# ISAPP 2020 Discussion Group Descriptions

## 1) What do we really know about the microbiome and health?

Karen Scott and Sarah Lebeer, Co-Chairs

There are numerous published studies investigating the composition of the intestinal microbiota, at different lifestages, geographical locations and disease states. However, inter-individual variation paired with the sheer diversity and differing abundance of specific members of the microbiota, means we are still struggling to define a 'healthy' microbiome, and consequently identify causative shifts leading to disease.

**Tentative Objectives**

1) How close we are to defining a 'healthy microbiome' and if this is even possible
2) Opportunities for modulating the microbiome to alleviate disease and restore health
3) Whether it is necessary to establish whether microbial changes are cause or consequence of disease.

## 2) Diet, probiotic, and prebiotic interactions

Maria Marco and Kevin Whelan, Co-Chairs

Diet strongly influences the composition and function of the human gut microbiome. Obesogenic diets rich in fats and simple sugars cause reductions in microbial species diversity and functional potential in the intestine, whereas diets high in fermentable fiber promote a more robust microbiota with increasing numbers of health-promoting bacteria. It is therefore plausible that microbiome-targeted interventions with probiotics and prebiotics are influenced by host dietary background.

**Tentative Objectives**

1) What is the current state of knowledge on how short and long term dietary patterns affect the human gut microbiome?
2) How could infant diets affect responsiveness to probiotics and prebiotics post-weaning?
3) What is the level of evidence from clinical studies that dietary background influences probiotic and prebiotic efficacy?
4) What are the plausible molecular mechanisms of diet-based effects on probiotics and prebiotics in the digestive tract?
5) Which dietary components or nutrients should be controlled in human studies of prebiotics and probiotics?
6) Are there probiotic and prebiotic delivery matrix interactions with the diet that should be considered?

## 3) Probiotic acute and long term safety: where do we stand in 2020?

Dan Merenstein, chair and Mary Ellen Sanders- co-chair

Commonly marketed probiotics are often thought of and assumed to be safe. In 2011, a large review published by the RAND Corporation found 11,977 publications, of which 622 studies were reviewed. In 235 studies, only nonspecific safety statements were made ("well tolerated"); the remaining 387 studies reported the presence or absence of specific adverse events. The review concluded, "The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence." However, RCTs do not represent the totality of evidence on probiotic safety. There have been large cohort studies without serious adverse events reported. Further, global consumption of probiotics (dominated by *Lactobacillus* and *Bifidobacterium* probiotics), estimated at about $40 billion USD retail sales in 2017, suggests that large amounts of common probiotics are being consumed without safety issues.

However, theoretical and proven adverse events from probiotic consumption exist. Additionally, the probiotic market is poised to change with development of probiotics without the long history of safe use and qualified presumption of safety (QPS) status applicable to common *Bifidobacterium* and *Lactobacillus* probiotics.

In addition to safety inherent to a probiotic, another concern is safety of the probiotic as manufactured. The manufacturing process must be sufficiently controlled to provide adequate assurance that the product will not be contaminated with potentially dangerous live microbes. Since probiotics are alive, product sterilization is not possible, and the risk of microbial contaminants must be mitigated through careful handling of the seed cultures through final product packaging.

Therefore further examination of probiotic safety is warranted. We will examine both acute and long term potential risks.

**Tentative Objectives**

1) What acute adverse events should be monitored in human probiotic trials?
2) Are there long-term adverse events that may result from probiotic-mediated microbiome alteration that need to be monitored?
    a. Should hypothetical (long term) microbiome alteration disqualify a strain for use by certain populations, specifically infants and young children?
    b. Should we hold probiotics to a standard that many microbiome-altering drugs (antibiotics, metformin, PPIs, etc) are not held to?
    c. If should be assessed, how can microbiota impact be measured in a meaningful way? Is it fecal samples? Is it 16S or metagenomics or metabolomics?
    d. Is the discussion different food versus supplement? Regulatory it is but scientifically?
3) Are there population groups where extra monitoring is indicated?
4) What hurdles exist for a path to develop safety assessment for non-QPS probiotics?

**Invited Experts**

| Name | Affiliation | Expertise |
|---|---|---|

| | | |
|---|---|---|
| Dan Merenstein, chair | Georgetown University Medical School | Clinical safety trials |
| Mary Ellen Sanders, co-chair | ISAPP | Commercial product quality, 3rd party verification |
| Maurits van den Nieuwboer | FFUND<br>The Netherlands | Paper on remaining controversies of probiotic safety |
| Maria Carmen Collado | Instituto de Agroquímica y Tecnología,<br>Valencia, Spain | Infant formula and OB/Safety infant formula- short and long term issues |
| Geoffrey Preidis | Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, USA | Expert on preterm and underweight newborns in the neonatal intensive care unit |
| Colin Hill | University College Cork, APC, Ireland | Pathogenic microbiology; antibiotic resistance genes in probiotics |
| Julia Barrett | Biologic Consulting | Expert on Biologics and Safety |
| Lorenzo Morelli | Università Cattolica del Sacro Cuore, Italy | Antibiotic resistance genes and phenotypes among probiotics; QPS |
| Bruno Pot | Yakult, The Netherlands | Immunology, pharma uses for probiotics |
| Chris Elkin | CDC | Public health and antibiotic resistance |
| Jesse Terhaar | IPA | |

