

# Probiotic Bulletin

## AN UPDATE FOR HEALTHCARE PROFESSIONALS

### International Yakult Symposium

A report by Dr Elisabeth Weichselbaum, Nutrition Scientist, British Nutrition Foundation



After a short opening speech by Dr Satoshi Kudo, Chief of Science of Yakult Europe, Prof Eric Claassen from Athena Institute, Vrije Universiteit, Amsterdam welcomed us, giving an overview on the history of probiotic research, presenting basic information about gut flora and discussing the potential of probiotics to influence our health. He presented some amazing numbers: the total surface of the gut is the size of a tennis court, there are one-hundred-thousand-billion microorganisms inhabiting the human body (1–1½ kilos of live bacteria), comprising of 400 to 600 different species. As I heard those numbers I wondered: is it possible that a relatively small number of one or a few strains of bacteria can influence our gut flora and our health? At the end of the symposium I knew that the answer to this must be: yes, there is great potential that they can.



Dr Satoshi Kudo

Prof Claassen's welcome was followed by two keynote lectures presented by Prof Stephan Bischoff from the University Hohenheim in Stuttgart, Germany, and Prof Jerry Wells from the University of Wageningen, Netherlands. Prof Bischoff stated that the current understanding of gut health is still rather limited. He explained that 'gut health' is difficult to determine, and although there are a number of measures available it is not quite clear how to deal with those. In particular, 'subjective sensations' are very hard to measure.

Prof Jerry Wells tried to answer the question of what we know about the barrier function of the gut. He explained the complex structure of the 'gut barrier' and how beneficial bacteria can have an impact on this, which is an important part of our immune system. I must admit that being a nutrition scientist and not a microbiologist, the complex gut barrier system with all its TLRs, IRFs and APIs was hard to comprehend, and it seemed unbelievable that all this was happening in my gut as I was listening to Prof Wells' words. It was obvious that important steps have been made in the past few years towards a better understanding of how bacteria can impact the gut barrier.

#### Session I: The digestive function of the gut

Dr Ad van Bodegraven from the University Medical Centre in Amsterdam spoke about the potentials for modulation of the intestinal flora to influence inflammatory bowel disease (IBD). Dr van Bodegraven discussed why influencing the gut bacteria could help patients with IBD. He explained the pathology of the disease and pointed out that there was a potential that probiotics may work in the treatment of IBD. However, he concluded that the evidence so far does not suggest that probiotics are effective in treating IBD.

Prof Robert-Jan Brummer from the University of Örebro in Sweden then discussed the interaction between the gut and the brain, the so-called 'gut-brain-axis', and the role of the gut flora in this interaction in patients with irritable bowel syndrome (IBS). He pointed out that some studies suggest that some probiotics could be effective in treating IBS patients. *continued P2...*

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*As I am currently working on a review on the health benefits of probiotics, I was keen on visiting the 5th International Yakult Symposium entitled 'The Gut and More; Probiotic Influences Beyond the Gut' on 18–19 June 2009 in Amsterdam. I was delighted to be invited and supported by Yakult UK to visit this event. From my experience at the last Yakult (UK) symposium in London in October 2008, I knew that I could expect a range of interesting presentations from high class speakers. Indeed, I was not going to be disappointed.*

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Left to right:  
Prof Rajiv Jalan, Prof Stella Knight and the Round table



## International Yakult Symposium *cont...*

### Session II: The defence function of the gut

Dr Kentaro Shimizu from Osaka University Hospital in Japan opened the second session and spoke about the application of probiotics in intensive care patients. He explained the role of the gut flora in systemic inflammatory response syndrome (SIRS), and how severe stress can lead to bacterial translocation, which can result in bacteraemia, pneumonia and renal failure and often leads to death. Dr Shimizu presented results of an intervention study and a few case reports from his intensive care unit that showed synbiotics can be effective in treating SIRS patients.

In the second presentation of this session Prof Rajiv Jalan from University College London, UK, explained how probiotics could potentially be applied in treating people suffering from liver cirrhosis. Prof Jalan explained that patients with cirrhosis show an altered gut flora and permeability. This can lead to endotoxaemia through translocation of bacteria, which contributes to neutrophil dysfunction, infection risk and mortality in patients with liver cirrhosis. He hypothesised that the risk of endotoxaemia and conditions associated with it in cirrhosis patients could be lowered by altering the gut flora with live bacteria. He presented one study where the use of *L. casei* Shirota in liver cirrhosis patients restored neutrophil function. However, this field of research is relatively new and he pointed out that more studies will be needed to confirm these findings.

