

Probiotic Bulletin

AN UPDATE FOR HEALTHCARE PROFESSIONALS

Probiotic Progress: Health Implications for the Gut and Beyond

Yakult UK Symposium
12th October 2010

How might probiotics help maintain the health of older people, athletes, people with allergies or gut disorders such as irritable bowel syndrome and inflammatory bowel disease? These were just some of the questions addressed at the recent Yakult UK Symposium in London. A day of interactive and fascinating presentations engaged the audience, in a meeting opened with a warm welcome from Dr Linda Thomas, (Science Director, Yakult UK), and chaired by Professor Jeremy Hamilton-Miller (Royal Free & University College Medical School London) and Catherine Collins (Principal Dietitian at St George's Hospital).

As once pondered by Arthur Dent (that famous galactic hitchhiker) – *is 42 really the meaning of life?* This was one of the many intriguing points in the opening talk from Professor Dermot Power (a consultant in Geriatric Medicine at the Mater Misericordiae Hospital, Dublin) on the theory of ageing. He revealed a surprising fact: whilst a higher percentage of us now reach old age, our maximum lifespan remains unchanged. So what influences the ageing process? Professor Power explained current theories: the influence of height (a shorter height may be associated with a longer life expectancy) biological clocks, pre-determined number of cell divisions and DNA damage. In the body, energy is usually invested in reproduction not repair, and this prioritisation allows genetic errors to accumulate and promote ageing. Whilst the ability to repair DNA may slow ageing, this cannot be the whole picture as it has been reported that survivors of atomic bombs, who may have DNA damage, often have reduced incidence of cancer. This and similar observations have led to the theory of

'hormesis', which postulates that small effects of damaging agents at a cellular and genetic level can actually toughen the body overall.

As people get older, diseases often present atypically, causing greater morbidity and mortality. On reaching the age of 65, it is currently estimated that individuals have a greater than 50% chance of spending some of their later years in a nursing home. Gastrointestinal (GI) problems are common for nursing home residents with at least 75% suffering from constipation and requiring the use of laxatives. With the developing world also rapidly reaching the same situation, this presents multiple challenges in this relatively new field of medicine. Some of the major GI problems for older people are constipation and diarrhoea, as explained by Professor Ian Rowland (University of Reading), however the aetiology of these disorders can be complex and multi-factorial. In reviewing the relevant probiotic evidence, he showed that there have been at least 17 studies which used probiotics for constipation and transit time, 12 of which have shown benefit in both areas. Evidence is also strong for some probiotics in the area of antibiotic-associated diarrhoea.

Another major issue for older people is the decline in their immune function. Professor Rowland's talk featured a number of studies that have investigated the effect of probiotics on the incidence, severity and duration of colds, respiratory infections and norovirus infections (a cause of gastroenteritis) in the elderly. In general, probiotics were associated with improved activity of specific immune cells and, in most cases, significant reduction of duration or severity of symptoms.

Left to right: Prof Ian Rowland, Prof Glen Gibson, Prof Jeremy Hamilton-Miller, Dr Linda Thomas, Prof Mike Gleeson, Prof Bob Rastall, Catherine Collins, Prof Eamonn Quigley, Dr James Lindsay, Prof Claudio Nicoletti





Image 1: Panel discussion; Prof Ian Rowland, Prof Claudio Nicoletti, Prof Bob Rastall, Dr James Lindsay
Image 2: Prof Eamonn Quigley
Image 3: Conference audience

...continued from P1

The morning session continued with this immune focus. Professor Mike Gleeson (Loughborough University) described the increased risk of colds and gastrointestinal problems faced by athletes. Prolonged, intense exercise (>90 mins) increases production of stress hormones and free radicals; which can suppress immune cell activity. When combined with the stress and anxiety of competitions and the increased exposure to pathogens, an athlete's risk of infection is often considerably higher than that of a relatively sedentary individual. After some rather disconcerting images of GI problems experienced by athletes (30% of distance runners suffer from 'runner's trots') the evidence for probiotic benefits was reviewed. A variety of effects have been illustrated in recent studies including reductions in incidence and severity of URTI symptoms, increased immune cell function and activity and decreased GI discomfort.

