2003 Annual Report
International Scientific Association for Probiotics and Prebiotics
January 1 – December 31, 2003

Contents

Introduction

ISAPP is an international non-profit collaboration of scientists dedicated to advancing the science of probiotics and prebiotics. The mission statement of ISAPP is: To engender and disseminate information on high quality, multidisciplinary, scientific investigation in the fields of probiotics and prebiotics, and to advance the development of scientifically substantiated, health-promoting probiotic and prebiotic products worldwide. ISAPP is the only scientific organization dedicated specifically to probiotics and prebiotics, bringing together scientists from all pertinent disciplines, including food science, microbiology, immunology, biochemistry, nutrition, molecular biology and medicine. As a scientific society, ISAPP strives to have all activities focused on science, not the promotion of any specific commercial products.

For additional details, see website www.isapp.net

Message from the President

The year 2003 was another building year for ISAPP. ISAPP continued with its dedication to hosting a scientific meeting and publishing science-based review articles. We also formalized an Industry Advisory Committee, which allowed ISAPP to have a forum for specific feedback from research-based companies involved in probiotic and prebiotic fields. ISAPP owes a great debt to Directors Glenn Gibson and Bob Rastall, who hosted a wonderful meeting in sunny England in August. I also want to express my gratitude to the dedication of the Board of Directors and IAC members who contributed in many ways to the continued success and direction of ISAPP.

Signed: Mary Ellen Sanders

2003 Board of Directors

Changes to the 2003 Board of Directors included the resignation of Christine Cherbut due to a demanding new position, and the election of Francisco Guarner, ISAPP's first MD on the board.

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2003 Accomplishments

- ***2003 ISAPP Annual Meeting***. Building on the momentum generated from the 2002 meeting in London, Ontario, Canada and the leadership of local host and Secretary Dr. Gregor Reid, ISAPP stretched across the Atlantic and sponsored its first meeting in a European venue. Hosted by Drs. Gibson and Rastall from the University of Reading at the stunning Henley Conference Center, Henley-on-Thames, England, this meeting followed the by-invitation format of the 2002 meeting. Of note, this meeting was the site for the first ISAPP Industry Advisory Committee meeting, chaired by Dr. Thomas Tompkins of Institut Rosell.

  70 scientists from 20 countries convened for general lectures and in 7 smaller discussion groups to discuss: (1) clinical study design/biostatistics (chaired by Ian Rowland); (2) Probiotics and prebiotics: the potential to impact worldwide health (chaired by Gregor Reid); (3) Genotype vs. phenotype (chaired by Todd Klaenhammer); (4) Biotechnology, stability, manufacture, biotechnological presentation of prebiotics and synbiotics (chaired by Bob Rastall); (5) Weight of evidence for a probiotic/prebiotic effect: what is needed? (chaired by Mary Ellen Sanders); (6) Pathogen modulation (acute and chronic illness mediated by pathogens) - what is the direct action of pro/prebiotics? (chaired by Harsharn Gill); (7) Probiotics and prebiotics through life - age relationships, use in infants, weaning, elderly (chaired by Glenn Gibson).

  The discussion from this meeting was published: Rastall R, Gibson G, Gill H, Guarner F, Klaenhammer T, Pot B, Reid G, Rowland I, Sanders ME. 2005. Modulation of the microbial ecology of the human colon by probiotics, prebiotics and synbiotics to enhance human health: an overview of enabling science and potential applications. FEMS Microbial Ecology 52(2): 145-152.

  Conclusions from the 2003 group on “Weight of evidence for a probiotic/prebiotic effect: what is needed?” was published: Sanders ME, Tompkins T, Heimbach JT, Kolida S. 2004. Weight of evidence needed to substantiate a health effect for probiotics and prebiotics. Regulatory considerations in Canada , E.U., and U.S. Eur J Nutr. 44(5):303-10.

  Concise responses to industry questions on immune biomarkers, gut flora improvement, probiotic dose, D,L-lactate, ‘human origin’ for probiotic strains, undefined probiotics, live vs. dead probiotics, definition of prebiotics and prebiotics with proven effects can be found in Appendix A.

