DECEMBER 2007
ISSUE 03

science for health

Probioticbulletin

Could probiotics reduce the rates of infection in patients with alcoholic liver disease? – Promising initial results

In November, Dr Vanessa Stadlbauer and her colleagues released exciting results from a small proof of concept study indicating that *Lactobacillus casei* Shirota (LcS) may benefit the immune system in patients with alcoholic liver disease (ALD). The results were presented as a late-breaking poster session at the 58th Annual Meeting of the American Association for the Study of Liver Diseases in Boston, Massachusetts. Vanessa is an Austrian research fellow currently working with the Liver Failure Group at University College London (UCL).

Vanessa in her lab at UCL.

Why is this study so interesting?

This is a very welcome area of research. One of the biggest causes of death in patients with ALD is infection - in fact, one-year mortality rates range from 10-82% depending on the severity of liver cirrhosis (Mansour *et al* 1997). The UCL research suggests that the simple intervention of giving a probiotic to patients with ALD could play a role in reducing infection rates.

Increased susceptibility to infection is likely to be due to endotoxin leaking from the gut, accumulating in the blood and not being cleared by the liver. The research group hypothesised that the **neutrophils** were exhausted due to their oxidative burst reaction to endotoxin in the blood, thus becoming unable to phagocytose properly when a real infection presented itself.

"This was a small open trial, but the results are very encouraging, indicating that probiotics such as Yakult may help reduce infections in patients with alcoholic liver disease." *Dr Rajiv Jalan, head of the Liver Failure Group.*

Neutrophils, endotoxin and probiotics… How does it work?

Previous studies have shown that patients with alcoholic cirrhosis have a **neutrophil dysfunction** and increased levels of circulating **endotoxin**.

The UCL Liver Failure group. Seated from left: Dr Rajiv Jalan, Dr Nathan Davies and Dr Gavin Wright. Standing from left: Dr Bala Subramanium, Dr Raj Mookerjee, Dr Stephen Hodges and Dr Vanessa Stadlbauer.

Probiotics can decrease gut permeability and positively alter the gut flora by increasing Gram-positive bacteria and reducing the number of those that are Gram-negative. "**We wanted to test whether giving a probiotic could restore neutrophil dysfunction, possibly by reducing the amount of circulating endotoxin**" said Vanessa.

Twelve patients were given three bottles of a probiotic containing LcS (Yakult) a day for four weeks. "**Compliance was unusually high at 86%**" said Vanessa, "**compliance rates in these patients are usually closer to 20%**". The LcS supplementation normalised phagocytic capacity and also the cytokine response to the lipopolysaccharides.

Although this was a small open trial, it is studies such as these that pave the way for bigger clinical trials to take place. "**The results shown here are very encouraging; significant differences are extremely difficult to achieve in such a small trial**" said Vanessa. The research team are now planning a large scale double-blind, randomised trial to determine whether probiotics such as Yakult can reduce infection rates in ALD. (*See table on page 2 for explanation of results.*)

Continued from page 1

RESULTS

1. Baseline neutrophil phagocytic capacity was significantly lower in patients compared with controls. *This normalised in the treatment group after drinking Yakult.*

2. Stimulated levels of **TNFR1, TNFR2** and **IL-10** were significantly decreased in the treatment group after drinking Yakult. *This anti-inflammatory response became normalised after drinking Yakult.*

3. There was a significant reduction in **TLR 4** surface expression compared to baseline. *This indicated a reduction of endotoxin in the blood.*

The other scientists involved in this research were Dr Rajiv Jalan, head of the team, Dr Rajeshwar Mookerjee, Dr Stephen Hodges, Dr Gavin Wright and Dr Nathan Davies. The poster was also presented recently at the International Yakult Symposium in Verona from the 22 to 23 November 2007, where Vanessa won 2nd prize for her poster.

For more information or a copy of the abstract please email **science@yakult.co.uk** with your request.

GLOSSARY

Endotoxin: Lipopolysaccharides from the cell wall of Gram-negative bacteria.

IL-10: Anti-inflammatory cytokine.

Neutrophils: A class of phagocytic white blood cells which are part of the innate immune system.

Neutrophil dysfunction: Evident as increased resting phase oxidative burst, together with a decreased phagocytic capacity. Associated with increased risk of infection.

TLR4: Receptor on the surfaces of immune cells. Recognises lipopolysaccharides found on Gram negative cell walls.

TNFR1 & TNFR2: Receptors for TNF alpha, their presence in plasma indicates a reaction to a proinflammatory stimulus.

