

Report of the 2022 Annual Meeting of the
**International Scientific Association for
Probiotics and Prebiotics**



**June 15-17th,
2022**

**Sitges,
Barcelona,
Spain**

*Sitges Church, Iglesia de San Bartolomé y Santa Tecla
Original art by Laurel Beckett, Davis CA*

EXECUTIVE SUMMARY



ISAPP Plenary Sessions – Dolce Hotel, Sitges, Barcelona, Spain

ISAPP held its annual meeting in Sitges, Barcelona, Spain June 15-17, 2022, celebrating 20 years of bringing together multidisciplinary scientists in probiotics, prebiotics and related fields. A group of 157 scientists from 23 countries attended: 80 industry representatives (Industry Advisory Committee – IAC - members), 54 invited experts and ISAPP board members, and 23 members of the ISAPP Students and Fellows Association.



EXECUTIVE SUMMARY, CONT.

The program reflected a diverse array of plenary lectures, a debate, interactive sessions, breakout discussion groups, posters and networking events. A few highlights:

- A joint session with the IAC and ISAPP Board of Directors opened the meeting. ISAPP President Dan Merenstein shared a summary of ISAPP outputs and measured successes. Then with Senior IAC Representative Marla Cunningham as moderator, all split into 5 smaller groups to discuss industry perspectives on key opportunities and challenges and ISAPP's role in addressing them. Summaries of this session are available [here](#) (IAC member access only).
- IAC organized a Learning Forum on the topic of "Precision Probiotics and Prebiotics", featuring Niv Zmora of Weizmann Institute of Science and Jens Walter of APC, University College Cork.
- Hania Szajewska and Sarah Lebeer presented the pro and con positions during a debate on the topic, "All probiotic effects must be considered strain-specific."
- Colin Hill presented a brief history of research on bacteriophage, along with the most recent developments, for the Todd Klaenhammer Memorial Lecture.
- Experts gave plenary lecture sessions on microbiota-mediated mechanisms driving health benefits, postbiotics, and clinical developments.
- A poster session featured 34 student and industry posters detailing state-of-the-art research from around the world. Two 'best poster presentation' prizes were awarded among SFA presenters, Glory Bui (University of California Davis, USA) for her poster, "Milk fermented by *Lactocaseibacillus casei* improve barrier function and alter sterol metabolism in intestinal epithelial cells" and Simone Renwick (University of Guelph, Canada) for her poster, "Screening the prebiotic effects of human milk oligosaccharides on 330 bacterial strains derived from the infant gut microbiota."
- Six breakout discussion groups allowed a deep dive into different topics on Thursday morning, with summaries of each group presented on Friday morning. The topics were:
 - [The impact of diet on health benefits conferred by probiotics and prebiotics. Maria Marco and Kevin Whelan, co-chairs](#)
 - [Probiotic acute and long term safety: where do we stand in 2022? Dan Merenstein and Mary Ellen Sanders, co-chairs](#)
 - [What do we really know about the microbiome and health? Karen Scott and Sarah Lebeer, co-chairs](#)
 - [The small intestinal microbiome – an ignored/undefined therapeutic target. Eamonn Quigley and Purna Kashyap, co-chairs](#)
 - [Establishing causality in probiotic and prebiotic intervention trials. Bob Hutkins and Jens Walter, co-chairs](#)
 - [The status of 'biotics' in fermented foods. Gabriel Vinderola and Kelly Swanson, co-chairs](#)



After a long day of work beginning with the discussion groups, all gathered at the Hotel Estela, for a Catalan dinner by the Sea.

Slides and abstracts for the meeting are available to meeting participants (and all IAC members) on the ISAPP website [here](#).

ISAPP gratefully acknowledges the record [62 member companies](#), who supported the mission of ISAPP in 2022.

The meeting program was developed and executed by the ISAPP Board of Directors with help from our local host, Francisco Guarner.



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THE 2021-2022 ISAPP BOARD OF DIRECTORS



ISAPP Board of Directors in 2021-2022: Seppo Salminen, Gabriel Vinderola, Sarah Lebeer, Eamonn Quigley, Mary Ellen Sanders, Hania Szajewska, Colin Hill, Dan Merenstein, Kelly Swanson, Maria Marco, Dan Tancredi, Anisha Wijeyesekera, Karen Scott, Bob Hutkins

SUMMARY OF THE INTERACTIVE SESSION

Dan Tancredi, Chair

Marking ISAPP's 20th anniversary, the assembled experts and guests were invited to explore "The Then, Now, and Future of the "Biotics" Family". Three invited speakers began the session by considering each phase in turn. Eamonn Quigley - wryly noting that being invited to review the past is a sure sign that one's time in that field is up - presented an overview of the application of microorganisms in improving health and progress and challenges in advancing the underlying science and in developing actionable clinical evidence. Kristin Verbeke noted that at present we have lost some illusions and now know that not one single microbiota configuration but many that may be associated with health. Going forward, the field will need to develop and expand systems biology approaches for understanding the taxonomic and functional composition of microbiomes and how those impact health.

Gazing into the future, Clara Belzer anticipated what may be to come for *Akkermansia muciniphila*, how nutritional strategies might be based on improved understanding of the interplay between microbes and mucosal health via mucin glycans, and the potential for synthetic communities to aid in scientific discoveries in ecophysiology and health. Some notable and growing massive citizen science education and research projects were also mentioned.

The assembly was then invited to join one of 11 tables and to spend 30 minutes discuss their answers to any of the 7 shared questions they wished to tackle. Afterward, each table leader reported back to the assembly a summary of their discussions. Notable themes will be summarized by Dan Tancredi in an upcoming ISAPP Blog Post. Special thanks to the table leaders: Irene Lenoir-Wijnkoop, Zac Lewis, Seema Mody, David Obis, Mariya Petrova, Amanda Ramer-Tait, Delphine Saulnier, Marieke Schoemaker, Barry Silkington, Stephen Theis, Elaine Vaughan, and Anisha Wijeyesekera.