- ***First meeting of Industry Advisory Committee.***
  At the 2003 meeting, representative scientists from contributing companies comprised the first Industry Advisory Committee. Companies represented on this committee were: Biogaia , Chr. Hansens, Danisco, Danone, Fonterra, Institut Rosell,
  Mead Johnson Nutritionals, Merck, Mofin Alce, Nestle, Novartis, Orafti, Procter & Gamble, Rhodia, Inc., Wyeth and Yakult. These representatives met with the ISAPP Board of Directors to discuss how ISAPP might provide support for the probiotics and prebiotics field as a whole. In addition, industry members posed questions to the Board; the answers are summarized in Appendix A.

- ***Development of Industry Advisory Committee Guidelines***

The Industry Advisory Committee was established for the purpose of advising the ISAPP Board of Directors on issues of importance to the science of probiotics and prebiotics. It is recognized that companies conducting business in this field can provide valuable insight into barriers to success and opportunities for development of this industry. As an organization committed to the advancement of the science of probiotics and prebiotics, ISAPP can benefit from such insight. The IAC exists in an advisory capacity only and does not hold any voting power or undue influence over the decisions of the Board of Directors of ISAPP. ISAPP activities are funded largely through IAC membership fees.

- Companies involved in, or developing involvement in, manufacture of probiotics or prebiotics or products containing them are appropriate for consideration for Industry Advisory Committee membership. Additionally, companies involved more peripherally with the industry will be considered. Overriding principles for inclusion for IAC membership are listed here. Companies should have:
- A science-based approach to probiotic and prebiotic product development;
- A commitment to and funding of related research;
- A commitment to responsible product formulation and communications;
- A commitment to the mission of ISAPP and a willingness to work to toward that mission in a collaborative manner with the ISAPP Board of Directors and other IAC members;
- Willingness to pay established IAC membership fees.
- Furthermore:
- IAC membership may be limited to assure a working group size conducive to accomplishing established goals.
- The representative of the company sent to participate in the IAC must be a scientist.
- The final decision of inclusion of a company on the IAC shall be made in the discretion of the ISAPP Board of Directors to best meet the needs and maximize the credibility of the IAC. Membership on the IAC may be terminated by the Board of Directors at any time for any reason by a vote of two-thirds of a quorum of the Board.

- ***List of ISAPP Publications to date***
  - Reid G, Guarner F, Gibson G, Tompkins T, Gill H, Rowland I, Rastall B, Pot B, Sanders ME. 2004. Discussion on toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. Gastroenterology. 127:366-7.
  - Reid G., Sanders ME, Gaskins HR, Gibson GR, Mercenier A, Rastall R, Roberfroid M, Rowland I, Cherbut C, Klaenhammer T R. 2003. New scientific paradigms for probiotics and prebiotics. J Clin Gastroenterol. 37:105-118.
  - Ferber D. 2002. Much ferment on the probiotics front. ASM News. 68:369-370.

- ***Website*****.** The www.isapp.net website is now being managed by WS Design and continues to be the key means of communication with ISAPP delegates.

- ***2003 Meetings of the Board of Directors***
  - May 21, 2003 in Washington DC. Board members Sanders, Reid, Gibson and Klaenhammer met with guests Rex Gaskins, Willem de Vos and Thomas Tompkins to discuss ISAPP issues, including meeting sponsorships and update on the UK meeting in August.
  - August 3 and 5, 2003 at Henley-on-Thames, UK.
  - November 13, 2003 in Nice, France. Present were Mary Ellen Sanders (Chair), Gregor Reid, Bruno Pot, Francisco Guarner, Ian Rowland and Lorenzo Morelli (Guest).

