2013 ISAPP Meeting Report
June 12-14, 2013
New York City, NY

CONTENTS:

I. EXECUTIVE SUMMARY

The 2013 ISAPP meeting was held over 3 days, the first day being an open-registration conference and days 2 and 3 being ISAPP-only events. June 12 was an open-registration plenary lecture session, June 13 comprised 5 breakout discussion groups, and June 14 was composed of a morning wrap up session summarizing the discussion groups and an afternoon IAC Learning Forum. The plenary lecture session on the first day of the meeting was a conference titled *Probiotics, Prebiotics and the Host Microbiome: the Science of Translation*. The conference was co-organized by ISAPP, NYAS and the Sackler Institute of Nutrition, and was held in the NYAS facilities on the 40th floor of 7 World Trade Center, overlooking the Manhattan skyline. This sold-out program was determined by a scientific organizing committee comprising experts in microbiology, bioinformatics, clinical medicine and research, with specialized knowledge of probiotics, prebiotics and the human microbiome. The ISAPP-only meeting was attended by 110 delegates, including 54 scientists from the ISAPP Industry Advisory Committee, 42 invited experts, 12 members of the ISAPP Board of Directors and 2 Student Fellow Association members serving as rapporteurs. Sixteen countries (Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Japan, the Netherlands, New Zealand, Scotland, Spain, Switzerland, England and United States) were represented. The details of the 3-day program are found in Appendix A. The meeting began with a Meet and Greet Pizza party for all speakers at Brick NYC restaurant on June 11. The conference dinner on June 13 was held aboard the New York Atlantica, cruising the Hudson River. Although rain precluded full enjoyment of the views of Manhattan along the way, the Statue of Liberty stood majestically as a reminder of the power of global friendships and the importance of freedom. Two poster sessions were featured. The first was held on June 12, and included 68 posters. The second was held off-site as part of the Student and Fellow Association program. The plenary session was summarized in a meeting report published in the Annals of the New York Academy of Sciences: Probiotics, prebiotics, and the host microbiome: the science of translation. Petschow B, Doré J, Hibberd P, Dinan T, Reid G, Blaser M, Cani PD, Degnan FH, Foster J, Gibson G, Hutton J, Klaenhammer TR, Ley R, Nieuwdorp M, Pot B, Relman D, Serazin A, Sanders ME. Ann N Y Acad Sci. 2013;1306:1-17. A summary of

discussion group 1 was also published: Probiotics and prebiotics: prospects for public health and nutritional recommendations. Sanders ME, Lenoir-Wijnkoop I, Salminen S, Merenstein DJ, Gibson GR, Petschow BW, Nieuwdorp M, Tancredi DJ, Cifelli CJ, Jacques P, Pot B. Ann N Y Acad Sci. 2014;1309:19-29.

II. WELCOME FROM THE PRESIDENT

Colin Hill, ISAPP President

June 3, 2013

Welcome to New York and to ISAPP 2013. This year we are starting with a one day symposium titled "**Probiotics, Prebiotics, and the Host Microbiome: The Science of Translation**" jointly organised by The Sackler Institute for Nutrition Sciences at the New York Academy of Sciences and ISAPP. The meeting reached maximum registration several weeks ago, which reflects the keen interest in these topics. ISAPP participants continue into day 2 with five parallel Workshops and day 3 with Workshop feedback in the morning and an IAC learning forum on "**Design and Reporting of Human Trials for Foods and Supplements**" in the afternoon. A very busy schedule, but in the evenings we also hope to have time for some social activities, including a dinner cruise on the Hudson River on Thursday evening.

There are many meetings every year on "**The role of the microbiome and [insert just about any aspect of human health and behaviour here]**". Scientists from industry and academia have to pick and choose the most appropriate meetings to attend in already very busy schedules. I would suggest that ISAPP is unique. In fact, since taking over as President I have been amazed at the number of times I am asked about the meeting, and how do you 'get to go to it' from industry and academic scientists from all over the world. ISAPP is very different to most meetings - attendance is limited to two participants per industry partner, and attendance by non-industry scientists is by invitation only. It is rare that these coveted invitations are refused, and so the quality of the plenary speakers and Workshop participants is truly outstanding, while the limited overall numbers enhances the interactive nature of the meeting. ISAPP also engages with industry partners to select relevant topics for the Workshops and for the IAC Learning Forum. We also have an active Student and Fellows Association to encourage participation by the next generation of scientific leaders.

We are at a very exciting time in the science of probiotics and prebiotics, and presumably other interventions 'mined from' or 'directed at' the microbiome. It is important that opportunities to convert the excellent science conducted in this area into solutions for consumers is not compromised by any sense of complacency that good science will always win out over public skepticism and regulatory barriers, or by indulging in overenthusiastic claims for the potential benefits. One only has to look at GM foods as an example of how a 'new' technology can cause controversy and generate fervent opposition. A decade ago it seemed self-evident that barriers to the importation and cultivation of GM food in Europe would soon collapse and that GM technologies would soon be accepted worldwide. GM crops such as Golden Rice seemed to offer real solutions for nutritional deficiencies in developing countries and herbicide and insect resistant crops seemed well on the way to being universally accepted. However, on May 25th of this year it was reported that an estimated two million protesters turned out in 436 cities in 52 countries to protest genetically-modified (GM) foods. In California, Proposition 37 which would have required labelling of GM food products was narrowly defeated by 51 to 49%. It is important

that probiotic, prebiotic and microbiome based interventions do not follow this path. We believe that organisations like ISAPP, which maintain scientific independence, will play an important role in keeping the debate focused on the best science. This will influence regulators, reward the industries who do the very best research and offer reliable advice to practitioners and consumers alike.

