreased the species diversity of GI microbiota of B. raddei; our results also represent a novel approach to uncover the toxic effects of pollution on amphibians.

Zhang, Y., Li, L., Guo, C., Mu, D., Feng, B., Zuo, X., and Li, Y. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. BMC.Gastroenterol. 2016; 16(1):62

ABSTRACT: BACKGROUND: Irritable bowel syndrome (IBS) is one of the most common functional gastroenterological diseases, affecting 11.2 % of people worldwide. Previous studies have shown that probiotic treatment may benefit IBS patients. However, the effect of probiotics and the appropriate type, dose, and treatment duration for IBS are still unclear. The aim of the current study was to assess the efficacy of different probiotic types, doses and treatment durations in IBS patients diagnosed by Rome III criteria via a meta-analysis of randomized controlled trials (RCTs). METHODS: Medline, EMBASE, and the Cochrane Central Register of Controlled Trials up to October 2015 were searched. RCTs including comparisons between the effects of probiotics and placebo on IBS patients diagnosed by Rome III criteria were eligible. Dichotomous data were pooled to obtain the relative risk (RR) with a 95 % confidence interval (CI), whereas continuous data were pooled using a standardized mean difference (SMD) with a 95 % CI. RESULTS: Twenty-one RCTs were included in this meta-analysis. Probiotic therapy was associated with more improvement than placebo administration in overall symptom response (RR: 1.82, 95 % CI 1.27 to 2.60) and quality of life (QoL) (SMD: 0.29, 95 % CI 0.08 to 0.50), but not in individual IBS symptoms. Single probiotics, a low dose, and a short treatment duration were more effective with respect to overall symptom response and QoL. No differences were detected in individual IBS symptoms in the subgroup analyses. CONCLUSION: Probiotics are an effective pharmacological therapy in IBS patients. Single probiotics at a low dose and with a short treatment duration appear to be more effective in improving overall symptom response and QoL, but more evidence for these effects is still needed.

Zhao, C., Lv, X., Fu, J., He, C., Hua, H., and Yan, Z. In vitro inhibitory activity of probiotic products against oral Candida species. J.Appl.Microbiol. 2016; 121(1):254-262.

ABSTRACT: AIMS: To evaluate the inhibitory activity of probiotics against oral Candida species. METHODS AND RESULTS: Four commercial probiotic products were screened. Bacillus subtilis R0179 was found to have a significant antifungal effect. Bacillus subtilis-Candida interactions were evaluated using disc diffusion tests, confocal laser scanning microscopy, scanning electron microscopy and interaction with engineered human oral mucosa tissue. Bacillus subtilis exhibited clear zones of inhibition for Candida albicans and Candida parapsilosis but not for Candida krusei. A remarkable reduction in the number of Candida cells and abundant Candida cell death were visualized with confocal laser scanning microscopy. Shrinkage and deformation of Candida cells was observed using scanning electron microscopy. Culture of C. albicans on engineered human oral mucosa tissues resulted in the presence of a large number of yeast cells on the tissue surface and the development of large-scale tissue damage. However,

comparatively fewer Candida cells were observed on B. subtilis-treated tissues. We also use ultra performance liquid chromatography/time of flight mass spectrometry (UPLC/TOF MS) to explore the preliminary antifungal mechanism of B. subtilis R0179 and to detect that whether it can secrete an antifungal agent, Iturin A. CONCLUSIONS: Bacillus subtilis R0179 exhibits a significant inhibitory effect on the growth of Candida species. SIGNIFICANCE AND IMPACT OF THE STUDY: Bacillus subtilis has the potential to be used in the prevention or treatment of oral candidiasis.

Zhao, Y. and Yu, Y. B. Intestinal microbiota and chronic constipation. Springerplus. 2016; 5(1):1130

ABSTRACT: Chronic constipation is a prevalent, burdensome gastrointestinal disorder whose aetiology and pathophysiology remains poorly understood and is most likely multifactorial. Differences in the composition of the intestinal microbiota have been demonstrated when constipated patients and healthy controls have been compared. Growing evidence indicates that alterations of intestinal microbiota may contribute to constipation and constipation-related symptoms. The intestinal microbiota is a collection of microorganisms that live within the gastrointestinal tract, and perform many important health-promoting functions. The intestinal microbiota aids in the breakdown of food products into absorbable nutrients, stimulates the host immune system, prevents growth of pathogenic bacteria and produces a great variety of biologically important compounds. In this review, we will summarize the current evidence supporting roles of the intestinal microbiota in the pathogenesis and management of chronic constipation. The discussion will shed light on the novel mechanisms of intestinal microbiota and gut function interactions, which is invaluable in ultimately developing new therapeutic tools for the treatment of chronic constipation.