- ***Co-sponsorship of ASM symposium, May 18, 2003, Washington DC***
  "Modulation of the intestinal and vaginal microflora: impact on pathogens, host response and health." Speakers:

Dr. Mary Ellen Sanders	Probiotics – Definition, importance to microbiology and health, and optimal standards for human use.
Dr. Willem De Vos	Understanding and manipulating the diverse intestinal microflora
Dr. Rex Gaskins	Immunity versus tolerance: implications for treatment and prevention of disease.
Dr. Glenn Gibson	Which bacteria should we be feeding when we eat dinner?
Dr. Gregor Reid	The potential for lactobacilli to reduce the risk of urogenital infections including HIV

2004 Objectives

- Host a 2004 by-invitation format meeting in Colorado with Mary Ellen Sanders as local host. Add "Late Breaking News" rapid session for delegates to present original research results.
- Explore ISAPP sponsorship of satellite symposia with other organizations, such as medical GI societies or microbiology organizations.
- Continue to explore ways the IAC companies can get an adequate return on their investment in ISAPP.
- Proceed with publication of meeting summaries.

Appendix A. Responses to Industry Questions Posed at 2003 Meeting

ISAPP response to IAC questions

Posed at the ISAPP IAC meeting August 3, 2003

Immune biomarkers that could be easily understood by consumers and healthcare providers

The group agreed that at this stage there are no 'clinically substantiated and widely accepted' immunological biomarkers. Although modulation of the host immune function is reported to be one of the most common health benefits of probiotics, little is known about the relationship between immunoactivity and health improvement. The cellular and molecular mechanisms by which probiotics influence the functioning of the immune system also remain poorly understood. Thus, a lot more work needs to be done before a recommendation on such immunological biomarkers could be made. Properly designed clinical studies that measure health outcomes as well as indices of immune function (in the same subjects) are required to validate potential biomarkers.

Strategies to advance science behind benefits of improved flora:

A multi-disciplinary approach is the key (microbiologists, dieticians, nutritionists, clinicians, immunologists etc.) to advancing our understanding of the value of probiotic- or prebiotic-induced alterations in gut flora. Research should be hypothesis driven and underpinned through sound mechanism-based explanations of effect. For tracking changes in the gut flora, a molecular approach is critical, with culture independent methodologies becoming more widespread. Peer reviewed publications are essential and the results gained should be repeatable in other laboratories. Human studies are preferred but these can be backed up by *in vitro* or animal work to confirm or test mechanisms. Good biomarkers are required to assess fermentation, enzyme profiles, impact on health, cognitive function etc. These include immune markers, organic acids and other metabolites, shifts in the flora, clinical outcome, wellbeing markers, genome expression and microbial activity indicators. Models should be validated as reliable. Some examples of research approaches that may shed some light on the question include:

- Gut flora-reconstituted animal models that are devoid of specific test species
- Correlative studies of the gut flora of diseased vs. healthy humans

To communicate the message on the value of gut flora changes, the health care profession and reliable media sources were seen as important. ISAPP clearly could play a major role in harnessing skills and expertise. Research output should combine applied and fundamental science and therefore is likely to depend on different funding sources depending on the issue being questioned.

Minimum effective dose for different applications:

Different levels are likely required for different age groups, depending on the starting population of native beneficial bacteria. For example, if you begin with a low probiotic level (such as often occurs in the elderly), then smaller changes in the flora levels may be more relevant than if the lactic flora is already high. Generally, at least a 0.5 log increase in response to prebiotics is suggested as evidence of an effect, but more likely a one log increase is required. Probiotic products should deliver viable probiotics at a level which has been documented to have a beneficial physiological effect. In general, products delivering less than 10^9 per day have not been effective, except perhaps in effecting minor alterations on fecal microflora. Furthermore,

there does not seem to be an upper limit to this, and in fact a published meta-analysis showed increased effectiveness with increased daily dose up to 10^{11}/day. The relevant factor, however, is the existence of scientific documentation to justify formulation levels. This is not the case for prebiotics where too high a dose may cause side effects such as gas distension. Different pro- and prebiotics are likely to be relevant for different populations. New advances in next generation synthesis and unraveling of genomic effects can help to inform product choice.

D, L -lactic acid:
The Group agreed with the position paper circulated by Eamonn Connelly (copy may be requested from Eamonn at ec@biogaia.se). Essentially, authorities have generated some concern over lactic acidosis. However, lactate will disappear very quickly in the gut as it is the preferred electron sink product for the flora. Without this occurring, the anaerobic fermentation would be compromised. Any levels of lactate generated by product intake should therefore not have any negative biological impact. ISAPP can produce a position paper on this if Board of Directors agrees.