We appreciate the support of everyone at this meeting, the scientists who give their time and efforts freely and the industry whose support makes it all possible and whose participation makes it worthwhile. I would pay special attention to the ISAPP Board, all leaders in their fields who give considerable time and effort to the many teleconferences and emails and phone calls required to keep ISAPP on track (a list of current Board members is provided further on in this letter). None of this would work without the dedication of our Executive Director, Dr Mary Ellen Sanders, who is the keeper of the ISAPP flame and the powerhouse ensuring that we stay on the straight and narrow despite whatever President is “in power”!

Once again, welcome to New York and enjoy the meeting,

Regards

Colin Hill, President ISAPP

This meeting would not be possible without the support and hard work of a large group of people and companies, which are acknowledged in Appendix B.

III. DISCUSSION GROUPS

Five discussion groups were convened June 13. The following are brief descriptions of the key points from the group (prepared by discussion group chairs) and a list of group participants.

Group 1. Evidence of probiotic and prebiotic benefits to public health - scientific and regulatory needs. Chairs: Mary Ellen Sanders, Seppo Salminen and Irene Lenoir-Wijnkoop

Probiotics and prebiotics are useful interventions for improving human health through direct or indirect effects on the colonizing microbiota. However, translation of these research findings into nutritional recommendations and public health policy endorsements has not been achieved in a manner consistent with the strength of the evidence. More progress has been made with clinical recommendations. Conclusions include that beneficial cultures, including probiotics and live cultures in fermented foods, can contribute towards the health of the general population; prebiotics, in part due to their function as a special type of soluble fiber, can contribute to the health of the general population; and a number of challenges must be addressed in order to fully realize probiotic and prebiotic benefits, including the need for greater awareness of the accumulated evidence on probiotics and prebiotics among policy makers, strategies to cope with regulatory roadblocks to research, and high-quality human trials that address outstanding research questions in the field.
This discussion group was more fully summarized in the publication: Probiotics and prebiotics: prospects for public health and nutritional recommendations. Sanders ME, Lenoir-Wijnkoop I, Salminen S, Merenstein DJ, Gibson GR, Petschow BW, Nieuwdorp M, Tancredi DJ, Cifelli CJ, Jacques P, Pot B. Ann N Y Acad Sci. 2014;1309:19-29

Participants:
Mary Ellen Sanders, Dairy & Food Culture Technologies
Seppo Salminen, University of Turku
Irene Lenoir-Wijnkoop, University of Utrecht; Danone Research
Bruno Pot, Institut Pasteur Lille
Max Nieuwdorp, University of Amsterdam, The Netherlands
John Hutton, University of York (formerly York Health Economic Consortium)
Ambroise Martin, University of Lyon
Dan Merenstein, Department of Family Medicine, Georgetown University Medical Ctr

Paul Jacques, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University
Ian Jeffery, Department of Microbiology, University College Cork
Dan Tancredi, University of California
Alexandra Meynier, Mondelez International R&D
Niklas Larsson, Probi AB
George Tzortzis, Clasado
Gregory Leyer, DuPont Nutrition and Health
Melanie Lalonde, BioK+
John Brett Theroux, Glycom A/S
Miguel Freitas, Dannon
Chris Cifelli, Dairy Research Institute
Hideyuki Shibata, Yakult
Stephan Theis, Beneo Institute
Roula Papaioannou, P&G
Eric Johansen, Chr. Hansens
David Keller, Ganeden Biotech
Brian Hansen, Pfizer
Pascal Molimard, Merck
Jingru Li, Kimberly Clark Corporation
Terhi Ahlroos, Valio
Brenda Watson, Renew Life Formulas
Brian Petschow, Transcend Biomedical Communications

Group 2. Use of probiotics and/or prebiotics to program fetal and newborn health / first 1000 days of life. Chairs: Michael Cabana and David Mills

Workgroup 2 presentations and resultant discussions were centered on the development of infant microbiota and links to health, as well some examples of pathology with etiologies rooted in the misassembly of aberrant microbial populations. Both fundamental and clinical research was targeted to inform near-term manipulations of resident microbiota to optimize health outcomes in infants and potentially other populations.

Our current understanding of the mechanisms underlying early infant colonization includes microbial-active human milk oligosaccharides (HMO) as well as other glycoconjugates secreted in breastmilk. There is growing evidence that HMO negatively regulates the breastfed infant microbiome, byflushing potential pathogens from the gastrointestinal tract by mimicking host attachment sites. In addition, HMOs exert a positive influence on the composition of the infant gut microbiome as it enriches the bifidobacterial fraction and potentially other oligo-saccharolytic microorganisms proficient in capturing and metabolism of the unique glycan structures found in milk. Whereas mechanistic studies may benefit from investigating the biological influence of a single HMO structure, some participants felt that it would be prudent to caution against ignoring potential wide-ranging synergistic effects of a panel of glycan structures. To this point, one participant labeled the observed panoply of HMO structures to be "diabolically numerous" and replete with bioactive potential. Along with milk oligosaccharide manipulations of the infant microbiome, the group discussed exploiting the natural abundance of agriculture plant fiber that may indeed fulfill or approximate some HMO functions. Despite the relative ease by which these polysaccharides are extracted, any strictly defined selective potential, as well as systemic circulation/function, is currently unknown.