Zheng, B., van, Bergenhenegouwen J., van de Kant, H. J., Folkerts, G., Garssen, J., Vos, A. P., Morgan, M. E., and Kraneveld, A. D. Specific probiotic dietary supplementation leads to different effects during remission and relapse in murine chronic colitis. Benef.Microbes. 2016; 7(2):205-213.

ABSTRACT: Although interest in using probiotics to prevent and treat intestinal diseases is increasing, the effects of specific probiotic strains still remain unclear. Here, we assess the therapeutic effects of two probiotic strains, Lactobacillus rhamnosus NutRes 1 and Bifidobacterium breve NutRes 204 on a dextran sodium sulphate (DSS)-induced chronic murine colitis model. The chronic colitis was induced by two DSS treatment cycles with a rest period of 10 days (the remission or resolution phase). The probiotic supplementation was started during the resolution phase, after the first DSS treatment cycle, and continued until the end of the experiment. In addition to clinical observations made during the experiment, cellular infiltration was measured along with mRNA expression of pro-inflammatory cytokines, T cell-associated cytokines, and Toll like receptors (TLR) in the inflamed colon after second DSS treatment cycle. L. rhamnosus, but not B. breve, rapidly and effectively improved the DSS-induced bloody diarrhoea during the resolution phase. However, a contradictory effect by both probiotic strains on the faecal condition was found after re-induction of colitis. The worsening of the faecal condition was accompanied by a reduced number of neutrophils and increased expression of interferon-gamma in the colons of DSS-treated mice. Furthermore, an increased expression of TLR2, TLR6 and pro-inflammatory markers including chemokine (C-C motif) ligand 2, interleukin (IL)-1beta, tumour necrosis factor alpha and IL-6 was found in DSS-

treated mice with L. rhamnosus supplementation. These results indicate that therapeutic administration of specific probiotics might be beneficial during the resolution phase of colitis. However, caution should be taken as specific probiotic treatments reduce neutrophil influx, which may be the reason of exacerbation of chronic colitis.

Zhu, D., Sun, Y., Liu, F., Li, A., Yang, L., and Meng, X. C. Identification of surface-associated proteins of Bifidobacterium animalis ssp. lactis KLDS 2.0603 by enzymatic shaving. J.Dairy Sci. 2016; 99(7):5155-5172.

ABSTRACT: Bifidobacteria are commensal microorganisms of the human and animal intestinal tract, and their surface proteins can mediate bacterial communication and chemical sensing in the environment, as well as facilitate interactions between bacteria and the host. However, a systematic study of the outer surface-associated proteome of bifidobacteria has not been undertaken. In the present study, the proteins located on the surface of Bifidobacterium animalis ssp. lactis KLDS 2.0603 were systematically identified by a nongel proteomic approach, which consisted of the shaving of the bacterial surface with trypsin and an analysis of the released peptides by liquid chromatography-tandem mass spectrometry. A total of 105 surface-associated proteins were found, of which 15 proteins could potentially be involved in adhesion and interactions between bifidobacteria and the host. The proteins related to adhesion and interaction between bacteria and the host include pilus structure proteins (Fim A, Fim B), 10 moonlighting proteins, an NLP/P60 family protein, an immunogenic secreted protein, and a putative sugar-binding secreted protein. The results provide the basis for future studies on the molecular mechanisms of the interactions between bifidobacteria and the host.

Zhu, J., Ren, T., Zhou, M., and Cheng, M. The combination of blueberry juice and probiotics reduces apoptosis of alcoholic fatty liver of mice by affecting SIRT1 pathway. Drug Des Devel.Ther. 2016; 10:1649-1661.

ABSTRACT: PURPOSE: To explore the effects of the combination of blueberry juice and probiotics on the apoptosis of alcoholic fatty liver disease (AFLD). METHODS: Healthy C57BL/6J mice were used in the control group (CG). AFLD mice models were established with Lieber-DeCarli ethanol diet and evenly assigned to six groups with different treatments: MG (model), SI (SIRT1 [sirtuin type 1] small interfering RNA [siRNA]), BJ (blueberry juice), BJSI (blueberry juice and SIRT1 siRNA), BJP (blueberry juice and probiotics), and BJPSI (blueberry juice, probiotics, and SIRT1 siRNA). Hepatic tissue was observed using hematoxylin and eosin (HE) and Oil Red O (ORO) staining. Biochemical indexes of the blood serum were analyzed. The levels of SIRT1, caspase-3, forkhead box protein O1 (FOXO1), FasL (tumor necrosis factor ligand superfamily member 6), BAX, and Bcl-2 were measured by reverse transcription-polymerase chain reaction and Western blotting. RESULTS: HE and ORO staining showed that the hepatocytes were heavily destroyed with large lipid droplets in MG and SI groups, while the severity was reduced in the CG, BJ, and BJP groups ($P<0.05$). The levels of superoxide dismutase (SOD), reduced glutathione (GSH), and high-density lipoprotein-cholesterol (HDL-C) were increased in BJ and BJP groups when compared with the model group ($P<0.05$). In contrast, the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total triglycerides (TGs), total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and malondialdehyde (MDA) were lower in BJ and BJP groups than in the model group ($P<0.05$). The level of SIRT1 was increased, while the levels of FOXO1, phosphorylated FOXO1, acetylated