The rather complex topic of allergies was then tackled by Professor Claudio Nicoletti (Institute of Food Research) who began with a clear explanation of the gut-associated immune system. He emphasised the need for effective therapies for allergy sufferers; around 3–5% of the adult population across Europe suffer from IgE-mediated food allergy and cases of severe immune reactions to foods are rising rapidly. It has been demonstrated repeatedly that the microbiota of allergic individuals differs from non-allergic ones, but a major 'chicken or egg' question, which remains unanswered is whether this is the cause or effect of allergy. Professor Nicoletti showed recent research by his group with the *Lactobacillus casei* Shirota strain showing downregulation of allergic responses in a small human trial. He concluded by discussing the potential of 'designer probiotics' as a delivery system for anti-allergy therapeutic agents – there was a need for this research, he said, because unfortunately 'God is not a post-doc in our lab'.

In recent years there have been many attention-grabbing headlines about probiotics such as 'Fat? Blame the bugs in your guts' and 'Can [probiotics] clean up your skin?'. Professor Bob Rastall (University of Reading) answered the challenge of deciphering and explaining the science behind such headlines. He showed a selection of articles and tried to identify the research studies that originally sparked the story. One set of newspaper articles, speculating on whether there was a link between the gut microbiota and obesity, originated from a collection of studies, with one showing that transplanting the gut bacteria from obese to control mice resulted in an increase in body fat percentage in the control mice. These data suggests that the microbiota in an obese state may promote a more efficient extraction of energy from nutrients that reach the colon, which might influence an individual's weight gain. Human trials have not shown any weight gain associated with probiotic intake, and there are positive results emerging from studies into obesity-

related disorders. After highlighting a number of headlines that have repeatedly used old interviews and quotes from experts in the field (including our moderator Professor Gibson), the delegates were entertained with some novel and entertaining uses for probiotics from the internet, such as probiotic aftershave lotion and probiotic beds. Professor Rastall found it difficult to find the science behind these.

Irritable bowel syndrome (IBS) is an increasingly prevalent condition, now affecting 10%–15% of the population as Professor Eamonn Quigley (University College Cork) explained. Professor Quigley also discussed symptoms, the Rome criteria and the pathophysiology of this disease. There is direct evidence that an altered gut microbiota can contribute to the development of this disease: from case studies of post-infectious IBS, small intestinal bacterial overgrowth and altered colonic microbiota. One of the most famous cases of post-infectious IBS occurred in Walkerton, Canada, in 2000 where the water supply was contaminated with animal waste, which led to an outbreak of acute gastroenteritis. Years later it was observed that of those who suffered from gastroenteritis at the time of the outbreak, over one third went on to develop IBS. It has since been suggested that when a disturbance of the gut flora occurs (i.e. due to an infection) in a susceptible individual it can result in a prolonged inflammatory response which can lead to physiological changes and development of IBS. Professor Quigley outlined a number of papers that have studied the effect of different interventions, which included probiotics, on IBS symptoms and have shown promising results, yet the precise mechanisms of action are still unclear.

For the final talk of the day, Dr James Lindsay (Barts & The London School of Medicine & Dentistry) emphasised the complexity of the relationship between the intestinal microbiota and the host and how this can influence inflammatory bowel disease. He remarked that it is a miracle that we don't all have inflamed digestive systems; the reason we don't is because our mucosal immune systems create a balance between tolerance and action. Studies have shown that the gut flora can both drive and protect our bodies from inflammation, depending on the balance of bacteria present. Dr Lindsay concluded by evaluating the current probiotic evidence and stressing the importance of strain specificity.

This latter point was a common theme throughout the informative day of talks, which finished with a lively debate between the speakers in answer to a range of questions from the delegates. This panel discussion, moderated by Professor Glenn Gibson (University of Reading), was an event in its own right.

Throughout the day, the interest and involvement of top scientists and healthcare professionals in probiotic benefits were very apparent. In the words of one delegate: 'It was an excellent and informative day, thank you!'

"It was refreshing to see so many professors providing their expertise on this very important area."

Recent publications of interest

Haukioja A (2010) Probiotics and oral health. *European Journal of Dentistry* **4**: 348–355
Traditionally, probiotic research has focused on gastrointestinal conditions, but over the last decade, oral health has emerged as a new area of interest. This review aimed to investigate the potential mechanisms of probiotic activity in relation to oral health, focusing mainly on lactobacilli and bifidobacteria.