A common theme permeating the meeting was the conflicting opinion of when does the first 1000 days of human-microbial interactions commence. Some posited that it is initiated with conception, or shortly thereafter. Several participants advocated for challenging the "dogmatic" view of a sterile intrauterine environment, as microbial signatures have been detected in amniotic fluid. In addition to fundamental science, a clear strength of this session was the breadth of clinical studies that were discussed. This included the use commercial probiotics to treat atopic dermatitis in which clinical scientists observed a reduction in eczema in subjects of two years of age. Interestingly, and worth noting, in communities in which probiotic use is an entrenched cultural norm (i.e. Finland), it is difficult to find subjects that do not

display probiotic colonization. In an additional clinical trial, the group discussed treatment of dysbosis-associated infantile colic that is described as afflicting between 5-25% of infants. An impressive study was presented that demonstrated the efficacy of lactobacilli-based probiotics that had a significant impact on improving the symptoms of colic. Needless to say, this product provided enrolled families much welcomed relief.

In an emerging topic, the potential links between microbiota and mental health was placed in context of early developmental programming that may have profound implications throughout one's life. Again, the question of if/when microbial interactions occur in fetal development was raised, as microbial-mediated signaling across the cervix during pregnancy was postulated.

An additional clinical study was presented with compelling evidence for the efficacy of probiotic and/or prebiotic treatment of necrotizing enterocolitis. Accordingly, we learned that designating a measurable health outcome is not always straightforward, as neonate growth was used as a surrogate marker as a non-disease endpoint. Furthermore, there was general interest in investigating multistrain interventions to treat diseases typically seen in infants. As such, evidence for this approach was provided by the reduction of late-onset sepsis in infants by using a three-species therapeutic strategy. Finally, there was spirited debate throughout the session about the relative contribution of breastmilk microbiota towards the establishment and maintenance of the infant microbiome, as well as the mechanism by which these microbes find themselves delivered in milk. One particularly intriguing concept that was introduced involved the rational manipulation of the mother's milk microbiome to promote a beneficial effect in the nursing infant.

There were several discernable themes that were repeated throughout the discussion sessions. This includes the recognition that not all of the beneficial effects of promoting a specific microbial subpopulation are direct. There are some indirect benefits that are no less profound and thus should be monitored and encouraged. A well-known example being the indirect increase of butyrogenesis that has been correlated with bifidobacteria concentration, irrespective of the inability of members of the genus to synthesize this short chain fatty acid. Moreover, current prebiotic strategies have typically focused on indigestible carbohydrates to promote desirable fermentative microbes. Whereas this is clearly a viable approach, other dietary bioactives should be considered as well, with many known to be secreted in milk (e.g. bioactive glycopeptides, TGF-beta, and so forth). There was a general agreement that clinician education should better reflect the scientific advances in understanding and promoting beneficial microbes to target specific deleterious conditions. Finally, several participants held that the community at large should appreciate the complexity of bioactive structures, illustrated well by milk oligosaccharide diversity.

Action items that were emphasized as current and future targets include improving education of scientists and physicians regarding pre/probiotics in general, and specifically how they may be applied in the first few years of life. Moreover, methodological differences between microbiome studies make them somewhat difficult to compare. While sequencing platforms continue to be innovated, and may not be easily standardized between studies, nucleic acid extraction and amplification may be considered an opportunity to issue recommendations to avoid inadvertent disregard of significant microbial subpopulations. Finally, leaders in the community should seek to continue larger partnerships that leverage the expertise of microbiologists, nutritionists, clinicians, neurobiologists, among others to solve the difficult questions that remain in this area. Of general agreement was the need for increasing research efforts into the glycomics/metabolomics/metagenomics of the first 1000 days of life, to be enabled by investment by both private and public funds towards this end.

Participants:

Michael Cabana, UCSF
David Mills, UC-Davis
Lars Bode, University of California, San Diego
Bruce German, UC-Davis
Samuli Rautava, The Hospital for Sick Children, Toronto
Francesco Savino, Università degli Studi di Torino
Mark Underwood, UC Davis School of Medicine
Gary Frost, Imperial College London,
Juliet Ansell, The New Zealand institute for Plant & Food Research
Gregor Reid, University of Western Ontario
Pat Hibberd, Harvard Medical School / Massachusetts General Hospital for Children
Joël Doré, Institut National de la Recherche Agronomique
Andrew Serazin, Matatu LLC
Jane Foster, McMaster University
David Sela, University of Massachusetts
Eamonn Connolly, Biogaia
Steven Davis , Abbott
Raish Oozeer, Danone
Enea Rezzonico, Nestlé
Margriet Schoterman, FrieslandCampina Domo
Martin Kullen, DuPont

Group 3. Influence of neurochemical-producing probiotics and the microbiome on the brain and its function including behavior. Chairs: Eamonn Quigley and Ted Dinan

1. Ted Dinan - overview

Multiple models and clinical scenarios provide evidence to support the concept of the microbiome-gut-brain axis:

- Germ-free animal studies; discordant stress response which is evident endocrinologically but not in behavioral terms. Impact on socialization.
- Studies of infectious disease outbreaks; e.g. the Walkerton outbreak
- Impact of antibiotics such as minocycline on depression and schizophrenia. The effect was assumed to be anti-inflammatory but the impact on the microbiota has not been explored
- Studies of fecal transplantation
- Studies of probiotics

Neurotransmitters are produced by bacteria and modulated by bacteria. Bifidobacteria produce tryptophan and folate; both have significant roles in the CNS.

Introduced the term psychobiotic, which he defined as a probiotic with a mental health benefit.