Human origin of probiotic strains:
The Group was asked its opinion if human origin was an important selection criterion for probiotics for human use. Several factors were considered. (1) The accepted definition of probiotic (FAO, 2001) does not stipulate any natural habitat for strains used as human probiotic. (2) There are many examples of probiotic strains from species not recognized as normal inhabitants of the human for which physiological benefits for humans have been documented. (3) Criteria do not exist to define use of the term 'human origin'. Often, isolation from human feces is considered adequate 'proof' of human origin. However, it is clear that although many strains may survive intestinal transit, this does not imply that they can adhere or colonize or possess traits which predispose them to a more intimate association with humans. The term 'human origin' implies more than 'survivability through the human GI system', but in practice the term may be used without scientific evidence of more. Taken together, it seems that the property of 'human origin', especially as commonly used, is not a relevant criterion for probiotic strains for human use.

Are undefined products probiotics?
This question was raised with regard to traditional products (fermented foods, kefirs, etc.) prepared with undefined blends of many different genera, species and strains of bacteria and/or yeast. Although some scientific literature supporting the probiotic nature of some strains of the species contained in these products may exist, the microbes used in these products have not been isolated, characterized or defined. Although it is clear that health benefits may result from consumption of these products, it is difficult to imagine being able to subject such undefined products to rigorous scientific testing for efficacy. As such, the health effects of these products cannot be substantiated and therefore cannot be termed 'probiotic'. A term such as 'functional food' would be more appropriate for these products.

Health benefits of live vs. killed or dead probiotic cells:
The definition of probiotic stipulates that the microbes administered be alive. Even though dead cells may mediate physiological benefits, albeit more moderate ones, they are not probiotics, and as such do not fall into the purview of ISAPP. Few studies specifically address the contribution of killed cells to any observed health benefit. Conducting such studies would contribute to the understanding of mechanisms of action of probiotics. Such comparative studies should be conducted.

Definition criteria for prebiotics:
The group felt that the following definition of prebiotic is fundamentally sound: A non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, that can improve the host health (Gibson, G.R. and Roberfroid, M.B. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J. Nutr. 1995; 125:1401-1412). This definition is based on knowledge of the number and identities of bacteria considered as desirable. Imminent research will certainly expand the understanding of this basic situation. It was also recognized that generalizing about the value of certain bacterial genera is neither prudent nor justifiable, as certain members of some genera (notably *Bacteriodes*) may be harmful or not, depending very much on which species is being considered. This is due to practical limitations in speciation of bacteria in complex environments and will improve in the future.

The group also felt that researchers and industry should respect the definition and not use the term prebiotic as equivalent to dietary fiber.

Potential health benefits of prebiotics and how these should be communicated?
The group felt that most of the health-related effects are the same as those proposed for probiotics although the weight of evidence for health benefits of prebiotics in humans is not as great and needs to be improved.

There may, however be health-positive outcomes of prebiotic intake that do not rely on bacterial fermentation - examples include stimulation of apoptosis in cancer cells and effects on blood lipids. The evidence for these effects is, however, at an early stage with little data coming from human studies.

What non-digestible oligosaccharides are proven prebiotics?
The group agreed that in order to be classed as a prebiotic, a carbohydrate had to be seen to have a prebiotic effect in at least one well-designed human trial with the microbial analysis being performed using culture-independent molecular techniques. Based on this criterion, the only proven prebiotics are fructo-oligosaccharides (whether derived from sucrose or inulin), inulin, galacto-oligosaccharides and lactulose. There are a range of prebiotics on the Japanese market that have been studied in humans although the studies have sometimes involved small numbers of volunteers and the microbiology has rarely been carried out using molecular techniques. There are still more candidate molecules not yet tested in humans.

Degree of evidence needed for claims and **Product labelling for content and claims**
These topics were the main focus of the Weight of Evidence group at the 2003 ISAPP meeting and will be addressed adequately here. Thorough conclusions will be prepared by this group and circulated in a document to be published with the conclusions of the other groups.