References:

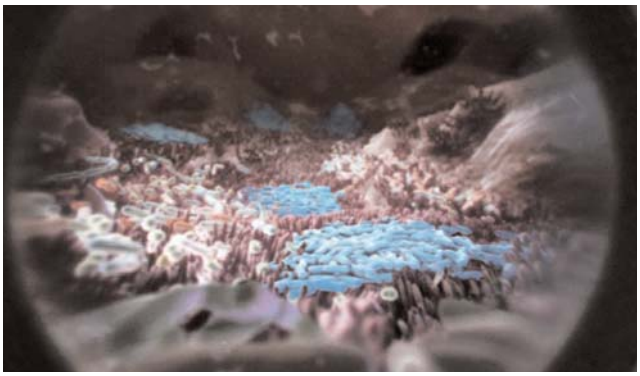
Mansour A *et al* (1997) Abdominal operations in patients with cirrhosis: still a major surgical challenge. *Surgery*.**122**; 730-735.

Mookerjee RP *et al* (in press) Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology.*

Stadlbauer V *et al* (2007) Restoration of the defective innate immune system following treatment with the probiotic *Lactobacillus casei* Shirota in patients with alcoholic cirrhosis: A proof of concept study. *Hepatology* (**4**,S): p. 864A-865A.

Free educational DVD

Some of you may have seen the recent Yakult TV ad that shows our digestive system in the style of David Attenborough's Planet Earth.



Since this was aired many lecturers, teachers and gastroenterologists have requested a copy for teaching purposes. Due to this high demand, our marketing team (with help from our science manager – a microbiologist) have produced a longer version with a more scientific commentary. A DVD of the commentary version is available (free of charge) to any healthcare professional, so if you feel it would be useful please contact us.

Yakult supports St Mark's Hospital Annual Congress

The science team has been out and about at various conferences over the last few months including: Nutrition and Health, Nursing in Practice and BAPEN.

St Mark's Hospital Foundation
Mosaic
APPEAL

In November, St Mark's Hospital in Harrow held its 5th Annual International Congress. Entitled Frontiers in Intestinal and Colorectal Disease, the event brought together over 500 national and international delegates. During the three-day event, delegates heard about the latest research on conditions such as inflammatory bowel disease and bowel cancer, watched live surgery and endoscopy in high definition and had the opportunity to visit an exhibition area to network with companies, including Yakult, who could provide tailored information and products.

St Mark's Hospital in North West London is one of the world's only specialist hospitals for colorectal diseases. Yakult is working in partnership with the St Mark's Hospital Foundation to actively support a better understanding of digestive health and probiotic benefit.

Visit **www.stmarkshospital.org.uk** for information on St Mark's Hospital, and **www.mosaicappeal.org** for information on the Foundation's key fundraising initiative.

Research round up

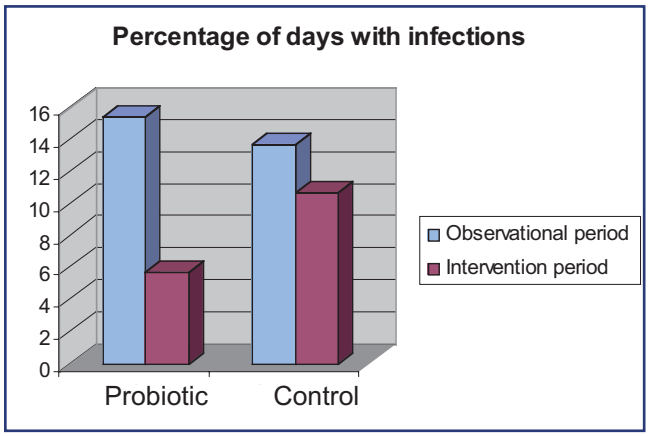
Infection in hospitalised enterally fed elderly

This study using *Lactobacillus johnsonii* La1 (NCC553) randomised 24 enterally fed patients over 70 years old to receive either a probiotic fermented milk drink or a placebo for 12 weeks.

Researchers discovered the percentage of days with infection was significantly lower during the intervention period in the probiotic group than in the observational period. There was also a significant increase in blood haemoglobin in the probiotic group. No significant differences were found in the placebo group (*see graph*).

Other trends (although not significant) found in the probiotic group were an increase in serum albumin levels, a reduction in TNF alpha and an increase in blood phagocytic activity (in subjects whose initial level was low).

This is an exciting piece of research, further indication that probiotics may have the potential to reduce infections in the elderly. It also demonstrated successful use of probiotics administered via enteral feeding tubes.



Fukushima Y *et al* (2007) Improvement of nutritional status and incidence of infection in hospitalised enterally fed elderly by feeding of fermented milk containing probiotic *Lactobacillus johnsonii* La1 (NCC533). *British Journal of Nutrition*. **98**; 969-977.

Probiotics and prebiotics in inflammatory bowel disease (IBD)

IBD represents a malfunction of the relationship between humans and their enteric microflora. So far, clinical trials using probiotics as a treatment for IBD have given conflicting results. Evidence for their use in pouchitis is the greatest; there is also considerable evidence for ulcerative colitis, although their use in Crohn's disease is less convincing.