The next presentation was from Prof Stella Knight from Imperial College London, UK, who explained the interaction between gut dendritic cells and the gut microbiota. The gut microbiota contributes to local control of gut immune activity by affecting the dendritic cells. Dendritic cells produce inflammatory markers and messengers including toll-like receptors and cytokines, and their production is increased in patients with inflammatory bowel disease (IBD). Prof Knight presented results of studies that showed probiotics can contribute to local control of gut immune activity via effects on dendritic cells by changing production of inflammatory markers (cytokines and toll-like receptors), fatty acid

storage, uptake and metabolism, leptin receptor expression and migration of cells in patients with IBD.

The last presentation of the day was by Prof Felix Stockenhuber from the General Hospital of Oberpullendorf, Austria. He spoke about the potential of probiotics in preventing antibiotic-associated diarrhoea focusing on *C. difficile* infections. He showed that the number of *C. difficile* infections and associated deaths has increased to a large extent in Austrian hospitals over the past years, making *C. difficile* a major concern in hospital treatment. Prof Stockenhuber presented a number of published studies on probiotics and *C. difficile* infections that have shown conflicting results; and results of a study that he carried out with more than 600 hospitalised patients receiving antibiotics. He showed that *L. casei* Shirota significantly reduced the incidence of antibiotic-associated diarrhoea and *C. difficile* infections compared to those not receiving the probiotic.

### Session III: Beyond the gut

The second day was kicked off by Prof Wim Teughels of the Catholic University Leuven in Belgium, who spoke about the oral flora and oral care with probiotics. After giving an overview on the association between the oral flora and different gum and teeth conditions, he presented results from studies examining the potential effects of probiotics on oral health, and concluded that current data is not sufficient to support the use of probiotics in oral care.

The second presentation of session three was held by Prof Erika Isolauri from Turku University in Finland. This presentation was one of the highlights for me as it showed how even microbial exposure during birth and the first days and weeks of our lives influences our health in later life. Prof Isolauri discussed how a different microbial exposure in babies delivered by caesarean can increase the risk of conditions such as allergies, asthma, eczema or possibly even obesity in later life. The gut of babies born via vaginal delivery generally showed a different microflora composition than those delivered by caesarean. Prof Isolauri presented a hypothesis that suggested that the gut flora in early life may have an impact on the risk of becoming overweight or obese later on. She raised the question whether part of the

obesity problem we are facing now could be linked to early microbial exposure. This theory is based around 'energy harvest' and immune responses. More research is needed to find out whether it can be confirmed or not.

Prof Natalie Delzenne from the Catholic University of Leuven in Belgium discussed in her presentation a possible role for probiotics and prebiotics in obesity-metabolic diseases. Prof Delzenne presented evidence showing a potential for probiotics to decrease the negative effects of a high-fat diet, such as hepatic fat accumulation, endotoxaemia and systemic inflammation. She suggested that probiotics and prebiotics could play a role in metabolic alterations such as obesity.

The last session of the symposium was opened with a talk by Prof John Bienenstock from McMaster University in Canada on the interaction between the gut microflora, the nervous system and the brain. Prof Bienenstock presented data that showed the effects of probiotics on behaviour in animals, and suggested that they may also affect behaviour in humans. He presented data from human studies that seem to support this theory. One study using *L. casei* Shirota showed that this strain had a significant effect on anxiety in patients with chronic fatigue syndrome, and studies using other strains seemed to influence our emotional sensations and behaviour.

Following Prof Bienenstock's presentation, all speakers of the symposium gathered for a round-table discussion in which they addressed questions from the audience and from the moderator, Prof Eric Claassen. This discussion session was followed by a presentation from Prof Michiel Kleerebezem from the University of Wageningen, the Netherlands, where he presented a number of studies on probiotics that his team has carried out in the past years. The symposium was closed by a short speech by the General Manager of Yakult Netherlands, Piet Dekkers, which included a short quiz on probiotics prepared by Prof Claassen.

