vocational pathways in science. Engineering apprenticeships are well established and well recognised, but science apprenticeships less so. The afternoon provided a useful interchange of ideas that reinforced my belief that, in addition to focusing its support for professional development on graduate-level outcomes (leading to RSci and IEng) or postgraduate-level outcomes (leading to CSci or CEng), IPEM should do more to set standards in its own subject areas for science and engineering technicians working in healthcare, in universities and in healthcare industries. I hope that we can work with the Gatsby Foundation and others to mill one small cog in the wider Professional Technician project.

IPEM's first three RSciTech registrants receive their certificates from the Rt Hon Vince Cable and Lord Sainsbury of Turville


Elizabeth Anne St Clair, St James' University Hospital, Leeds


Francis Pillai, Addenbrookes Hospital, Cambridge


Hemalatha Ganeshamurthy, East & North Hertfordshire NHS Trust

All seven RSciTech registrants with Krishnan Guru-Murthy (chair for the event), Lord Sainsbury and the Rt Hon Vince Cable

FOOD AND GUT HEALTH

Meeting of the Parliamentary and Scientific Committee on Tuesday 15th May

FRIENDS IN LOW PLACES AND HOW TO HELP THEM: Gut microbiology and health


Professor Glenn Gibson
The University of Reading

Chronic diseases, including cardiovascular complaints, Type II diabetes, many cancers, some dementias, acute and chronic gut disorders are a major and growing societal and financial concern for humankind (Gibson and Williams, 2000). Moreover, an increasingly obese and ageing population means there is greater prevalence of chronic disease. Increasingly there is a recognition that the 21st century health model will comprise both preventative life style and therapeutic entities, including dietary intervention. For example the "functional foods" concept suggests that dietary ingredients can be used for purposes over and above their normal nutritional value. The Global Market Review of Functional Foods estimates that by 2013 the worldwide functional food market will reach a value of at least US$90.5bn. Currently around 60% of functional foods in use in Europe are targeted at gastrointestinal health.

The biological and clinical importance of resident gastrointestinal microflora in humans is becoming increasingly recognised by consumers and healthcare workers. Although it is known that many disease states involve bacterial metabolism, the human gut microflora may also be considered as extremely relevant for improvements in host health (Gibson and Roberfroid, 2008). For instance, bifidobacteria and lactobacilli are seen as positive components of the human gut microflora that can improve host health. They are thought to help resistance to gut infections by directly inhibiting the growth of harmful bacteria, reduce cholesterol levels, sustain the immune response and synthesise vitamins (Steer *et al*., 2000).

Scientific concepts underpinning directed modulation of the human gut microflora towards a more beneficial composition have had *probiotics* as a principal focus. While probiotics have been ingested by humans for several hundred years, their development has progressed markedly over the last 2 decades. Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (United Nations Food and Agriculture Organisation of the United Nations 2002). Probiotics must be safe (ie the USA Food and Drug Administration standard of Generally Regarded As Safe), should be amenable to industrial processes necessary for commercial production, they must remain viable in the food product and during storage, need to persist in the gastrointestinal tract long enough to elicit an effect and they must improve host health (Kolida *et al*., 2006). The use of live bacteria in the diet has been successful scientifically and economically. The best products need to maintain strain integrity and consistency, have survivability in the product and following ingestion.

In contrast, *prebiotics* are a far more recent concept than probiotics, being first developed in the mid 1990's. They are dietary ingredients that can selectively enhance beneficial components of the indigenous gut microbiota, such as lactobacilli or bifidobacteria, and are finding much increased application in the food sector. In contrast to probiotics, they can be added to many ingredients including heated products. Prebiotics were therefore originally developed to selectively enhance beneficial components of the gut microbiota, such as lactobacilli or bifidobacteria, and are finding increased application. In the future, it is likely that this may be expanded towards other genera, eg *Eubacterium, Faecalibacterium* and *Roseburia*. Prebiotics were first defined as 'non digestible food ingredients that are selectively metabolised by colonic bacteria which have the capacity to improve health' (Gibson and Roberfroid, 1995). As such, their use is directed towards favouring beneficial changes within the indigenous gut microbial milieu itself. They are distinct from most dietary fibres like pectin, celluloses, xylan, which are not selectively metabolised in the gut. Criteria for classification as a prebiotic are (Gibson *et al*., 2011):

- resists gastric acidity, hydrolysis by mammalian enzymes and gastrointestinal absorption
- is fermented by intestinal microflora
- selectively stimulates the growth and/or activity of intestinal bacteria associated with health and well-being.