## 4) Environmental Probiotics

Gregor Reid and Greg Gloor, Co-Chairs

**Tentative Objectives**

1) Emphasize the importance of biodegradation and bioremediation but state that these are not probiotic applications. Eg Suncor toxins; drugs
2) Provide a list of products that use the term probiotic for environmental applications but should not be called probiotic. Eg for buildings and mattresses.
    a. https://www.scdprobiotics.com/pages/our-technology-platform;
    b. https://www.airbiotixzone.com/products/copy-of-yogibiotix-probiotic-yoga-mat-spray;
    c. https://www.usairpurifiers.com/betterair-environmental-probiotic-large-spray.html;
    d. https://betterair.com.au/;
    e. https://purebioticsusa.com/;
3) Discuss 'environmental' applications of probiotics to plants, fish, honey bees, cows, and identify gaps in knowledge and ways to fill them. Include use of honey bees as probiotic delivery vehicles

**Invited Experts**

| Name | Affiliation | Expertise |
|---|---|---|
| Greg Gloor – co-chair | Western U | Suncor toxins; corn probiotics |
| Gregor Reid – co-chair | U of Western Ontario | |
| Akos Kovacs | Lyngby, Denmark | Plant growth |
| John Al-Alawneh | U of Queensland | Plant health and milk productivity |
| Elina Lastro Niño | UCDavis | Honey bees and probiotics; use honey bees as delivery vehicles to kill plant pathogens |
| Jeanne Kagle | Mansfield U, PA | Microbial biodegradation of drugs |
| Rao Changanti | U of Michigan | Waste water and fish |

## 5) Prebiotic and probiotic use in special populations

Bob Hutkins and Glenn Gibson, Chairs

Probiotics and prebiotics are for anyone. However, there may be specific instances where they are more desirable than is otherwise the case. This includes people suffering from microbiome mediated disorders, people who are at increased risk, or otherwise healthy individuals seeking improved performance. The purpose of this workshop is to identify "specialist" populations where probiotics and prebiotics may have influences that are relevant to the specific group. (Infants, which were the topic of a 2019 ISAPP discussion group, will not be included.) We will choose up to 5 of these for discussion. In each case, an expert in the area will give a brief overview of the problems and issues that can be tackled by pro/prebiotics, including existing studies. The group will then discuss recommendations in terms of health biomarkers that can be assessed, symptomology (where relevant), how products can be chosen and or administered; technological developments; special needs and future perspectives.

**Options for populations to be discussed are:**

- elite and sub-elite athletes
- military
- hospitalised persons (exclusive of those treated for GI conditions)
- persons in day care centres
- autistic children who have gut disorders
- frequent travellers
- "stressful" occupations (police, firefighters)
- prison populations
- healthcare staff e.g. looking after infectious patients
- others suggested by the group

6) **The small intestinal microbiome – an ignored/undefined therapeutic target**

Eamonn Quigley and Purna Kashyap, Chairs

Though, in terms of surface area, it comprises by far the greatest part of the gastrointestinal tract, is the primary site for the digestion and absorption of nutrients and contains the most abundant immune tissue in the gut, the small intestine remains poorly understood in terms of its microbiome and interactions with the host. Given what we know of the anatomy, ultrastructure, physiology and immunology of the small intestine it should be the target for microbiota-modifying interventions that seek to impact on metabolic processes and host immune responses. Yet the composition of the small intestinal microbiome remains poorly defined.

**Tentative Objectives**

1. The human small intestinal microbiome – what do we know?
    a. Composition:
        i. 16S studies
        ii. Metagenomics
        iii. Metabolomics
        iv. Metatranscriptomics
    b. Small intestinal microbiome-host interactions
        i. At the epithelium – gut barrier impacts
        ii. With the mucosa/gut-associated lymphoid system (MALT/GALT)
        iii. Metabolic impacts
        iv. Impacts on the ENS and CNS
    c. Small intestinal bacterial overgrowth (SIBO)
        i. Definition
        ii. Diagnosis
        iii. Clinical spectrum
        iv. Management
2. The future
    a. Better definition:
        i. Sterile sampling
        ii. Dynamic gas sampling
        iii. Other novel applications
    b. The small intestinal microbiome as a therapeutic target
        i. How can this be achieved?
        ii. What are the best disease/disorder targets?
        iii. Opportunities for bacteriotherapy