Overall, I found this symposium very informative and interesting as it gave a good overview on what research is currently going on in the field of probiotics and health. It seems like we can expect exciting new findings in the next few years.

# *L. casei* Shirota & immune function in healthy adults

By Elisabeth O'Connell



Elisabeth O'Connell

Previous studies have found that probiotics may modulate immune function in the gut and in the peripheral blood. Changes in gut immunity may also be reflected at other mucosal sites, however there has been limited research into the effects of probiotics on salivary immune components. The function of salivary sIgA is to neutralise pathogens within saliva and the buccal cavity, and assist destruction of pathogens by immune cells. Each IgA subtype contributes separately to protection against a broad range of pathogens whilst IFN- $\gamma$  up-regulates cellular immunity and has anti-viral activity and IL-12 stimulates IFN- $\gamma$  production and drives cell mediated Th1 responses.

This study asked nine healthy adults aged 20-45 to consume two interventions of  $6.5 \times 10^9$  live cells of *L. casei* Shirota (LcS) (two bottles of Yakult) daily for four weeks. Timed, un-stimulated saliva samples were collected at baseline, during consumption of LcS and two weeks after cessation of consumption. Salivary immunoglobulin sIgA and the cytokines IL-12 and IFN- $\gamma$  were quantitated by radial immunodiffusion and ELISA respectively.

The mean sIgA secretion rate was significantly greater at week four, in comparison to baseline levels (Fig 1). Secretion of both subtypes of IgA (types one and two) was also increased at week four and remained elevated two weeks after cessation of LcS consumption (Fig 2). IL-12 was not detected in any of the samples. IFN- $\gamma$  showed a transient increase, significant at week two (Fig 3).

This pilot study therefore suggests that LcS increases salivary sIgA, IgA1, IgA2 and IFN- $\gamma$  secretion in healthy adults. Consumption of probiotics has been previously associated with a reduced duration and severity of winter respiratory infections, thus this pilot study suggests that increased IgA and IFN- $\gamma$  secretion may be the mechanisms behind the reported protective effects and warrants further work.

- O'Connell EJ, Allgrove JE, Pollard LV, Xiang M & Harbige LS (2009) A pilot study investigating the effects of Yakult fermented milk drink (*L. casei* Shirota) on salivary IFN- $\gamma$ , sIgA, IgA1 and IgA2 in healthy volunteers. Poster presentation at the Yakult International Symposium, Amsterdam, 18–19 June.

Figure 1: sIgA

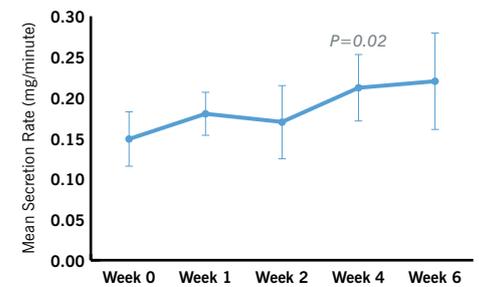


Figure 2: IgA1 and IgA2

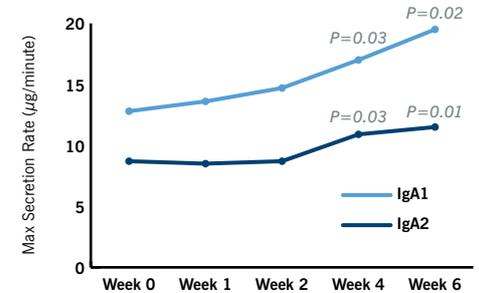
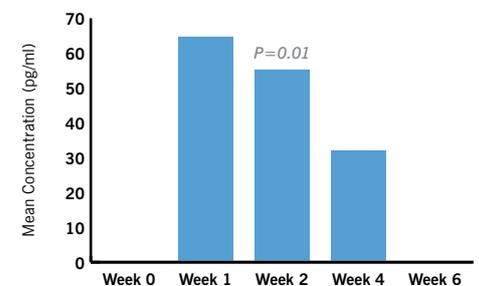


Figure 3: IFN- $\gamma$



## GLOSSARY

**Cytokines** are chemical messengers in the immune system.

**IFN- $\gamma$**  is a cytokine made by T-cells. It has antiviral activity and is able to activate macrophages.

**IgA** is an antibody produced at mucosal lymphoid surfaces; it can be sub-divided into IgA1 and IgA2.

**IL-12** is a cytokine produced by antigen-presenting cells which turns virgin T-cells into Th1 cells and activates NK cells.