SUMMARY OF THE INDUSTRY FORUM

Marla Cunningham, Chair

ISAPP industry scientists organized a forum titled “Precision probiotics and prebiotics”. Jens Walter of University College Cork presented an ecological perspective on the topic, harnessing learnings from deterministic and stochastic understanding of microbiome development to guide practical insights for directional microbiome modulation. He highlighted the importance of determining availability of compositional and functional niches and their influence on microbiome as well as clinical endpoints during probiotic and prebiotic interventions.

Niv Zmora of Weizmann Institute of Science presented on key findings from experimental work in both animals and humans on the effect of probiotic interventions on both microbial and physiological endpoints, with a focus on microbiome restoration models such as antibiotic-induced disruption. He explored the concept of colonization-resistant and colonization-permissive individuals, highlighting inter-individual differences in probiotic response, and sharing insights from luminal microbiome analysis. The session concluded with a panel discussion, with both presenters providing their guidance on future directions for the field.



DEBATE:

All probiotic effects must be considered strain-specific

Pro position: Hania Szajewska, The Medical University of Warsaw, Poland

Con position: Sarah Lebeer, University of Antwerp, Belgium

Moderator: Colin Hill, University College Cork, Ireland

Panel: Dan Merenstein, Maria Marco, Gabriel Vinderola

Summary of the debate prepared by Gabriel Vinderola

Hania Szajewska stated that various options are available to compare probiotic strains, including head-to-head comparisons, pairwise meta-analyses, and network meta-analyses. The last of these is a technique to gather evidence from direct and indirect comparisons. Evidence supporting the hypothesis that the efficacy of probiotics is strain-specific was presented, including prevention of antibiotic-associated diarrhea, management of irritable bowel syndrome and treatment of acute gastroenteritis. The most effective strains for each of these indications were presented. However, very few studies comparing different strains within the same study are available, leaving little direct evidence to address this hypothesis. Changing bacterial and fungal nomenclature over time, the lack of a global standard for naming strains, and the incomplete identification of some strains can lead to a lack of clarity on which strains are used in RCTs.

Given the evidence presented, Szajewska concluded that probiotic effects should be considered strain-specific, as documented

for the moment by the still few head-to-head and indirect comparisons for a limited number of indications. Clinicians should recommend specific strain(s) based on available evidence for given conditions.

Sarah Lebeer argued that not all probiotic effects are necessarily strain-specific. She based this statement on comparative genomics studies on lactobacilli. Some effector molecules that are likely important in mediating certain health effects are conserved at a species and even at genus level. For example, *Lactobacillus crispatus* is very well associated with vaginal health at species level. Its key mode of action is the production of lactic acid through fermentation of glycogen released by vaginal epithelial cells. Another example is the species-specific presence of a manganese-dependent catalase in all strains of the species *Lactocaseibacillus casei*. This enzyme has been postulated to be important for certain anti-inflammatory and anti-oxidative mechanisms in the nose and in the intestine.



Yet clinical trials comparing efficacy of strains that differ in expression of these catalase genes have not been conducted. The production of vitamin B12 was also discussed as an example of a species- (and possibly genus-) conserved characteristic of *Furfurilactobacillus rossiae*. With these examples, Lebeer reminded us that certain probiotic effector molecules are conserved at taxonomic levels higher than the strain. Based on comparative genomic and biochemical analyses, it is reasonable to believe that all strains of *L. crispatus* can produce lactic acid from glycogen if they have an intact amylopullulanase enzyme, that all strains of *L. casei* produce a catalase enzyme and that all strains of *F. rossiae* produce vitamin B12. Therefore, it is reasonable to assume that any number of strains producing these molecules could evoke the same health benefit that depends on this mechanism.

Relevant to this discussion is that the only approved probiotic claim accepted by EFSA is for a species-level effect. Any yogurt cultures (*Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*), regardless of the strains, can be claimed to improve lactose digestion. All yogurt cultures are expected to contain sufficient β -galactosidase activity or lactase enzyme levels to improve lactose digestion in lactose maldigesters.

Given the above, why are we (scientists, regulators, clinicians) stricter for all other possible probiotic health benefits?

This may be because evidence is lacking at the mechanistic and clinical levels. Both speakers agreed that there are likely some effects that are strain-specific, but that with more clinical evidence, it may become clear that other effects may be conserved to the species (and maybe even higher) taxonomic level. Specific immunomodulatory effects that depend on a complex interplay of various immunologically active molecules from the probiotics and specific host immune receptors must always be considered at strain level, because small structural changes can make big differences in final observed effects. Following from this, probiotic-induced improved vaccine responses should likely be only considered at the strain level.

A key limitation in currently available data is that head-to-head comparisons of a sufficient number of different strains of the species evaluated for the same health benefit are currently deficient. This makes both sides of this debate difficult to convincingly substantiate. The most cautious position is to approach probiotic effects as strain-specific, even if the case of yogurt cultures to improve lactose intolerance symptoms argues against this.

From a clinician's perspective, patients may express that they are being helped by probiotics for a condition for which no evidence is available. Although physicians should perhaps not recommend such a product, it is important to recognize that absence of evidence for a benefit is not evidence of absence of a benefit.



DEBATE SUMMARY, CONT.

A probiotic for which there are no studies documenting a health effect may be still efficacious. Considering individual responses to probiotics likely vary, if a patient perceives a benefit from an unstudied probiotic, a reasonable approach is to not discourage such use.

Companies that sponsor well-designed clinical trials have an expectation to benefit from the outcomes of those trials. If probiotic benefits are not necessarily strain-specific, this could discourage investment in clinical research. However, extrapolating evidence from one

strain to a broader taxonomic group will require a level of mechanistic and clinical evidence that is currently not available. Therefore, as indicated above, a strain-specific approach is still needed at this time.

Throughout the debate, an important question constantly arose: what is a strain? What genomic differences determine different strains? The speakers and panelists provided their views on this issue, yet it was not fully resolved and could be the topic for a future discussion group or even a consensus paper.