2. Nathalie Delzenne – prebiotics modulate endocrine function of the gut

- Role of prebiotics in regulation of food intake and appetite. Prebiotics have been shown to decrease food intake. Her focus has been on three hormones, GLP-1, PYY and Ghrelin. Prebiotics increase GLP-1 and PYY in the portal venous circulation and reduce Ghrelin in the systemic circulation. Prebiotics promote the differentiation of L cells in the intestine. SCFA (specifically, acetate and propionate) could mediate these effects through binding to the GPR43/41 receptor on L-type cells. Specific bacteria (Akkermansia, F. prau) interact with L cells and are diminished in obesity.
- Proposed a model linking obesity to changes in the microbiota which, by generating increased levels of LPS, combine with increased intestinal permeability lead to metabolic endotoxemia with resultant inflammatory response and effects on insulin sensitivity. Importance of dose effect.
- Alcohol increases intestinal permeability and alters microbiota, promotes inflammation and leads to depression and anxiety via enhanced pro-inflammatory cytokines which reinforce alcohol craving. Again, a possible role for F prau and its role in permeability.

3. Jim Adams – autism and the gut flora

Estimated that 38% of the etiology of autism is genetic leaving a substantial environmental component. Evidence to suggest a role for the microbiota:

- Risk increased with oral antibiotic use
- Autism temporarily improved with vancomycin, especially, GI symptoms. Also suggestion that anti-fungals may benefit
- Reduced SCFA in autism
- Changes in the microbiota: reduced diversity, markedly decreased Prevotella enterotype

4. Mark Lyte - microbial endocrinology

"Defeated" mouse more susceptible to Yersinia enterocolitica

Microbiota generates catecholamines. Norepinephrine, in turn, enhances growth of Yersinia enterocolitica.

Hormones in food: 8g of L-dopa in tribal pulses. Long list of neurochemicals produced by microbes, e.g. GABA produced by various lactobacilli and bifidobacteria, histamine produced by Lactobacilli; in biologically significant amounts. Antidepressant effects of a GABA producing Lactobacillus (in black soybean milk) as impressive as fluoxetine in an animal model.

In evolutionary terms late horizontal gene transfer of machinery for hormone synthesis from bugs to man.

Importance of gut-appropriate media/culture conditions in studying gut bugs; they should be studied in the context in which they normally reside

5. John Bienenstock – microbiota-gut-brain connections

Bacterial stimulation of IDO (indoleamine 2,3-dioxygenase) which promotes the synthesis of kynurenine from tryptophan. Kynurenine is not only a potent immunomodulatory agent but its metabolites (quinolinic acid, kynurenic acid) are also neuromodulatory via the glutamate system.

Different bacteria act in different ways on the CNS: via ENS, vagus etc.

Early exposure to gut microbiota reduces HPA axis response in adults; modulation of autonomic responses by commensals (e.g. L rhamnosus JB-1 reduces the autonomic response to colo-rectal distension). HPA activation leads to cortisone and catecholamine release which enhances growth of organisms such as E coli and pseudomonas, activates virulence genes and promotes pro-inflammatory response culminating in sepsis.

Lactobacillus inhibits calcium-activated potassium channels in the ENS (increasing neuronal excitability), stabilizes mast cells and along with B fragilis and the product polysaccharide A, excites IPANs.

Bacterial microvesicles (exosoomes) contain membrane components and also DNA and RNA and, in this way, can recapitulate the effects of the whole bacterium.

6. Emeran Mayer – CNS responses to modulation of the microbiota in man

Major differences between rodent and human brain related, in particular, to the size of the forebrain and anterior insula; which play major roles in the affective response to pain and other sensations. No wonder rodent models have served so poorly as tools for drug development in pain.

Effects of 4-weeks of feeding of a probiotic preparation on brain responses in normal healthy volunteers: decreased connectivity of an extensive brain network including somato- and viscerosensory regions in response to a given task as well as blunted reactivity of interoceptive and somatosensory regions.

7. Helen Raybould

Supernatant and conditioned medium activate endocrine cells. Importance of medium; Bif infantis ATCC 15697 grown with milk oligosaccherides had greatest effect on intestinal epithelial function (an example of diet-bacterial interaction).

Change in phenotype of vagal afferents with high-fat feeding. Leptin resistant very early on; later develop hyperphagia and obese phenotype.

8. Harry Burns

Impact of deprivation in early life on later health mediated by cortisol and associated with elevated CRP levels; real-life example of the critical importance of early life events. More human, fewer animal studies. Need to develop a coherent story on the microbiota in health and disease for public policy makers.

Participants:

Ted Dinan, University College Cork
Eamonn Quigley, The Methodist Hospital and Weill Cornell School of Medicine
Nathalie Delzenne, Université catholique de Louvain
James B. Adams, Arizona State University
Mark Lyte, Texas Tech University Health Sciences Center
John Bienenstock, McMaster University
Emeran Mayer, UCLA
Helen E. Raybould, University of California - Davis
Harry Burns, Scottish Government
Janine Barlow, Probiotics International Ltd
Maciej Chichlowski, Mead Johnson Nutrition
Johan Van Hylckama Vlieg, Danone
Rosaline Waworuntu, Mead Johnson Nutrition
Tami Mackle, Pfizer Consumer Health
Saskia van Hemert, Winclove

Group 4. Is a "normal" microbiome a "healthy" microbiome, and can a more optimal one be created through probiotic/prebiotic manipulation? Chairs, Karen Scott and Todd Klaenhammer

This ISAPP discussion group consisted of ten presentations on the following overarching topics:

- Defining the microbiome
- Manipulation of the microbiome
- Distinguishing the healthy-unhealthy microbiomes

A general discussion followed these presentations, addressing these key questions:

- Can we define a healthy and normal microbiome?
- Can we manipulate the microbiome - How do we decide what to aim for?
- Can probiotics/prebiotics have a lasting impact?