This is a review of the trials that have used pro- and prebiotics for IBD. General conclusions were that there is some evidence for the use of both probiotics and prebiotics for IBD; however it is very difficult to draw strong conclusions from these studies due to the use of different strains, doses, patient groups and methodologies. The review calls for more large trials to be done that use the same methodology.

Hedin C *et al* (2007) Evidence for the use of probiotics and prebiotics in inflammatory bowel disease: a review of clinical trials. *Proceedings of the Nutrition Society.* **66**;307-315.

Probiotics for the treatment of acute diarrhoea in children

In this RCT, five different probiotic products were tested for their efficacy in treating acute diarrhoea in 571 children. The products were *Lactobacillus rhamnosus* strain GG (LGG), *Saccharomyces boulardii, Enterococcus faecium* SF68, *Bacillus clausii* or a probiotic mixture consisting of *L delbrueckii* var *bulgaricus, Streptococcus thermophilus, L acidophilus* and *Bifidobacterium bifidum.*

The children were randomised to receive a product or a control (oral rehydration fluid).

There was a significantly shorter median duration of diarrhoea in those that took LGG & *Bacillus clausii* compared to the control. Also, after day one the daily number of stools was significantly reduced in those that took LGG or *Bacillus clausii*. There were no significant outcomes with the other probiotic products.

Take home message:
Always refer back to the original papers to check for effectiveness of each strain when using them.

Canani RB *et al* (2007) Probiotics for treatment of acute diarrhoea in children: randomised clinical trial (RCT) of five different preparations. *BMJ* e-pub p340.

Yakult UK Symposium 2008 – date for your diary

Some of you may have attended the 2006 Yakult UK symposium, where experts reviewed and discussed probiotic evidence. We're now busy planning the next one which will take place on 21st October 2008 at 76 Portland Place, London. The theme of the day is *Probiotic Relevance: Putting Theory into Practice*. We will update you with more details in future issues of this bulletin, but in the meantime please email **science@yakult.co.uk** if you would like further information. Reserve this date in your diary!

The International Yakult Symposium – Verona 22nd-23rd November

Conference report by science and medical journalist, Jerome Burne

Had you wandered by mistake into the final session of the 4th International Yakult Symposium in Verona, you could have been forgiven for thinking that you had strayed into a philosophy conference devoted to epistemology. How can we prove that probiotics work? Just because we know one strain has an effect, that doesn't tell us anything about the effects of another one or different combinations of strains. Even if the same strains are used how do we know the pills or liquids contained the same quantities of bacteria? Even if epidemiological studies show benefits, how do we know the results weren't because the population was healthier anyway?

As the doubts multiplied under the rigorous sceptical questioning of chairman Professor Janusz Jankowski of Oxford University, it seemed that we couldn't trust any health boosting intervention at all. If real hard evidence for the benefits of probiotics was lacking, the case for fibre protecting the colon was pronounced equally flimsy; even fruit and vegetables apparently had never really been shown to lower the risk of colon cancer. Could we believe anything? At one point only four or five of an audience of 200 or more felt confident enough to put their hands up when asked if they believed fruit was protective against colon cancer.

> ***"...Supplementing with probiotics obviously has enormous potential both for prevention and treatment..."***

It had all begun so well with a fascinating presentation by Professor Sander Gussekloo of the University of Utrecht about the way animals' colons respond to environmental change. It's not just the microbial fauna that fluctuates. For instance, a rise in predators can cause a reduction in colon size because resources are shifted to developing the muscles needed to flee; when predator numbers decline, however, it can expand. A change from a carnivorous diet to a herbivorous one can make the colon grow. Whether human colons shift shape is unknown but the conference produced plenty of evidence that probiotics can change the way the guts behave in all sorts of ways. The proteins that control the tightness of the gaps between the cells making up the gut wall can be boosted by probiotics, as Professor Jerry Wells of Wageningen University showed. Another talk described the intimate relationship between our diet, gut bacteria and the production of vital short chain fatty acids.

A delegate from the floor spoke for many when he said: "**We know there is a link between obesity, diabetes and gut flora; it also seems likely that children with autism and ADHD have a disregulated gut. Probiotics can help in all of these.**"

But the sceptical voices were there from the beginning too. "**We know that probiotics raise the activity of NK (natural killer) immune cells; could that be a marker for an effect against cancer?**" asked Professor Carsten Watzl of the University of Heidelberg. After reviewing human and animal studies and showing the awesome complexity of the system for ensuring NK cells don't attack the wrong targets, he concluded with a cautious "maybe".

In a similar vein Professor Kristin Verbeke of the Catholic Leuven University, after running through the evidence that probiotics could reduce the chances of developing colon cancer, concluded with a marginally more positive "probably".