DISCUSSION

Group 1: The impact of diet on health benefits conferred by probiotics and prebiotics

Maria Marco and Kevin Whelan, co-chairs

Our group was guided by the question - does diet impact the capacity of probiotics and prebiotics to improve human health? The rationale for this question stems from the preponderance of evidence that diet has direct and significant consequences on the structure and function of the gut microbiome. During our session, it was explained that the human gut microbiome is in part shaped by habitual diet, but also can fluctuate in response to short-term dietary shifts. Therefore, the group concluded that it is highly plausible that probiotic activity and prebiotic-mediated gut microbiome modulation may also be impacted by host dietary intake.

But to what extent has diet been recorded or included as a variable in studies? A review of the literature showed that dietary records have been reported in a handful of prebiotic studies. One prebiotic study stratified individuals based on habitual fiber intake and in doing so found that the gut microbiome of individuals consuming high fiber diets exhibited more taxonomic changes than individuals with low fiber intake, including enrichments in *Bifidobacterium* (that also occurred in those with low fiber intake) as well as numerous other taxa, including butyrate-producing Firmicutes (which did not occur in those with low fiber intake) (Healey et al 2022 Brit J Nutr).



GROUP 1 DISCUSSION, CONT.

Prebiotics also resulted in improved feelings of satiety, but only among high fiber diet consumers. For probiotics, we found no evidence of published human RCTs on probiotics wherein diet was recorded as a confounder for effectiveness. This is notable in light of the fact that host diet affects the metabolic and functional activity of probiotic lactobacilli in the digestive tract. Moreover, the food matrix may also provide further impacts via the way in which the probiotic is released *in situ*.

Hence, the group agreed that diet should be considered in the development of new human studies on probiotics and prebiotics, as well as other 'biotics and fermented foods. The need for this is urgent since diet may be a main factor affecting outcomes of clinical trials, but because diet is not recorded, this "hidden" factor cannot be evaluated.

However, there are challenges to taking diet into account, such as allowing habitual dietary intake or to provide a prescribed diet for the duration of the trial. Others are clear definition of the dietary intervention (nutrient, food, or whole diet) and determining how to measure diet (e.g. prospective or retrospective methods). There are also challenges and limitations in the ways in which dietary intake is recorded as well as the selection of dietary exclusion criteria. Hence, it was advised that dietitians are included in human study design.

Based on these points and the urgency to provide researchers with a usable approach, we concluded with the action item to develop a manuscript providing guidelines for including dietary assessments in prebiotic, probiotic, and other 'biotic human studies.



DISCUSSION

Group 2: Probiotic acute and long-term safety: where do we stand in 2022?

Dan Merenstein and Mary Ellen Sanders, co-chairs

Theoretical and documented adverse events from probiotic consumption exist, leading some to question the safety of probiotics in several high-profile publications ([here](#), [here](#) and [here](#)). Furthermore, 'next-generation' probiotic strains from species without a history of safe use or those using recombinant DNA technologies are under development. Recently a Cochrane review reported an increased risk of pre-eclampsia with probiotic administration during pregnancy. Safety of probiotics has been addressed in two previous ISAPP discussion groups (2007 and 2011).

The outcome of one is published [here](#); the other was not published. However, due to recent criticisms and reports of probiotic-associated deleterious observations, including [delay of microbiome recovery](#), [increase in resistome](#), and an [increased risk of pre-eclampsia](#), as well as concerns

with 'next-generation' probiotics, we believed this topic should be addressed again. Specifically, we sought to provide updated direction for reporting adverse events (AEs) in probiotic trials. Our group reached the following conclusions considering both acute and long-term potential risks.

General conclusions:

- Probiotics should not be held to safety standards more stringent than those required for other substances. For example, several common drugs, including antibiotics, PPIs and others, perturb the microbiome, but impact on the microbiome is not required to be demonstrated for these substances prior to approval.
- Proper reporting of AEs from clinical trial is essential. Well-established methods for this are available from regulatory agencies (e.g., FDA, EMA, EFSA) and others (e.g., [CONSORT](#), [STORMS](#)).





GROUP 2 DISCUSSION, CONT.

Acute issues:

- Monitoring changes in the microbiome due to probiotic administration should not be a required component of a clinical trial. Such assessments comprise interesting research endpoints but lack clinical significance. When funding is available and study hypotheses support doing so, such measures are encouraged.
- The presence of antibiotic resistance genes remains a hypothetical concern.
- Dead microbes have been shown to donate DNA that can be taken up by live microbes through transformation ([Winter et al, 2021](#); [McInnes et al, 2020](#)). Since probiotic products may contain a high proportion of dead cells and since postbiotics are increasingly being marketed, such products may not be exempt from concerns about transfer of antibiotic resistance genes. Such genes would not need to be flanked by mobile genetic elements to be transferred. This is a hypothetical concern and estimates of risk are not currently available.

Chronic Issues:

- Long-term safety data should not be required for probiotics, consistent with other substances.
- Reports of probiotic strains able to colonize long term are increasing ([Sumara et al. 2022](#); [Maldonado-Gomez et al. 2016](#); [Frese et al. 2017](#); [O'Brien, et al. 2022](#); Krumbeck, JA, PhD thesis, Characterization of the Role of Host and Dietary Factors in the Establishment of Bacteria in the Gastrointestinal Tract, University of Nebraska, pages 172-186). It will be prudent to follow such strains longer and look for anticipated and unanticipated AEs.
- Some bacterial enzymes, such as β -glucuronidase, azoreductase, carboxylesterase, and nitroreductase, are known to impact drugs and the prevalence of such enzymes in probiotics is unknown.

- Further research is advised to determine if they should be assessed or not allowed in probiotic strains.
- Microbiome and/or resistome assessments are not required, due to lack of clinical correlation, but are still encouraged, while recognizing that long-term assessments are inherently difficult and not required by regulatory authorities, beyond day 180.