The conclusions from these group discussions were the following:

The composition of the microbiota differs considerably over the varying stages of life - Infants, Children and Adults. Our view of what constitutes a 'healthy' or 'normal' microbiota often comes from comparing the microbiotas of healthy individuals with those of diseased individuals or people with altered nutritional states. Body locations with high or low microbial content and diversity are also important considerations. For example, different regions of the body or GI tract possess low (small intestine and vagina) or high (colon) microbial diversity. It was considered by the panel that a microbiota with a low microbial diversity may be more easily perturbed by external influences, than a microbiota with high diversity. This resilience could, in part, be explained by the abundance of functional redundancies inherent in the more diverse population. It was noted that low bacterial diversity is often identified in association with colonic disease, although it is difficult to determine whether this is a cause or effect relationship. From the discussion, it was widely accepted that important functional roles can be maintained by variation and that diverse microbiota may perform similar metabolic activities and interactions.

Potential manipulations of the microbiota will depend on many factors, including: the stage of life, breast or formula feeding, impact of diet (fats, protein and carbohydrates), impact of antibiotics on lowering or eliminating members of the microbiota, and the influence of delivering probiotics and/or prebiotics. Considerable evidence was discussed that antibiotics, probiotics and prebiotics can all significantly alter the composition and diversity of the microbiome.

Health conditions where microbiota alterations have been reported, and may be potentially be manipulated, included diabetes, lactose intolerance/tolerance, IBD, IBS, cardiovascular disease, obesity, diarrhea and malnutrition. Manipulating the microbiota of such individuals may mitigate or abolish the symptoms of these conditions. The group decided that although probiotics and prebiotics have the potential to modulate the microbiota, they do not have a lasting impact after they are removed from the diet, and a short ingestion period does not change the gut microbiota indefinitely. To elicit a persistent effect, probiotics and prebiotics need to be taken consistently. Possible exceptions to this rule include infectious diseases (where the disease-causing pathogen can be permanently removed from the microbiota) and infant microbiota development (where it may be possible to permanently shape the adult microbiota and immune functions).

Participants:

Karen Scott, Rowett Institute of Nutrition and Health
Todd Klaenhammer, North Carolina State University
Francisco Guarner, Hospital Vall d'Hebron
Martin Blaser, New York University School of Medicine
Ruth Ley, Cornell University
Jens Walter, University of Nebraska
Michiel Kleerebezem, Wageningen University
George Fahey, University of Illinois
Paul Sheridan, Rowett Institute of Nutrition and Health
Maeve Murphy, General Mills
Linda Duffy, NIH National Center for Complementary and Alternative Medicine
Gun-Britt Fransson, Probi AB
Emma Salomonsson, Glycom A/S
Michael Moore, Clasado
Howard Cash, Ganeden Biotech
Thierry Saint-Denis, The Dannon Company
David Pridmore, Senior IAC rep
Jacoline Gerritsen, Winclove
Douwina Bosscher, Cargill
David Hayashi, Mondelez
Nicolas Pagé, Nestlé
Koji Nomoto, Yakult
Rebecca Vongsa, Kimberly Clark Corp
Tommy Watson, Renew Life Formulas
Brenda Watson, Renew Life Formulas
Ashley Mueller, Biocodex USA

Group 5. Personalized probiotics and prebiotics. Chairs: Colin Hill and Fredrik Bäckhed

The workshop was divided in two phases, in the first the speakers gave an overview of recent data pertaining to the role of the microbiome and prebiotics and probiotics in personalised settings (targeting individual sub-populations or disease groups). In the second phase the group had a more general

discussion as to how the emerging microbiome literature can assist industry to develop effective and economic products.

Seminar session

Microbiome: In brief, Fredrik Backhed and Rob Knight emphasised the need for and importance of more metagenomic studies on larger numbers of subjects, across ages, body sites and populations. Rob also stressed the difficulties inherent in analysing datasets generated in different research groups because of methodological variations. However, Fredrik also referred to a recent study from his group which gives a sense of the potential of these analyses, in that they were able to use the microbiome data to robustly predict risk of developing Type 2 diabetes. This gives a glimpse of the potential of the microbiome to be used to stratify populations for trials, or to act as a potential endpoint in pre and probiotic interventions. The group also discussed the issue of sequencing depth in most current protocols and the probability that many organisms undetected in current protocols are present as 'seeds', which can flourish under appropriate preturbations or interventions.

Interventions: Partice Cani, Cormac Gahan, Susan Lynch and Chaysavanh Manichanh gave overviews of recent studies which focussed on interventions. Susan described recent advances in protecting animals against respiratory antigen challenge using house dust from home with or without pets, and using the outcomes to identify lactobacilli which could provide protection against similar insults. Chaysavanh described how a 4 strain mix can stabilise the microbiome in UC patients, a very interesting example of using the microbiota stability as a potential endpoint for a probiotic intervention.

In one of two mechanistic presentations, Patrice described an elegant study which supports a role for the induction of host produced antimicrobial peptide Reg3gamma by prebiotics, and by *Akkermansia muciniphila*, thus influencing barrier function and endotoxaemia. Cormac described recent unpublished work which indicates a significant role for bile salt hydrolase activity (a common enzymatic function in probiotics and commensals) in host signalling and weight gain in animal models.