Even Professor Ian Rowland of Reading University, a long-time champion of probiotics, agreed on the need for bigger and better trials. "**There's good evidence that probiotics can reduce toxic elements in the guts of rats**," he said "**and pretty convincing evidence they reduce the chance of rats' precancerous cells becoming cancerous**." But in humans, he admitted, there was still a need for a full-scale, placebo controlled trial to show that they actually reduce cancer risk.

But does all this count as gradual progress or is it better described as going round in circles? Supplementing with probiotics obviously has enormous potential both for prevention and treatment but hard evidence for its effectiveness is still lacking. One solution might be to adopt the drug model of research. Statins, for instance, target a biomarker for heart disease (lower cholesterol). Should something similar be done for probiotics?

"**Absolutely**" said Professor Kevin Collins of University College of Cork. "**We don't have good biomarkers for cancer but pick something else, maybe inflammation or quality of life. Then you do proper big trials on single strains for specific conditions**." If you are going to be rigorous about the evidence you have to standardise treatments, commented another speaker. "**The genetic difference between two strains can be as great as that between a human and goldfish**."

But apart from the cost and the years it would take, wouldn't that be missing the whole point about probiotics? They aren't drugs and they aren't *like* drugs, they are part of an ecology; they work together, the waste product of one strain can act as the feed for another. If you reduce inflammation you may help both eczema and diabetes.

Bigger and better trials are obviously needed and as always the key question is: Who's going to pay for them? Professor Jankowski believes the government has a duty to play a role in prevention; his hope was that his sceptical questioning would prompt some hard thinking about how best to do those trials.

Recent ISAPP meeting

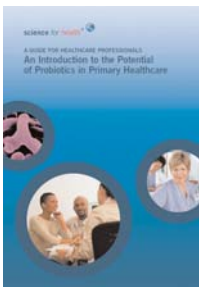
The International Scientific Association for Probiotics and Prebiotics (ISAPP) (http://www.isapp.net) is an association of academic and industrial scientists involved in research on fundamental and applied aspects of probiotics and prebiotics. These scientists have a common interest in generating high quality scientific information for the probiotic and prebiotic fields, and providing guidance for collaborative and multidisciplinary research. An ISAPP meeting was held in London in June 2007. Yakult scientists Dr Jia Zhao (front row, fourth from right) and Dr Linda Thomas (front row, first on the right) attended the Industry Advisory Committee meeting before the event, and then joined over 120 delegates from 13 countries at the following two-day open forum and the evening reception sponsored by Yakult. Most of the board members are shown here (photo taken by Prof Mary Ellen Sanders).

Can you find Prof Todd Klaenhammer, Prof Glenn Gibson, Prof Ian Rowland, Dr Jim Versalovic, Prof Harsharn Gill, Dr Karen Scott, Prof Gregor Reid, Prof Bob Rastall and Prof Bruno Pot?

Helping healthcare professionals

If you need to find out more about probiotics please visit our website **www.yakult.co.uk/hcp** where you can request free probiotic literature, download the Probiotic Bulletin and read up on evidence for the health benefits associated with probiotics. The science team at Yakult offers presentations about probiotics and the latest research; these can be very useful for CPD sessions*. If you are interested in this, please email **science@yakult.co.uk** and we will send you more information.

*Presentations require a minimum of ten attendees



New Booklet – order your free copy

We have written a new booklet highlighting the potential of probiotics in primary healthcare. The resource is aimed at nurses and GPs but is a valuable tool for anyone interested in probiotics. For your free copy please email us at **science@yakult.co.uk** with your name and address and write Primary Care booklet in the subject line.

Travel Award – apply now

Many of you will be familiar with our Travel Award but for those of you that aren't, it is for scientists and healthcare professionals who are researching gut health and probiotics and are planning to present their work at a conference. Applicants are asked to submit an abstract of their work which will be judged by an independent panel. The winner will receive a monetary award towards their travel costs. Our 2008 Travel Award is now up and running, the deadline for applicants is 1st February 2008; please visit our website **www.yakult.co.uk/hcp** to download the application form.

Contacting the science team

You can contact us in a number of ways: email **science@yakult.co.uk**, telephone 020 8842 7600 or write to us at Yakult UK Ltd, Artemis, Odyssey Business Park, West End Road, South Ruislip, Middlesex, HA4 6QE.

Where to find us

Meet the Yakult science team and their science stand at the following conferences:

The 5th Annual Nurse Prescribing conference,
London, 14th January

Topics in Infection,
London 24th – 25th January

The Education Show,
Birmingham, 28th Feb – 1st March

Health and Wellbeing at Work,
Birmingham, 5th - 6th March

And finally...

Everyone in the Yakult science team would like to wish you all a very merry Christmas and a Happy New Year!

Editor: Hannah Baker, Science Officer,
Yakult UK Ltd. hbaker@yakult.co.uk