**sIgA** is the secretory form of IgA and is the main immunoglobulin in mucous secretions.

**Th1** activates macrophages and secretes IFN- $\gamma$  or TNF- $\alpha$ .

**Th2** secretes IL-4, IL-5, IL-10 and IL-13 and is important in the allergic response.

Elisabeth O'Connell has recently completed a BSc (Hons) in Human Nutrition at the University of Greenwich; as part of her final year project she investigated the effects of *L. casei* Shirota on the secretion of salivary immune components in healthy adults. Elisabeth is now moving to King's College London where she will study an MSc in dietetics.



## Research round-up

### Probiotics & chronic fatigue syndrome (Rao *et al* 2009)

This randomised, double-blind, placebo-controlled, pilot study investigated whether the probiotic bacteria, *Lactobacillus casei* Shirota could reduce depression and anxiety symptoms in people with chronic fatigue syndrome. Previous studies have shown that the gut flora of these patients is often altered (Logan *et al* 2003) and many sufferers experience gastrointestinal disturbances (Aaron *et al* 2000). In this trial 39 patients were randomised to receive a placebo or  $24 \times 10^9$  CFU of *L. casei* Shirota every day for two months. The results showed a significant increase in lactobacillus and bifidobacteria

in the faeces of the probiotic group and a significant reduction in anxiety symptoms ( $p=0.01$ ) compared with the placebo group. These results are promising and indicate the need for larger trials in this area.

- Aaron LA, Burke MM & Buchwald D (2000) Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia and temporomandibular disorder. *Archives of Internal Medicine* **160**: 221–227.
- Logan AC, Rao AV & Irani D (2003) Chronic fatigue syndrome: lactic acid bacteria may be of therapeutic value. *Medical Hypotheses* **60**: 915–923.
- Rao AV, Basted AC, Beaulne TM, Katzman MA, Lorio C, Berardi JM & Logan AC (2009) A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathogens* **1**:6 doi: 10.1186/1757-4749-1-6.

### The binding of different probiotic bacteria to aflatoxin B<sub>1</sub> (Hernandez-Mendoza *et al* 2009)

Previous studies have shown that some lactic acid bacteria have anti-mutagenic properties with specific strains able to bind to aflatoxin B<sub>1</sub> and remove it from liquid solutions. Aflatoxin B<sub>1</sub> is produced by fungi and is one of the most carcinogenic aflatoxins. This trial was designed to compare the binding strength of five different probiotics to aflatoxin B<sub>1</sub>. The different probiotics used are given in Table 1. The results showed

that *Lactobacillus reuteri* NRRL14171 and *Lactobacillus casei* Shirota were most efficient at binding aflatoxin B<sub>1</sub>. The authors concluded that their results supported the hypothesis that the absorption of aflatoxin into the gastrointestinal tract could be prevented by probiotics.

<i>Lactobacillus reuteri</i> NRRL14171
<i>Bifidobacterium bifidum</i> NCFB2715
<i>Lactobacillus casei</i> Shirota
<i>Lactobacillus johnsonii</i> NCC 533
<i>Lactobacillus casei</i> defensis DN-114-001

Table 1: List of five probiotic bacteria compared within the trial

- Hernandez-Mendoza A, Guzman-de-Peña D & Garcia HS (2009) Key role of teichoic acids on aflatoxin B<sub>1</sub> binding by probiotic bacteria. *Journal of Applied Microbiology* **107**:2, 395–403.