Probiotic and Prebiotics: Paul Ross and Glenn Gibson shared strategies developed within their groups towards personalised probiotics and prebiotics. Paul outlined a strategy which begins with a desirable function (enzymatic activity, carbohydrate synthesis, bacteriocin production) and then screens tens of thousands of strains for the desired trait. Those at the top of the 'league table' were then deployed in animal models to test efficacy – a strategy which has been very successful for the Cork group. Glenn used a very elegant 'reverse biochemical engineering' approach to induce selected probiotic strains to convert lactose in to complex oligosaccharides like GOS. The bacterially derived GOS can then be successfully used to select for the 'progenitor' strain or species in complex faecal models.

A view from industry. Ravi Menon shared some 'real world' economic perspectives, emphasising that while stratification is important to detect effects, food is marketed to the masses. However, Ravi shared that GM research has found that some specific products may only be fully effective in sub-populations (in this example in people of a specific genotype), and it is important to know the prevalence of the 'responders' in the general population. He also reminded us that consumers are generally not willing to pay more for healthier foods, or compromise on taste and the eating experience. Lastly, consumers self-diagnosis may confuse outcomes or confound expectations of consumers purchasing individual products.

General discussion

There was an open discussion about how soon the exciting microbiome-based research is likely to support the development of health claims for existing or new products. It was generally agreed that 'personalised' pre and probiotics are unlikely to be developed by the food industry, but may lend themselves to pharma-type applications. However, a better understanding of a 'healthy microbiome' or assistance with stratification of patient or consumer cohorts will support industry goals.
Several general conclusions were drawn as follows:

- Microbiome science at a critical point. Lots of exciting correlations, new technologies, new non-traditional organisms under investigation, but….
- …. have we identified how best for industry (food and pharma) to engage fully with outcomes from microbiome initiatives?
- Personalised probiotics and prebiotics in food unlikely in near future. May develop a better sense of which sub-populations may respond to individual pre or probiotics (better stratification).
- Personalisation may be more likely for therapeutic applications for pre and probiotics
- Many health benefits likely to be 'diluted out' by non-responders (not always microbiota related).
- More robust and generally accepted protocols for microbiome analysis
- Better stratification of subjects into responders and non-responders will help to unravel probiotic and prebiotic effects.
- Bigger microbiome studies are required across populations and ages and patient groups.
- Differing regulatory frameworks represent a very real problem for the field.

In the final feedback session, Colin Hill concluded with comments that all were agreed that microbiome research is important and will yield significant insights, and will change both food and pharma industry in years to come. Nonetheless, it is important to remember that probiotic and prebiotic research does not have to 'wait' for these insights and deliverables, and that valuable research can be conducted, and interventions performed with robust end-points and validated biomarkers even in the absence of a more complete understanding of the role of the microbiome in health and disease.

Participants:

Colin Hill, University College Cork
Fredrik Bäckhed, University of Gothenburg
Patrice Cani, Université Catholique de Louvain
Glenn Gibson, University of Reading
Paul Ross, Alimentary Pharmabiotic Centre, Teagasc Food Research Centre
Rob Knight, University of Colorado - Boulder
Susan Lynch, UCSF
Cormac Gahan, Alimentary Pharmabiotic Centre
Chaysavanh Manichanh, Hospital Vall d'Hebron
Ravi Menon, General Mills
Bo Möllstam, BioGaia
Arthur Ouwehand, DuPont
John Troup, Metagenics
Serge Carrière, BioK+
Benedicte Flambard, Chr. Hansen
Brooke Grindlinger
Sylvie Binda, Danone
Mike Janusz, Procter & Gamble Company

IV. Student and Fellows Association Program

The 2013 ISAPP Student and Fellow Association Conference was held from June 11-June 14 in New York City. This overlapped with the annual ISAPP meeting and allowed SFA to interact with ISAPP Scientists and Industry Members, many of whom have shown interest in attending SFA events and leading panel discussions geared towards young scientists. Posters were presented by 37 SFA members from 10 countries. Related documents: Fall SFA 2013 Newsletter. Student Fellow Association 2013 Program and Poster Abstracts.

ISAPP-SFA members at the 2013 SFA meeting, New York City

APPENDIX A. PROGRAM FOR THE ISAPP MEETING JUNE 12-14, 2014

11th Meeting of the
International Scientific Association for Probiotics and Prebiotics

June 12-14, 2013
New York Academy of Sciences, 7 World Trade Center, 250 Greenwich St, 40th Floor, New York, NY

JUNE 12: *PROBIOTICS, PREBIOTICS, AND THE HOST MICROBIOME: THE SCIENCE OF TRANSLATION*.
Open-registration conference co-organized by ISAPP, New York Academy of Sciences and Sackler Institute of Nutrition Sciences

Organizing Committee

Francisco Guarner, MD, PhD
University Hospital Vall d'Hebron, Spain
Patricia L. Hibberd, MD, PhD
Harvard Medical School / Massachusetts General Hospital for Children
Colin Hill, MSc, PhD, DSc, MRIA
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Speakers

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Sir Harry Burns, DSc, MPH
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Victoria E. Ruiz, PhD
New York University School of Medicine
Andrew Serazin, DPhil
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Program for Conference Lectures June 12 (Speaker Abstracts and Poster Abstracts)

Session I: Putting Probiotics, Prebiotics, and the Microbiome into Translational Context
Economic Assessment of Disease Reduction and Prevention — Challenges & Perspectives for Probiotics and Prebiotics, John Hutton, University of York, United Kingdom
Impact of Antibiotic Exposures on the Developing Microbiota, Martin J. Blaser, MD, New York University School of Medicine