Probiotic Quality Considerations:

- Fermentation, drying, and finished product manufacturing are performed under strict conditions and in compliance with appropriate regulations (USFDA 21CFR111 and 117; FSSC22000; EU GMP – EudraLex-Volume 4 (Europe.eu). Some organisms are tested consistently across the industry (*E. coli*, *S. aureus*, *Salmonella* spp.) However, some facilities produce strains destined for high-risk populations and end-users such as infant formula companies or hospital formularies can ask for more stringent specifications as they see fit. This is not generally known by hospital formularies, making it an important topic for an ISAPP infographic or other communication to hospitals/healthcare providers regarding probiotic manufacturing standards.
- Several times during the meeting, and also during our discussion group, the idea of a ‘Glossary’ of terms was suggested as an ISAPP activity. Clearly defining terms such as colonization and LBP could be useful.

In summary, several important watch-outs based on recent research observations were identified, but these did not constitute big changes in current approaches to probiotic safety. These will be summarized in a peer-reviewed paper. ISAPP should target communication about probiotic testing standards with healthcare providers and hospitals with the goal of improving quality of probiotic products used in vulnerable populations.

DISCUSSION

Group 3: What do we really know about the microbiome and health?

Karen Scott and Sarah Lebeer, co-chairs

The topic was split into four areas, with some debate and some consensus, for more than four hours. The outcomes of those discussions are summarized here:

How close are we to defining a ‘healthy microbiota’? Is this even possible?

There is still no consensus on the definition of a ‘healthy microbiota’, but the group agreed that we do know much more than we knew 20 years ago when the field developed. There are age-specific differences in the optimal composition of the microbiota, but generally in adults important features are a diverse, rich, resilient, functionally balanced microbiota. Indeed, the functionality of the microbiota is at least as important as the composition, perhaps even more so. Key functions include: butyrate and other SCFA production (maintaining healthy epithelial cells, lowering pH and inhibiting growth of pathogens); vitamin production; production of anti-inflammatory molecules, production of molecules maintaining an antimicrobial barrier, and production of molecules having endocrine or neurological functions such as GABA or indole-derived compounds.

We have to be wary of over-simplifying the system. The microbiota is not only the bacterial component – we need to include

archaea, fungi and bacteriophages and their contributions. Interactions between specific members of the microbiota are important in relation to functional outcomes, but must be properly demonstrated. Co-occurrence is not evidence of ecological interactions. There are also important interactions between the diet – microbiota - host that all shape the microbiota composition and function.

Thus, while we may not know what defines a healthy microbiota, we do know more and more about what defines a microbiota for health.

What are the opportunities for modulating the microbiome to alleviate disease and restore health?

Dietary changes provide an opportunity for modulating the gut microbiota, and there are definite ‘windows’ when changes can become more stably established (e.g. in infancy). Outcomes should focus on functionality and processes, not only microbial (definitely not just bacterial) composition. Large diet changes have an observable effect, but the addition of single categories of substances (probiotics, prebiotics, synbiotics, postbiotics, vitamins, other supplements) can also be effective in changing functional outcomes. Microbiota transfer can be used as an ‘ultimate complex treatment’ with varying success, while it is also important to establish causality.



GROUP 3 DISCUSSION, CONT.

Several microbiome companies are standardizing donor-derived material and processing for ‘cleaner’ transfers of complex microbiota mixtures.

Future interventions need to think beyond current targets that focus on increasing microbial richness or reducing inflammation, and include targeting intestinal permeability and restoring oxidative stress. All such interventions can interrupt the downward spiral of decreasing health.

Is it necessary to establish whether microbial changes are cause or result of disease?

The group agreed that this is important for therapeutic and regulatory approaches for product development. To get approval for new products and claim a health benefit, you need to know both what a product does, and how it does it. This requires good choice of samples and endpoints in a study, quantifiable findings that are clinically relevant. There are many difficulties in comparing studies due to non-standard sample collection, storage and processing, and differences in collection of associated data (diet, transit time, stool frequency, etc.). Small animal models and microbiota transfer have proved that microbes cause and alleviate symptoms of disease, but often the mixed microbiota is effective and specific active components remain unknown.

In contrast, in the clinic, specific microbial changes can be used as a diagnostic

biomarker to indicate disease presence, without necessarily being causative, and for a patient/consumer they only require disease symptoms to improve, and not mechanistically how it happens.

What are the challenges in taking the science into the clinic?

Many challenges were identified, some already considered above. Study design is crucial, and also collecting as many and as relevant samples as budgets will permit. Appropriate data sharing between different researchers and companies advances science much more quickly, as demonstrated with the rapidity of vaccine development against Covid-19. Identifying disease-specific biomarkers for use in the clinic remains a major challenge. Data generation is no longer a challenge, but data processing, and knowing what the data means and how to use it for benefit are becoming the major hurdles.

Finally a major challenge is impatience. We (scientists) have developed knowledge and understanding of the role of our microbial symbionts in health and disease from virtually nothing in two decades. It is unrealistic to expect that we would have learnt all the secrets of this complex ecosystem in only 20 years. Microbial evolution been going on for millennia, microbes and host co-evolution has occurred for fewer millennia, but still a long time. It will take more than 20 years for us to unravel the complexities and find our answers.



DISCUSSION

Group 4: The small intestinal microbiome – an ignored/undefined therapeutic target

Eamonn M M Quigley and Purna Kashyap, co-chairs

Though a disordered small intestinal microbiome is commonly implicated in the pathogenesis of various ills through the much-disputed entity of Small Intestinal Bacterial Overgrowth (SIBO), the makeup and biologic functions of the small intestinal microbiome in humans remain undefined. This reflects the inaccessibility of the small intestine and its more distal reaches.

As we discussed, new technologies such as high throughput sequencing, metagenomics and metabolomics are now being applied to the study of small intestinal bacterial and other microbial populations. Purna Kashyap and Sean Spencer presented results from available studies, emphasizing the unrepresentative nature of stool microbiomes to the small intestine microbiome. The small intestine has critical homeostatic functions for nutrient digestion and absorption, immune engagement and interactions with the enteric and central nervous systems, as well as neuroendocrine systems.