FOXO1, FasL, caspase-3, BAX, and Bcl-2 were decreased in CG, BJ, and BJP groups (P<0.05). Meanwhile, SIRT1 silence resulted in increase of the levels of FOXO1, phosphorylated FOXO1, acetylated FOXO1, FasL, caspase-3, BAX, and Bcl-2. CONCLUSION: The combination of blueberry juice and probiotics reduces apoptosis in AFLD by suppressing FOXO1, phosphorylated FOXO1, acetylated FOXO1, FasL, caspase-3, BAX, and Bcl-2 via the upregulation of SIRT1.

Zhu, Y. and Wang, Y. Administering Probiotics in Duodenal-Jejunal Bypass Surgery Induces More Weight Loss in Sprague-Dawley Rats. Obes.Surg. 2016; 26(5):1116-1117.

No abstract currently available.

Zoccali, G., Cinque, B., La, Torre C., Lombardi, F., Palumbo, P., Romano, L., Mattei, A., Orsini, G., Cifone, M. G., and Giuliani, M. Improving the outcome of fractional CO2 laser resurfacing using a probiotic skin cream: Preliminary clinical evaluation. Lasers Med.Sci. 7-13-2016;

ABSTRACT: As known, fractional CO2 resurfacing treatments are more effective than non-ablative ones against aging signs, but post-operative redness and swelling prolong the overall downtime requiring up to steroid administration in order to reduce these local systems. In the last years, an increasing interest has been focused on the possible use of probiotics for treating inflammatory and allergic conditions suggesting that they can exert profound beneficial effects on skin homeostasis. In this work, the Authors report their experience on fractional CO2 laser resurfacing and provide the results of a new post-operative topical treatment with an experimental cream containing probiotic-derived active principles potentially able to modulate the inflammatory reaction associated to laser-treatment. The cream containing DermaACB (CERABEST) was administered post-operatively to 42 consecutive patients who were treated with fractional CO2 laser. All patients adopted the cream twice a day for 2 weeks. Grades were given according to outcome scale. The efficacy of the cream containing DermaACB was evaluated comparing the rate of post-operative signs vanishing with a control group of 20 patients topically treated with an antibiotic cream and a hyaluronic acid based cream. Results registered with the experimental treatment were good in 22 patients, moderate in 17, and poor in 3 cases. Patients using the study cream took an average time of 14.3 days for erythema resolution and 9.3 days for swelling vanishing. The post-operative administration of the cream containing DermaACB induces a quicker reduction of post-operative erythema and swelling when compared to a standard treatment.

Zorriehzahra, M. J., Delshad, S. T., Adel, M., Tiwari, R., Karthik, K., Dhama, K., and Lazado, C. C. Probiotics as beneficial microbes in aquaculture: an update on their multiple modes of action: a review. Vet.Q. 4-14-2016; 1-14.

ABSTRACT: Wide and discriminate use of antibiotics has resulted in serious biological and ecological concerns, especially the emergence of antibiotic resistance. Probiotics, known as beneficial microbes, are being proposed as an effective and eco-friendly alternative to antibiotics. They were first applied in aquaculture species more than three decades ago, but considerable attention had been given only in the early 2000s. Probiotics are defined as live or dead, or even a component of the microorganisms that act under different modes of action in conferring beneficial effects to the host or to its environment. Several probiotics have been characterized and applied in fish and a

number of them are of host origin. Unlike some disease control alternatives being adapted and proposed in aquaculture where actions are unilateral, the immense potential of probiotics lies on their multiple mechanisms in conferring benefits to the host fish and the rearing environment. The staggering number of probiotics papers in aquaculture highlights the multitude of advantages from these microorganisms and conspicuously position them in the dynamic search for health-promoting alternatives for cultured fish. This paper provides an update on the use of probiotics in finfish aquaculture, particularly focusing on their modes of action. It explores the contemporary understanding of their spatial and nutritional competitiveness, inhibitory metabolites, environmental modification capability, immunomodulatory potential and stress-alleviating mechanism. This timely update affirms the importance of probiotics in fostering sustainable approaches in aquaculture and provides avenues in furthering its research and development.

Zuccotti, G., Albani, E., and Meneghin, F. How Solid Is the Scientific Evidence on Probiotics? J.Clin.Gastroenterol. 2016; 50(8):686.

No abstract currently available.

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