Session II: Programming the Microbiome
Microbiome Assembly in Early Childhood, David A. Relman, MD, Stanford University School of Medicine
When the Programming Goes Awry: Diabetes, Obesity, and Beyond, Patrice D. Cani, PhD, Université Catholique de Louvain, Belgium

Session III: Future Directions for Translating Research to Transform Healthcare
Translating Research into Public Policy, Sir Harry Burns, DSc, MPH, Scottish Government, Scotland
Open Discussion: Probiotic / Prebiotic / Microbiome Research Outcomes and Policy Strategies that Have the Potential to Transform Healthcare
Moderator: Gregor Reid, PhD, MBA, Western University / Lawson Health Research Institute, Canada
Panelists: Sir Harry Burns, DSc, MPH, Scottish Government, Scotland
Rowena Pullan, Pfizer Consumer Healthcare
David A. Mills, PhD, University of California, Davis
Bruno Pot, PhD, Institut Pasteur de Lille, France

Session IV: Who Is in Control — the Brain or the Microbes?
How Bacteria Can Influence Brain Development, Circuitry, and Behavior, Jane A. Foster, PhD, McMaster University, Canada
Prebiotic Supplementation Alters Hypothalamic Neuronal Activity and Protects Against the Obesogenic Environment, Gary Frost, PhD, Imperial College London, United Kingdom

Session V: Hot Topics in Prebiotic and Probiotic Research and Development
Effect of Early-Life Pulsed Antibiotic Treatment on T-Lymphocyte Populations, Victoria E. Ruiz, PhD, New York University School of Medicine
Beneficial Effects of Prebiotics and Probiotics on the Gut-Brain Axis and Regulation of Body Weight, Helen E. Raybould, PhD, University of California, Davis
The Effect of Nutrition on the Microbiome in Pregnant Women and the Use of Micronutrient Supplemented Probiotic Yogurt to Improve Outcomes, Megan Enos, Western University
Impact of a Short Chain Galactooligosaccharide on the Human Microbiome and Symptoms of Lactose-Intolerant Individuals, Todd Klaenhammer, PhD, North Carolina State University

Session VI: Reaching People in Need with Innovative Probiotic Interventions
Getting Serious: Defining a Critical Path for Microbiome Products, Andrew Serazin, DPhil, Matatu LLC
From Yoghurt to Vaccine for the Developing World, Gregor Reid, PhD, MBA, Western University / Lawson Health Research Institute, Canada; Patricia L. Hibberd, MD, PhD, Harvard Medical School / Massachusetts General Hospital for Children
Fecal Transplantation for Obesity and Type 2 Diabetes Mellitus, Max Nieuwdorp, MD, PhD, University of Amsterdam, The Netherlands
Faecalibacterium prausnitzii and other Bioactive Commensals for Immune-Mediated Diseases, Joël Doré, PhD, Institut National de la Recherche Agronomique (INRA), France
Overcoming the Regulatory Roadblocks to Non-Drug Applications of Microbiome-Based Health Interventions, Fred H. Degnan, JD, King & Spalding LLP

JUNE 13. PRORAM FOR BY-INVITATION MEETING, ORGANIZED BY ISAPP

Date/Time	Event
Tuesday, June 11	
1:00-3:00 PM	Board of Directors (BoD) meeting (BoD only)
3:00-3:30 PM	Coffee break
3:30-4:30 PM	Industry Advisory Committee (IAC) meeting (IAC only)
4:30-5:30 PM	BoD+IAC meeting (BoD+IAC only)
6:00-9:00 PM	Meet and Greet Pizza Party (BoD+IAC+speakers from June 12 Conference only)
Wednesday, June 12	
7:45 AM – 7:30 PM	**Probiotics, Prebiotics, and The Host Microbiome: The Science of Translation**
7:45 AM	Registration
7:45 AM	Continental breakfast
8:30 AM	Meeting opens
9:45-10:15 PM	AM Coffee break
12:30 – 1:30 PM	Lunch and posters
3:30 – 4:00 PM	PM Coffee break
6:00-7:30 PM	Networking reception and posters
Thursday, June 13	**Discussion Groups**
7:45-8:30	Registration
7:45 AM	Continental breakfast
8:30 AM – 3:00 PM	1. Evidence of probiotic and prebiotic benefits to public health - scientific and regulatory needs. Chairs: Mary Ellen Sanders, Seppo Salminen and Irene Lenoir-Wijnkoop
	2. Use of probiotics and/or prebiotics to program fetal and newborn health / first 1000 days of life. Chairs: Michael Cabana and David Mills
	3. Influence of neurochemical-producing probiotics and the microbiome on the brain and its function including behavior. Chairs: Eamonn Quigley and Ted Dinan
	4. Is a "normal" microbiome a "healthy" microbiome, and can a more optimal one be created through probiotic/prebiotic manipulation? Chairs: Karen Scott and Todd Klaenhammer
	5. Personalized probiotics and prebiotics. Chairs: Colin Hill and Fredrik Bäckhed
3:00-5:00 PM	Wrap up presentation preparation
	AM Coffee break, lunch
5:30 PM pick up **10:30 PM drop off**	Hudson River Dinner Cruise, Pier 61 Chelsea Piers Bus transportation pick up from Club Quarters World Trade Center and Club Quarters Wall Street
Friday, June 14	
7:45-8:40 AM	Continental Breakfast
8:40-9:00 AM	**Report from ILS-Europe. Immune biomarkers for probiotic/prebiotic studies. Arthur Ouwehand**
9:00-Noon	**Wrap-Up Session.** Discussion groups 1-5
10:00-10:30 PM	AM Coffee break
Noon-1:00 PM	Lunch
1:00-3:30 PM	**IAC Learning Forum. Effective design and reporting of clinical trials (IAC, SFA, and ISAPP invited participants)**
3:30-5:00 PM	Board of Directors Meeting (BoD only)

Discussion Groups
Five concurrent discussion groups were held Thursday, June 13. These groups are focused on specific topics, are organized by the discussion group chairs and are attended by invited content experts and IAC representatives (who have chosen that group). It is not possible to attend more than one discussion group. The intent of these groups is to address evolving research on topics of particular interest to the probiotic, prebiotic and/or microbiota areas, hopefully with a written outcome.