Ludovica Marinelli discussed the front line for microbiota-host interactions – the gut barrier. Silvia Melgar explored another interaction, with the mucosa or gut associated lymphoid tissue. Diet plays a critical role in symptoms in many gastrointestinal disorders, discussed by Kristina Martinez-Guryn. Eamonn Quigley and Magnus Simren tackled the thorny subject of SIBO and illustrated the limitations of current definitions and diagnostic methods. Help may be at hand with the advent of technologies for real-time sampling of intestinal gases and contents.

Meanwhile, we recommend restraint in diagnosing SIBO and its implication as the cause of everything from irritable bowel syndrome to Alzheimer's disease. Optimal methods for the sampling of small intestinal microbes and its metabolic products through the application, in well-defined populations, of the full range of 'omics should lead us to new therapeutic interventions.



DISCUSSION

Group 5: Establishing causality in probiotic and prebiotic intervention trials

Bob Hutkins and Jens Walter, co-chairs

The panel noted that nearly all intervention studies with probiotics or prebiotics have reported associations with effects on the gut microbiota, but none have demonstrated a causal contribution of the microbiome. Nonetheless, for health claims, causality is often considered important by regulatory agencies, including EFSA, and it is essential for a compound being considered a prebiotic. Although the Bradford Hill criteria is the gold standard for establishing causality in epidemiology studies, the group considered that several criteria could be applied to probiotic and prebiotic studies, including replication, dose-response, biological plausibility, temporality, and analogy.

The group considered that a mechanistic understanding of the mode of action was not a requirement, but mechanistic data was important to inform causality. Mechanistic insights can be obtained from appropriate animal models, in vitro experiments, metabolomics and other omics. Given the difficulty of making causal inferences, the panel discussed statistical approaches to establish a causal contribution of the microbiome in pro- and prebiotic studies and proposed the application of tools from fields like causal inference analysis and machine learning/AI.



DISCUSSION

Group 6: The status of biotics in fermented foods

Gabriel Vinderola and Kelly Swanson, co-chairs

The main objective of this discussion group was to discuss if and how fermented foods may be a vehicle to provide probiotics, prebiotics, and/or postbiotics. Invited speakers in the discussion group included ISAPP BoD members and other academics that have served on the ISAPP consensus panels for probiotics, prebiotics, synbiotics, postbiotics, or fermented foods. They were joined by a handful of other

academics and industry members interested in the topic.

To begin the session, Gabriel Vinderola provided an overview of the biotics and fermented foods terms recently defined by ISAPP, and ideas of how they may be combined together. Jonathan Swann followed by providing the biochemical complexity of fermented foods.





GROUP 6 DISCUSSION, CONT.

Kelly Swanson spoke about synbiotics and if the complementary synbiotic concept could be applied to fermented foods and biotics. The presentations then shifted from concept to application, with oat-based fermentation products (Seppo Salminen), kimchi and sauerkraut (Hannah Holscher), kefir (Paul Cotter), and yogurt starter cultures (Patricia Ruas-Madiedo) being presented.

The final presentation was provided by Miguel Gueimonde, who discussed the potency of live and dead microbial cells in biotic and fermented food products. The group had an active discussion between and after all presentations were completed. At the end of the discussion, there was general agreement that the topics covered would make for an interesting and valuable perspectives or opinion publication.

Similar to previous ISAPP discussion groups, possible publication targets include Trends in Microbiology, Nature Microbiology, Gut Microbes, and Current Opinion in Biotechnology. Part of the discussion focused on what a fermented food with biotic components would be called, with 'multi-biotic' being the term most agreed upon.

Because yet another term would likely cause more confusion to consumers and provide more angst to industry members, the publication should avoid mention of any new terms and focus on the description of fermented foods and their potential bioactives and benefits, the ISAPP biotic definitions, and how they may be combined to deliver health benefits. It could clarify the fermented food versus probiotic fermented food issue, provide an overview or examples of what is currently available, and suggest ideas for the future.

LATE-BREAKING NEWS

Chaired by Prof. Gregor Reid, this session offered participants 5-minute slots to present late-breaking news in an informal, interactive atmosphere.

Does early LGG supplementation prevent upper respiratory infections (URIs) in toddlers? A secondary analysis of the TIPS Study. Michael D. Cabana, Children's Hospital at Montefiore/Albert Einstein College of Medicine, Bronx, USA

Effect of vitamin C, B2 and D on probiotic *L. rhamnosus* GG DSMZ 32550 and *B. lactis* DSMZ 32269 using the SHIME® technology. Robert Steinert, DSM, Aargau, Switzerland

Probiotic-induced recovery of the microbiome: a proposed ISAPP panel. Mary Ellen Sanders, ISAPP, Centennial, CO, USA

ESPGHAN position paper: Probiotics for the management of pediatric gastrointestinal disorders. Hania Szajewska, The Medical University of Warsaw, Poland

How Isala wants to inspire vaginal microbiome research across the world. Sarah Lebeer, University of Antwerp, Belgium

PROVID-LD: a cohort to investigate the impact of probiotics on the gut microbiota in COVID-positive patients. Isabelle Laforest-Lapointe, Université de Sherbrooke, Quebec, Canada



Electric probiotics: discovery of hybrid electrogenic metabolism of lactobacilli. Maria Marco, University of California – Davis, USA

Experimental evaluation of ecological principles to understand and modulate the outcome of bacterial strain competition in gut microbiomes. Amanda Ramer-Tait, University of Nebraska-Lincoln, USA

Food for Thought: Psychobiotics and Diet. Robert Dixon, Unilever, Bedford, UK

Supplementing yogurt with bifidobacteria to counter chronic kidney disease in developing countries. Gerrit A. Stuivenberg, Lawson Health Research Institute and Western University, London, Canada

POSTERS

Both Students and Fellows Association members and industry members contributed posters at the meeting:

SFA Posters

[Riboflavin-overproducing *Limosilactobacillus reuteri* for biofortification of fermented foods.](#) Sarah Ahannach, University of Antwerp, Belgium

[Honey varieties impact survivability of *Bifidobacterium animalis* ssp *lactis* in commercial yogurt through simulated in vitro digestion.](#) David Alvarado, University of Illinois, USA