Kaji R *et al* (2010) Bacterial teichoic acids reverse predominant IL-12 production induced by certain *Lactobacillus* strains into predominantly IL-10 production via TLR2-dependent ERK activation in macrophages. *Journal of Immunology* **184**: 3505–3513
There are indications that the cytokine response of macrophages to probiotics is strain-dependent and that the IL-10/IL-12 ratio is important in determining immune responses. This study gives further insight into the mechanism of action that dictates this cytokine ratio. Activation pathways important in determining the IL-10/IL-12 balance were identified. Particular probiotic cell wall components were found to be essential for this pathway.

Chiba Y *et al* (2010) Well-controlled proinflammatory cytokine responses of Peyer's patch cells to probiotic *Lactobacillus casei*. *Immunology* **130**(3): 352–362
This is another paper that adds to the scientific understanding of how *Lactobacillus casei* Shirota can modulate the immune response. Chiba *et al* 2010 investigated cytokine production from murine spleen and Peyer's patch cells in response to different probiotic and pathogenic bacteria. Seven different probiotic strains were investigated and the results showed that the type and degree of response was strain specific.

Maragkoudakis PA *et al* (2010) Lactic acid bacteria efficiently protect human and animal intestinal epithelial and immune cells from enteric virus infection. *International Journal of Food Microbiology* **141 Suppl 1**: S91–S97
This in vitro study was designed to investigate the antiviral effects of selected lactic acid bacteria (LAB) on human and animal cell lines. Epithelial and monocyte or macrophage cell lines were incubated with a selection of probiotics, then challenged with two separate viruses. All LAB strains exhibited a protective effect on the human and animal cell lines by considerably improving cell survival percentage against infection by both viruses.

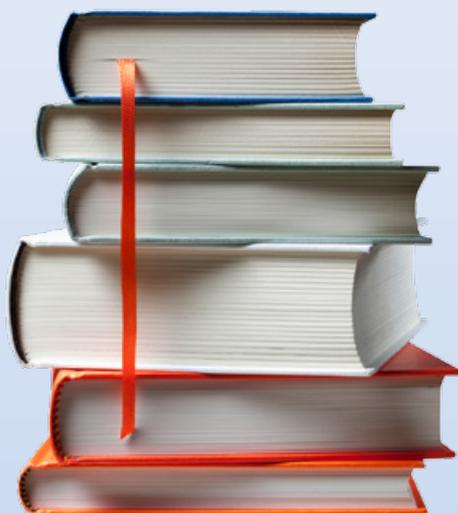
Iannitti T & Palmieri B (2010) Therapeutical use of probiotic formulations in clinical practice. *Clinical Nutrition* doi: 10.1016/j.clnu.2010.05.004
This review describes the intestinal microbiota, dysbiosis, probiotics, prebiotics and synbiotics and analyses the main clinical studies in the following areas: immunity, eczema and allergy, surgery, urogenital infections, renal disease and gastrointestinal disease (diverticular, IBS, IBD, *Helicobacter pylori*, cancer & diarrhoea).

Dethelefsen & Rehlman (2010) Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *PNAS Early Edition* doi: 10.1073/pnas.1000087107
There are few data available which show how the microbiota can be affected by repeated disturbances, such as regular antibiotic use. This small study analysed stool samples from three people over ten months, during which they had two courses of ciprofloxacin. The effect of this on the microbiota was profound and rapid. Usually the gut flora composition recovered but often not fully and sometimes with a permanent change of some bacterial species.

Morotomi M *et al* (2010) *Succinatimonas hippei* gen. nov., sp. nov., isolated from human faeces. *International Journal of Systematic Evolutionary Microbiology* **60**(8): 1788–1793
YCIMR (2010) *Bacteroides clarus* sp. nov., *Bacteroides fluxus* sp. nov. and *Bacteroides oleiciplenus* sp. Nov., isolated from human faeces. *International Journal of Systematic Evolutionary Microbiology* **60**(8): 1864–1869
One new genus and four new species of anaerobic Gram-negative bacteria, isolated from human faecal samples, have been discovered by Yakult researchers in Japan.

And finally, a news item spotted by one of our colleagues in the Amsterdam Metro newspaper...

Nurses can sometimes detect patients with *Clostridium difficile* infection by a distinctive odour of their faeces. Inspired by this, staff at the University Medical Centre in Amsterdam trained a beagle dog called Cliff to 'sniff out' patients harbouring the pathogen. Apparently the dog detected 90% of the infected patients. In two cases, the dog indicated a 'hit' whilst the laboratory did not – was the dog more sensitive than the lab?