Wrap-Up Session
Summary presentations from chairs of each of the 5 discussion groups to all meeting participants.

IAC Learning Forum: Design and Reporting of Human Trials for Foods and Supplements

Session Date: June 14, 2013, 1:00 – 3:30 PM
Location: New York Academy of Sciences, Auditorium
Invited to attend: This session is designed to address a specific request from the ISAPP Industry Advisory Committee to the Board of Directors. Therefore, the target audience for this session is the **IAC members**. However, the IAC has agreed that any participants in the ISAPP meeting (including **invited experts** and **SFA members**) are welcome to participate as well.

Chairs: David Pridmore and Greg Leyer (IAC representatives to the Board of Directors)

Session Description: It is not always clear how to efficiently conduct human efficacy studies to substantiate foods and dietary supplements. In many cases, the lack of predictive, scientifically validated markers for health or disease endpoints means that companies must conduct studies on specific symptoms. Since regulators demand that studies be conducted on healthy, or at-risk, populations or subpopulations, studies usually need to recruit large numbers of subjects, and often it isn't clear if a subpopulation more likely to respond to the intervention can be identified. This forum is designed to address these issues, with specific examples from metabolic syndrome, cognitive function, digestive function and immune function. Talks will address if it is possible to conduct human studies focused on physiological function, such as intestinal transit (not diarrhea) or improved IgA response to an oral antigen. Each speaker will describe a focused approach to human studies in topic areas, and describe scientific validity of markers for assessment. They will provide a basic plan for the study, including the number of subjects, the actual study design, the primary and secondary objectives, and other important parameters.

The program will begin with a general discussion of how to prepare, implement and report a clinical trial. This talk will present requirements for a good quality study and common mistakes made in probiotic/prebiotic research.

Program: Design and Reporting of Human Trials for Foods and Supplements

Topic	Speaker
Preparing, implementing and reporting a clinical trial	Dan Tancredi, PhD, University of California Dan Merenstein, MD, Georgetown University, Washington DC, USA
Endpoints of studies: biomarkers or patient-oriented outcomes	
• Metabolic syndrome	Patrice Cani, PhD, Université Catholique de Louvain,

Start with definition, confounding factors, what is target	Brussels, Belgium
• Cognitive function	Ted Dinan, PhD, University College Cork, Ireland
• Digestive function	Eamonn Quigley, MD, The Methodist Hospital and Weill Cornell School of Medicine, Houston, TX USA
• Immune	Bruno Pot, PhD, Institut Pasteur, Lille, France

APPENDIX B. ACKNOWLEDGMENTS

This meeting would not be possible without the support and hard work of a large group of people and companies, which are acknowledged here.

NYAS
ISAPP would like to acknowledge Kerstin Hofmeyer and Brooke Grindlinger, with the assistance of Sherryl Usmani and Melanie Brickman Stynes, of the New York Academy of Sciences and Mandana Arabi of the Sackler Institute of Nutrition Sciences.

IAC partners (led by David Pridmore and Grey Leyer)
ISAPP is fortunate to be sponsored by probiotic and prebiotic companies around the globe, who value research and discovery. Through their generous support, ISAPP has the funds to conduct its annual meetings. ISAPP expresses appreciation for the support provided by the 2013 IAC companies.

Abbott Nutrition
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Biocodex
BioGaia
BioK+
Cargill
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Dairy Research Institute
The Dannon Company
Danone Research
DuPont/Danisco
Fonterra
Friesland Campina
Ganeden
General Mills
Glycom
Kimberly Clark
Mead Johnson
Merck
Metagenics
Mondelez
Nestle
NIZO
Nutricia
Procter & Gamble
Pfizer
Probi
Probiotics International Ltd. (Protexin)
Renew Llife Formulas
UAS Laboratories
Valio
Winclove
Yakult

IAC companies who provided funding beyond normal yearly dues to help us to manage the extra costs associated with a New York venue:

- Chr Hansen - Meet and Greet Pizza party
- DuPont - June 13 breakfast
- Yakult - June 13 coffee break
- Beneo- June 13 Lunch, coffee break and wine/beer on cruise
- Dannon - Cruise
- Mead Johnson - Cruise
- Mondelez - Bus transportation to cruise
- P&G - June 14 breakfast
- Metagenics - June 14 coffee breaks and lunch

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Speakers for the IAC Learning Forum:

- Dan Tancredi, PhD, University of California
- Dan Merenstein, MD, Georgetown University, Washington DC, USA
- Patrice Cani, PhD, Université Catholique de Louvain, Brussels, Belgium
- Ted Dinan, PhD, University College Cork, Ireland
- Eamonn Quigley, MD, The Methodist Hospital and Weill Cornell School of Medicine, Houston, TX USA
- Bruno Pot, PhD, Institut Pasteur, Lille, France