[Milk fermented by *Lactocaseibacillus casei* improve barrier function and alter sterol metabolism in intestinal epithelial cells.](#) Glory Bui, University of California Davis, USA

[Physicochemical and microbiological evaluation of a probiotic carrot bio-yogurt stored under refrigeration conditions.](#) Angel Camargo, Universidad Nacional de Colombia, Colombia

[In Silico study of efficiently producing fructooligosaccharides using a novel strain of *Fusarium* sp. HKF-74.](#) Atul Chavan, CSIR-National Environmental Engineering Research Institute, India

[Extending probiotic science beyond human health: Design and application of a novel spray-based formula for sustainable disease management in California honey bees.](#) Brendan Daisley, University of Guelph, Canada

[Diversifying the offer of regional plant-based functional foods: development of a probiotic fermented drink of beets and strawberries.](#) Maria Florencia, Universidad Nacional del Litoral, Argentina

[Bacteriocin structural gene shuffling reveals multiple diverse structural gene homologues in the *S. bovis*/*S. equinus* complex pangenome.](#) Daragh Hill, APC Microbiome Ireland, Ireland

[The bacteriocinogenic potential of the Hungate1000 culture collection of rumen isolated micro-organisms.](#) David Hourigan, University College Cork, Ireland

[Integrative multi-omics analyses reveal the therapeutic impact of probiotics via modulating microbial-based signatures in chronic kidney disease.](#) Hsiao-Wen Huang, National Taiwan University, Taiwan



POSTERS, CONT.

[Effect of an *Aspergillus oryzae* derived postbiotic on heat stress in *Drosophila melanogaster* and dairy cows.](#) Ignacio Ipharraguerre, University of Kiel, Germany

[Influence of food matrix on prebiotic efficacy of inulin-type fructans.](#) Peter Jackson, University of Reading, UK

[In silico prediction and in vitro assessment of microbial substrate utilisation among recently identified health-associated gut taxa.](#) Cathy Lordan, University College Cork, Ireland

[Gamma-aminobutyric acid \(GABA\) production by probiotics.](#) Andrea Monteagudo-Mera, University of Reading, UK

[Investigation of the Gut Microbiota Composition and Activity in Acute Myeloid Leukemic Patients: First Results of the MicroAML Study.](#) Sarah Pötgens, Université Catholique de Louvain, Belgium

[Screening the prebiotic effects of human milk oligosaccharides on 330 bacterial strains derived from the infant gut microbiota.](#) Simone Renwick, University of Guelph, Canada

[Integrating Dietary Data into Microbiome Studies: A Step Forward for Nutri-Metaomics.](#) Zaida Soler Luque, Vall d'Hebron Institute of Research, Spain

[Probiotic bifidobacteria mitigate the deleterious effects of para-cresol in a *Drosophila melanogaster* toxicity model.](#) Gerrit Stuivenberg, Western University, Canada

[Development of anaerobic fermentation techniques for measuring the impact of prebiotic supplementation on human gut microbiota in clinical studies.](#) Alexander Thorman, University of Cincinnati, USA

[Introducing a CRISPR-Cas9 based prime editing system for precision mutagenesis in lactobacilli.](#) Dieter Vandenheuevel, University of Antwerp, Belgium

[Comparison of the effect of fidaxomicin, thuricin CD, vancomycin and nisin on the human gut microbiota, both in vitro and ex vivo.](#) Lauren Walsh, University College Cork, Ireland

[Prebiotic attribute of chitin oligosaccharides derived from sea food waste.](#) Rahul Warmoota, Panjab University Chandigarh, India

[FunOMIC: Pipeline with built-in Fungal Taxonomic and Functional Databases for Human Mycobiome Profiling.](#) Xie Zixuan, Vall d'Hebron Institute of Research, Barcelona, Spain



Industry Posters

[Effects of a prebiotic soluble fiber NUTRIOSE® on intestinal immune system and gut homeostasis.](#) Caroline Perreau, Roquette

[Prebiotic properties exploration of various insoluble fibers using the ex vivo SIFR® technology.](#) Clémentine Thabuis, Roquette

[Structure and function of non-digestible carbohydrates in the gut microbiome.](#) Frédérique Respondek, CP Kelco

[Summary of research studies revealing health-related effects of a specific prebiotic galactooligosaccharide mixture.](#) Ged Baltulionis, Clasado Biosciences

[The postbiotic Lactofidus in combination with GOS/FOS prevents diarrhoea in a suckling rat model of rotavirus infection.](#) Jan Knol, Danone Nutricia Research

[Long-term safety and efficacy of prebiotic intake in infants and young children.](#) Jessica Van Harsseelaar, BENE0

[Effect of prebiotic oligosaccharides on bowel habit and the gut microbiota in children with functional constipation: study protocol for a randomised, placebo-controlled, multi-centre trial using a validated modified Bristol Stool Form Scale.](#) Margriet Schoterman, FrieslandCampina & Elaine Vaughan, Sensus BV

[Potential of pectins to modulate the human gut microbiota evaluated by in vitro fermentation: a systematic review.](#) Nélide Pascale, CP Kelco

[Updated concise monograph – Dietary probiotics, prebiotics and the gut microbiota in human health.](#) Stephan Theis, BENE0

[Prebiotic inulin and resistant starch mixture-specific effect on distal colonic fermentation and metabolic health.](#) Veerle Dam, Sensus BV

[A Design of Experiments \(DoE\) approach to accelerate the optimization of viability droplet digital PCR conditions for probiotics enumeration in blends.](#) Zhengfei Lu, Herbalife

STUDENTS & FELLOWS ASSOCIATION

The SFA's goal is to create an interactive network of graduate students and postdoctoral fellows across the globe working on probiotics, prebiotics, or related fields. Fewer students (total: 23) participated in the program this year as compared

to previous years, in part due to visa and travel restrictions, but those who attended created a dynamic, memorable meeting. Poster abstracts and the conference summary are available [here](#).