Research round-up

Acute diarrhoea in children: probiotic trial in an Indian slum

Enteric disease is responsible for 1.7–2.5 million deaths per year, with highest incidence in infants and young children in developing countries. The most obvious and urgent preventive measures should be clean water, safe food and better hygiene but alternative strategies are also being explored. This community study investigated whether a daily probiotic (*L. casei* Shirota; Yakult) could reduce the incidence of acute

diarrhoea in children (1–5 years) living in an urban slum community. Results showed a statistically significant reduction in incidence of diarrhoea in those taking probiotic compared to placebo (14% reduced illness, $P < 0.01$). This effect could not be attributed to any particular pathogen, although detection of *Aeromonas* and *Cryptosporidium* spp. was significantly lower in the probiotic group.

Sur D *et al* (2010). Role of probiotic in preventing acute diarrhoea in children: a community-based, randomized, double-blind placebo-controlled field trial in an urban slum. *Epidemiology and Infection* **30**:1–8

Postoperative infectious complications: synbiotic benefit with living donor liver transplant

This small, open, controlled study investigated the benefit of living donor liver transplant patients taking a synbiotic for two days before the operation and two weeks after the operation. The synbiotic contained *L. casei* Shirota, *Bifidobacterium breve* Yakult and an oligosaccharide prebiotic; it

was administered orally or via a jejunostomy. As part of their standard care, the patients were given intravenous antibiotics for four days and immunosuppressive treatments. A significant reduction in infectious complications was observed in the synbiotic group (1/25, 4%) compared to the control (6/25, 24%) ($P < 0.05$).

Eguchi S *et al* (2010) Perioperative synbiotic treatment to prevent infectious complications in patients after elective living donor liver transplantation. A prospective randomized study. *American Journal of Surgery* doi: 10.1016/j.amjsurg.2010.02.013.

Infants with severe congenital anomaly: benefit with early use of probiotics

This is a report of the case studies of four babies born with congenital abnormalities who were given two probiotics (*B. breve* Yakult, *L. casei* Shirota) straight after birth, and later also prebiotic galactooligosaccharide. Faecal analysis showed a microbiota initially dominated by the probiotics, then a change to commensal

anaerobes, and eventual establishment of a microbiota similar to that of healthy babies. Despite their clinical problems, the babies grew well and pathogens were rarely detected in their faeces. Microbial analysis was also conducted on other babies with congenital anomalies who had been in hospital for over a year since birth, and had undergone surgery and received antibiotics. Their faecal microbiota appeared aberrant, which the authors believed contributed to their increased susceptibility to infection.

Kanamori Y *et al* (2010) Early use of probiotics in infants with severe congenital anomaly. *Paediatrics International* **52**: 362–367.

Improvement in bowel habit for IBS-D subjects: probiotic study

This small double-blind, placebo-controlled probiotic trial investigated a group of healthy adults who had a high rate of defecation, and who passed stools with a high water content with unusually high numbers of enterococci. Four weeks of a daily probiotic (fermented milk drink; 4×10^{10} CFU *L. casei* Shirota)

resulted in a significant improvement (i.e. reduction) in their defecation frequency, compared to the placebo group. The stool quality also improved, and there was a significant increase in bifidobacteria.

Matsumoto K *et al* (2010) Effects of a probiotic fermented milk beverage containing *Lactobacillus casei* strain Shirota on defecation frequency, intestinal microbiota, and the intestinal environment of healthy individuals with soft stools. *Journal of Bioscience and Bioengineering* **110**(5):547–52

Yakult Awards

Society of General Microbiology (SGM) More than a gut feeling...

Dr Gemma Walton was awarded the 2010 Microbiology Outreach Prize at the SGM's meeting in Nottingham. Gemma has been involved in a number of outreach activities, as she describes below:

'I have always enjoyed outreach activities with school groups visiting labs – seeing the “urgh moment” when a class realise that to study bacteria within the gut we have to use faeces, and further enjoy it when members of the group become interested and enjoy the activities.

Thanks to Professor Glenn Gibson, I have been involved with a number of media activities including the cowboy themed episode of the BBC's “The truth about food”. It was an unmissable chance to convey the concepts of prebiotics and probiotics in a

humorous way, in the beautiful setting of Colorado. Of course it was not all glamour; I was studying the faeces of cowboys on different diets!

Following this, the cBBC program ‘Gastronuts’ was making an episode on flatulence. I was quizzed by children and their presenter, Stephan Gates, on the what, whys and hows of flatulence, while they tried to eat the most flatulence inducing diet – making for an amusing look at microbiology.