### Glucose regulation & the potential for probiotics during pregnancy (Laitinen *et al* 2009)

This double-blind, placebo-controlled trial investigated whether probiotic supplementation combined with dietary counselling could affect glucose metabolism in normoglycaemic pregnant women. Probiotics were chosen because some evidence suggests that the gut flora has a role in the extraction and storage of nutrients (Ley *et al* 2005). The study randomised 256 women in their first trimester to receive dietary counselling or controls. Those that received the counselling were then randomised to receive a daily placebo or probiotic (*Lactobacillus rhamnosus* GG ( $10^{10}$  CFU) and *Bifidobacterium lactis* Bb12 ( $10^{10}$  CFU) per day). Results showed that blood glucose concentrations were lowest in the group who were given dietary counselling and

the probiotic compared with those receiving only dietary counselling and the control group ( $p=0.025$ ). Furthermore, in the last trimester of pregnancy significant improvements were seen in the intervention group compared with the dietary counselling and control groups, including a reduced risk of elevated glucose concentration ( $p=0.013$ ), the lowest insulin production ( $p=0.032$ ) and the highest quantitative insulin sensitivity check index ( $p=0.028$ ). These findings were sustained during the 12-month postpartum period and suggest potential for probiotics and dietary counselling to help regulate glucose control in normoglycaemic women during pregnancy.

- Laitinen K, Pousa T, Isolauri, E & the Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group (2009) Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. *British Journal of Nutrition* **101**: 1679–1687.
- Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD & Gordon JI (2005) Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America* **102**: 11070–11075.

## Yakult publications

This year, Yakult Ireland has written three articles that were published in *Nursing in General Practice*, the journal for the Irish Practice Nurse Association, with a fourth article due by the end of 2009. The articles make up a four-part series on probiotics with particular relevance to probiotics in primary care. The three articles have appeared in the March/April,

July/August and September/October issues of *Nursing in General Practice* and cover areas such as antibiotics and *Clostridium difficile*, irritable bowel syndrome and probiotics in the elderly. A description of these articles written by Deirdre Jordan, Science Officer, Yakult Ireland and Dr Linda Thomas, Science Director, Yakult UK can be found below.



### A question of balance: antibiotics, *Clostridium difficile* and probiotics. Part 1.

This article focuses on antibiotic usage and the prevalence of antibiotic-associated diarrhoea (AAD) and *C. difficile*-associated disease (CDAD). The article reviews the current guidelines regarding the management of CDAD and gives an overview of recent trials investigating the benefit of probiotic fermented milk products in reducing the risk of AAD and CDAD.

### Probiotics and IBS: is there a scientific rationale for recommending? Part 2.

The use of probiotics as therapeutics in the treatment of irritable bowel syndrome (IBS) is becoming increasingly topical. The National Institute for Health and Clinical Excellence (NICE) have published guidelines that highlight probiotic usage for people with IBS. This article focuses on the rationale for recommending probiotics for IBS and the supporting scientific research.



### Health benefits for the elderly: the potential of probiotics. Part 3.

Due to age-related changes in the gut flora, research has been conducted to explore the potential of probiotics in restoring the balance of our microflora. This article reviews the evidence for gut function benefits, modulation of the immune system and reduction of risk of AAD and CDAD in the elderly on probiotics.



If you wish to receive one or all of these articles and reserve a copy of the yet unpublished Part 4 which will focus on probiotics and immune function please email [science@yakult.ie](mailto:science@yakult.ie) leaving your name, postal address and stating your request.

## Science team notice board

### Conferences and events

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

#### INDI AGM

10th October  
Radisson SAS  
Golden Lane  
Dublin 8

#### IPNA Conference and AGM

16th–17th October  
Castlecourt Hotel  
Westport  
Co Mayo

### Probiotics and health – summing up the evidence A British Nutrition Foundation conference



On the 1st October 2009 the British Nutrition Foundation are hosting a one-day probiotic conference at the Society of Chemical Industry in London. The conference will cover a broad range of health issues related to probiotic consumption and will play host to eminent speakers such as Professor Glenn Gibson, Professor Peter Whorwell and Professor Ian Rowland.

Visit [www.nutrition.org.uk](http://www.nutrition.org.uk) for more details and to download a registration form.

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If you have any questions about probiotics, please don't hesitate to get in touch.

+353 (0)1 459 9580

Yakult Ireland  
Berkeley House  
21 Cookstown Industrial Estate  
Tallaght  
Dublin 24

[science@yakult.ie](mailto:science@yakult.ie)

*Editor: Hannah Baker*  
Science Officer, Yakult UK Ltd  
[hbaker@yakult.co.uk](mailto:hbaker@yakult.co.uk)