2022 MEETING

PROGRAM
June 15-17, 2022
Sitges, Barcelona, Spain

All lecture events and poster session are located in the [SITGES PLENARY ROOM](#), unless otherwise noted. Lunch will be served at [VEREMA RESTAURANT](#) and the Welcome Reception held in [VEREMA GARDEN](#).

WEDNESDAY – JUNE 15

- 7:30-19:30 **Registration Desk**
- 7:30-10:30 **Poster Setup**
- 8:30-10:30 **Industry Advisory Committee (IAC) + ISAPP Board of Directors**
This session is for ISAPP industry members and board members only. All industry members are welcome to attend this update on ISAPP activities and provide feedback to the ISAPP Board
Chairs: Marla Cunningham, Metagenics, Northgate, Australia and Dan Merenstein, Georgetown University School of Medicine, Washington DC, USA
- 8:30-10:30 **Students and Fellows Association (SFA) Program** [GARRAF ROOM](#)
This introductory program is for SFA attendees only
Chair: Daragh Hill, University College Cork, Ireland
- 10:30-11:00 **Break & Poster Viewing**
- 11:00-12:30 **Industry Forum**
This industry-member organized session is open to all meeting participants
Precision probiotics and prebiotics
Jens Walter, University College Cork, Ireland
Niv Zmora, Weizmann Institute of Science, Rehovot, Israel
Chairs: Marla Cunningham and Kelly Swanson, University of Illinois, Urbana - Champagne, USA
- 12:30-13:30 **Lunch**
- 13:30-13:45 **Welcome to ISAPP 2022**
Dan Merenstein, ISAPP President
Marla Cunningham, Sr. IAC Representative
Brendan Daisley, SFA Vice-President, University of Guelph, Canada
- 13:45-15:30 **Interactive Session**
The Then, Now, and Future of the "Biotics" Family
Eamonn Quigley, The Methodist Hospital and Weill Cornell School of Medicine, Houston, TX, USA
Kristin Verbeke, KU Leuven, Belgium
Clara Belzer, Wageningen University, The Netherlands
Chair: Dan Tancredi, University of California-Davis, USA



2022 MEETING

WEDNESDAY – JUNE 15 (CONTINUED)

- 15:30-16:30 **Debate**
All probiotic effects must be considered strain-specific
 Pro position: Hania Szajewska, The Medical University of Warsaw, Poland
 Con position: Sarah Lebeer, University of Antwerp, Belgium
 Panel: Dan Merenstein, Maria Marco, University of California - Davis, USA and Arthur Ouwehand, IFF, Kantvik, Finland; Gabriel Vinderola
 Chair: Colin Hill, University College Cork, Ireland
- 16:30-17:00 **Break & Poster Viewing**
- 17:00-18:30 **Featured Talks**
 Q&A following each talk
- *Personal predictions for the future of prebiotics (science only, don't ask me about economy).* (25 min)
 Glenn Gibson, University of Reading, UK
 - *Live dietary microbes and health. An update of an ISAPP project.* (20 min)
 Maria Marco
 - *Antiviral potential of topically applied lactobacilli in the respiratory tract: from mechanisms to application.* (15 min)
 Irina Spacova, University of Antwerp, Belgium
 2021 Glenn Gibson Early Career Researcher Prize Winner
 - *Human milk oligosaccharide-utilizing bifidobacteria produce immunomodulatory aromatic lactic acids in the infant gut.* (15 min)
 Martin Laursen, National Food Institute, Technical University of Denmark, Kgs. Lyngby
 2022 Glenn Gibson Early Career Researcher Prize Winner
 - *IAC talk: Individual and group-based differences in gut microbiota responses to in vitro fiber interventions: Can mixtures of prebiotics contribute to harmonized beneficial effects?* (15 min)
 Frank Schuren, TNO, The Netherlands
- Chair: Kelly Swanson
- 18:30-19:30 **Late Breaking News**
 Chair: Gregor Reid, University of Western Ontario, London, Canada
- 19:30-21:30 **Welcome Reception & Poster Viewing**
 Drinks and food to be served



2022 MEETING

THURSDAY – JUNE 16

- 7:30-9:00 **Registration Desk**
- 8:30-13:00 **Discussion Groups**
1. *The impact of diet on health benefits conferred by probiotics and prebiotics.* **GARRAF ROOM**
Chairs: Maria Marco, University of California Davis, USA and Kevin Whelan, King's College London, UK
 2. *Probiotic acute and long term safety: where do we stand in 2022?* **MOSCATELL ROOM**
Chairs: Dan Merenstein and Mary Ellen Sanders, ISAPP, Centennial, CO, USA
 3. *What do we really know about the microbiome and health?* **GINESTA ROOM**
Chairs: Karen Scott, University of Aberdeen, Scotland and Sarah Lebeer
 4. *The small intestinal microbiome – an ignored/undefined therapeutic target.* **GARNACHA ROOM**
Chairs: Eamonn Quigley and Purna Kashyap, Mayo Clinic, Rochester, MN, USA
 5. *Establishing causality in probiotic and prebiotic intervention trials.* **MACABEO ROOM**
Chairs: Bob Hutkins, University of Nebraska, Lincoln, USA and Jens Walter, University College Cork, Ireland
 6. *The status of 'biotics' in fermented foods.* **MONASTRELL ROOM**
Chairs: Gabriel Vinderola, National University of Litoral, Argentina and Kelly Swanson
- 8:30-13:00 **Students and Fellows Association Program** **SITGES PLENARY ROOM**
Chair: Daragh Hill
- 13:00-14:00 **Lunch**
- 14:00-15:30 **Plenary Session: Microbiota-mediated mechanisms driving health benefits**
- *Unravelling health promoting microbiota-mediated mechanisms using metabolic profiling*
Anisha Wijeyesekera, University of Reading, UK
 - *Do probiotics promote health through microbiota-mediated mechanisms?*
Michiel Kleerebezem, Wageningen University & Research, The Netherlands
 - *Probiotics and chronic constipation: mechanisms of action and effectiveness*
Eirini Dimidi, King's College London, UK
2022 Glenn Gibson Early Career Researcher Prize Winner
- Chair: Karen Scott
- 15:30-16:00 **Break**