The great thing about the area of gut microbiology for science communication is everyone can relate to it!



Dr Gemma Walton receiving award from Prof Joanna Verran, SGM Education & Public Affairs Officer

International Scientific Conference on Probiotics & Prebiotics (IPC2010)

Justyna Sutula (PhD student, Manchester Metropolitan University)

I had an opportunity to attend this event, held in the second largest city in Slovakia, Kosice, between 15-17th of June. Around 350 participants from 85 different countries gathered to discuss recent advances in the science and research of probiotics and their role in maintaining health and preventing diseases. The president of IPC2010, Professor Alojz Bomba, opened the meeting with a literal ‘kick-off’, kicking a football into the audience, as expected from an enthusiastic former footballer. This was an authentic introduction into the light-hearted nature of the Slovakian hosts.

The highlight of Day One was an introduction to functional genomics (a field of molecular biology which describes function and interactions of genes). The total human genetic make-up, together with the 100 times more microbial genes present on and in our body, influence how probiotics function. The idea that ethnicity, as well as lifestyle or diet, might influence probiotic effects, was developed by co-chair Dr Mary Perry (National Institute of Health, USA), who talked about the Human Microbiome Project (www.human-microbiome.org), launched to preliminarily characterise bacteria and viruses present on/in humans and assess their role in health and diseases.

The second day focused on prebiotics and the scientific evidence of prebiotic potential

of organic components found in some regional foods, e.g. yacon (a native root crop of the South America), straw mushrooms and seaweeds. Another recurring subject that day was the microencapsulation of probiotics. This is a process of entrapping beneficial live bacteria inside protective microscopic capsules to maintain their viability during transit and digestion, or to extend their storage period. According to Dr Kasipathy Kailasapathy (University of Western Sydney), who works closely with this technique, there are tough challenges to overcome before this process can be successfully applied in the production of bio-functional foods.

Current methods of assessment of probiotic effect on the digestive system were questioned by the keynote speaker Dr Ger Rijkers (St. Antonius Hospital, Netherlands). He pointed out that microbial analysis of faecal samples, routinely used in human and animal studies, may not necessarily reflect the situation in situ. He suggested that new sampling methods should be considered, such as ingestible devices able to collect localised samples.

My talk, entitled ‘*Commercial probiotic and oral health of healthy dentate people*’, was received with interest and the topic was also presented on posters, which focused on reduction of anaerobic bacteria responsible for periodontal disease with some interest in this as a novel application for probiotics.

I would greatly recommend this conference to any young scientists working in pro- and/or prebiotics. This gathering provided a perfect opportunity for international networking and exchange of ideas in a constantly expanding area of research. I would like to take this opportunity to thank Yakult UK Ltd for sponsorship towards my attendance at IPC2010.

IPC2010



Science team notice board

New IDF Dairy website

The International Dairy Federation (IDF) has launched a brand new website providing nutrition and health information on milk and milk products. The IDF, founded in 1903, is the representative body for the dairy sector worldwide and provides scientific expertise and support for the development and promotion of dairy products. Visit www.idfdairynutrition.org for more information.



75th Anniversary concert

Yakult celebrated its 75th Birthday in July of this year, with an exclusive evening of music and entertainment hosted by John Sergeant in London's Cadogan Hall. The Royal Philharmonic Concert Orchestra, conducted by Phillip Ellis, opened the show by performing many of everyone's favourite classics and, in the second act, were joined by the distinguished soprano Lesley Garrett CBE.



Conferences & Events

Where to meet the science team

Come and visit the science team and the Yakult stand for information about the latest probiotic research at the following events:

SfAM

The Society for Applied Microbiology will be holding their 2011 Winter Meeting in London on 12th January. With a programme of eminent speakers, the topics of probiotics, prebiotics and anaerobic microbiology will be discussed. Visit www.sfam.org.uk for more information or to download a registration form.



St Mark's Intestinal Congress

From the 30th November to 3rd December, St Mark's Hospital is holding a congress covering many of the most pressing topics on intestinal and colorectal disease. The four day event begins with a symposium on IBD, hot topics in gastroenterology and an afternoon of live endoscopy. Day two focuses on cancer, the dilemmas and the consequences. Day three will cover gastrointestinal surgery and day four, colorectal emergency care. Visit www.stmarkshospital.org.uk for more information or to download a registration form.



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Contact us

If you have any questions about probiotics, please do not hesitate to get in touch.

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