2022 MEETING

THURSDAY – JUNE 16 (CONTINUED)

- 16:00-16:45 **Todd Klaenhammer Memorial Lecture**
Bacteria and bacteriophage - are they fighting or are they dancing?
 Colin Hill
 Chair: Mary Ellen Sanders
- 16:45-17:30 **Mini-Plenary: Postbiotics**
- *A decade of research on Akkermansia muciniphila: what do we know now?*
 Clara Belzer
 - *Regulatory perspectives on the first EFSA-approved novel food*
 Seppo Salminen, University of Turku, Finland
- Chair: Seppo Salminen
- 19:00 Buses loading for Hotel Estela event
- 19:15 Buses depart
- 19:30-22:30 **Dinner at the HOTEL ESTELA near the sea in Sitges**
Join meeting participants and guests for a gala Catalanian dinner with Spanish wines and beers.

FRIDAY – JUNE 17

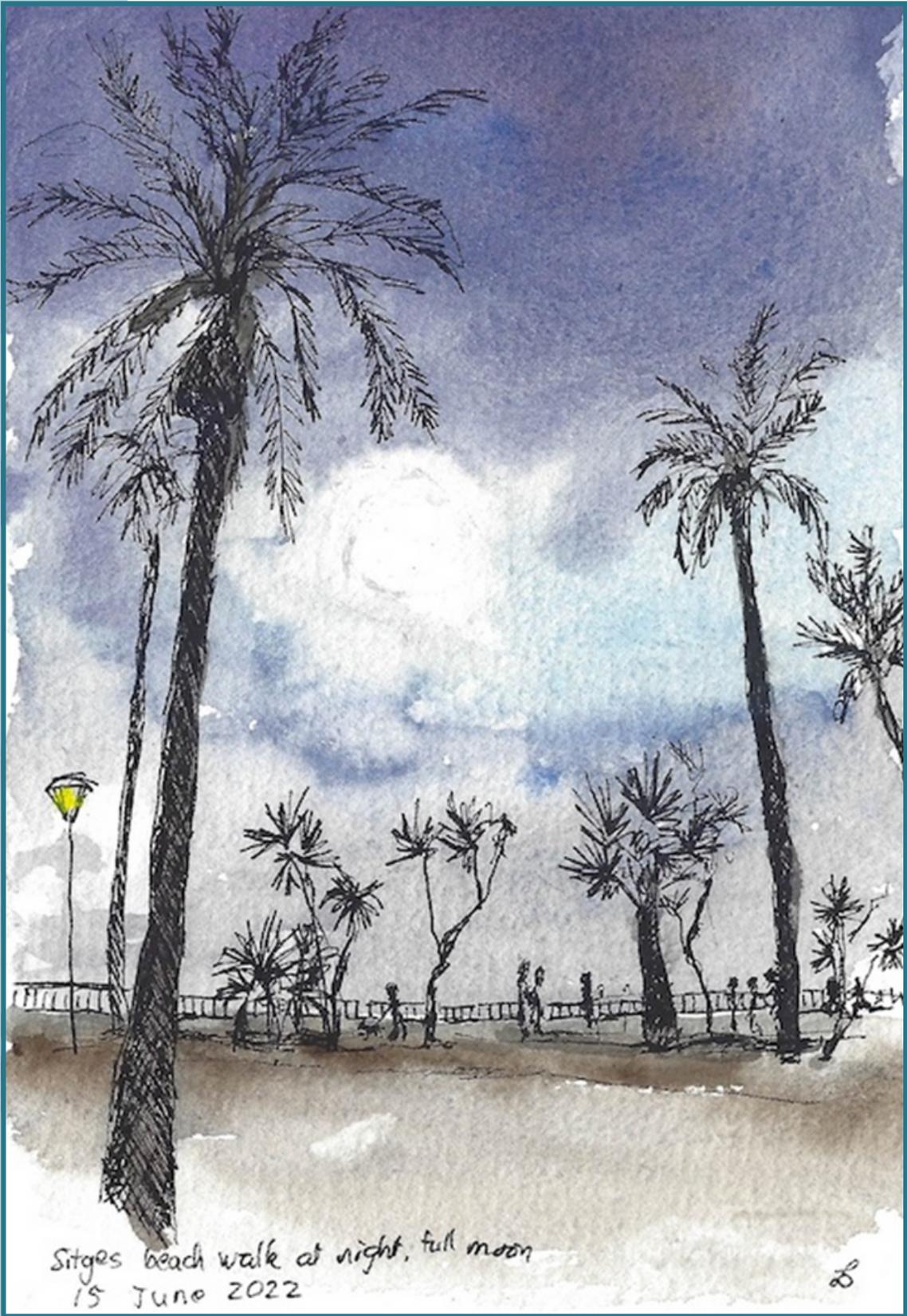
- 7:30-9:00 **Registration Desk**
- 8:30-10:00 **Plenary Session: Clinical developments**
- *Pain in the NEC: Choosing the Right "Biotic" for Preterm Neonates*
 Geoff Preidis, Baylor College of Medicine and Texas Children's Hospital, Houston, USA
 - *Microbiota and gas related complaints*
 Francisco Guarner, University Hospital Vall d'Hebron, Barcelona, Spain
 - *IAC talk: Prebiotic Galacto-oligosaccharides Impact Stool Frequency and Fecal Microbiota in Self-reported Constipated Adults: A Randomized Clinical Trial*
 Marieke Schoemaker, FrieslandCampina, The Netherlands
- Chair: Eamonn Quigley
- 10:00-10:30 **Break**
- 10:30-12:30 **Summary Reports from Discussion Groups & Students and Fellows Association**
 Discussion Group Chairs and SFA President
 Chair: Gabriel Vinderola



APPENDIX B: ACKNOWLEDGEMENTS

Thank you to the 62 member companies for their support of ISAPP in 2022.





Sitges beach walk at night, full moon
15 June 2022

LB

Original art by Laurel Beckett, Davis CA