Any dietary component which reaches the colon intact is a potential prebiotic, however it is the third criteria which is the most difficult to fulfil. Much of the interest in the development of prebiotics is aimed at non-digestible oligosaccharides such as fructooligosaccharides (FOS), *trans*-galactooligosaccharides (GOS), lactulose, isomaltooligosaccharides (IMO), xylooligosaccharides (XOS), soyoligosaccharides (SOS), and lactosucrose. In Europe, FOS, GOS and lactulose have been shown to be prebiotics, through numerous volunteer trials, as evidenced by their ability to change the gut flora composition after a short feeding period (Gibson and Roberfroid, 2008).

At the University of Reading, we have generated and tested a new prebiotic galactooligo-saccharide (GOS). This has powerful effects upon beneficial gut bacteria (bifidobacteria). The ingredient was manufactured from 'gut model' fermentation studies (Fig 1) and is made through the enzymatic activities of a probiotic. The prebiotic and its biomass were scaled up to pilot plant production level in our Food Processing Hall (Fig 2). We have characterised and cloned the microbial enzymes responsible for production. This research has led to a new health food product (BiMuno). It was given the Frost and Sullivan Award for European Innovation in 2009.

The GOS is a synthetic lactose based oligosaccharide that, following ingestion, passes unchanged to the colon, where it serves as an energy source for saccharolytic colonic bacteria. It specifically increases populations of beneficial colonic bifidobacteria and is therefore a recognised prebiotic. The following summarises our research and impact of the product:

- The GOS is synthesised from enzymes in *B. bifidum* 41171. Traditionally, GOS is made from yeasts or bacilli. However, use of a known probiotic is relevant as the bifidobacteria are the target genera for GOS metabolism. This strain has

Figure 1. Human colonic model used to simulate the large intestine (and identify mechanisms of prebiotic effects). The model gives a close reflection to in vivo events and is used to plan subsequent human trials. Its use obviates the need for animal experimentation in prebiotic testing.

Figure 2. "Pilot plant" food processing hall at the University of Reading. This was used to develop a new galactan based prebiotic which is now commercially available. The pilot plant is used to test the prototypes of a range of new food ingredients, including novel functional foods. (http://www.reading.ac.uk/food/businessdevelopment/foodnut-processresearchcentre.aspx)

now been fully genome sequenced and was one of the first non-USA probiotics to be included in the NIH's Human Microbiome Project: (http://www.broad.mit.edu/annotation/genome/Bifidobacterium_group/MultiHome.html)

- BiMuno has been tested *in vitro*, in pigs and in humans for its prebiotic effect (Tzortzis et al. 2005a,b; Depeint et al. 2008)
- Human studies in IBS (Silk et al. 2009), elderly persons (Vulevic et al. 2008) and traveller's diarrhoea (Drakoularakou et al. 2010) are complete
- The synbiotic (probiotic and prebiotic combination) effects are now being researched with appropriate probiotics
- Its influence as an adjunct to the influenza vaccine is being researched at Reading
- The prebiotic has been trialled in 80 high level sportspersons (mainly Team GB rowers). This is driven by the hypothesis that intake will reduce the risk of gastroenteritis and concomitant effects upon performance
- The Welsh team competing at the Commonwealth Games in Dehli in October 2010 took the supplement – to reduce risk of gastroenteritis. The English badminton and bowls sides also did so. Feedback has been extremely positive: http://www.bimuno.com/bimuno-avoids-'dehli-belly'-at-the-commonwealth-games/
- Recent research has shown that the gut microflora of both obese humans and mouse models of obesity is altered compared to lean counterparts. This raises the possibility of modulating the gut microflora as a novel strategy in tackling the epidemic of obesity and diabetes sweeping the developed world. A human study in markers of metabolic syndrome and dietary based microbiota modulation by the GOS is almost complete.

Both probiotics and prebiotics have been researched for their abilities to alter the microbiome in a manner that improves health. Reduced risk of gastroenteritis, inflammatory conditions, atopic reactions and digestive cancers are among the conditions targeted. For the next generation of gut micobiome based interventions, microbial and metabolic profiling strategies should be applied in parallel to assess both the compositional and functional status of the microbiome and its interaction with the host. Such functional assessments of pro/prebiotic interventions and the identification of specific microbial-metabolic connectivities will facilitate the rational design of dietary interventions that are finely targeted in terms of their health attributes and underpinned by mechanisms of effect.

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FOOD AND GUT HEALTH

A PROBIOTIC INSIGHT: PAST, PRESENT AND FUTURE

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THE ORIGINS OF A NEW MICROBIAL CONCEPT

A key figure in probiotic history was the Nobel prize-winner Professor Metchnikoff, who believed ageing was related to toxic metabolites produced by putrefactive bacteria in the large intestine. In his 1907 thesis, 'The Prolongation of Life', he argued that this could be suppressed by eating foods fermented with lactic-acid producing bacteria. Two decades later a scientist in Japan, Dr Shirota, believed that this strategy might help prevent infectious disease but realised that, to be effective, the bacteria needed to remain alive through the gut. After screening many strains, he selected one (see Figure p37) to develop a simple fermented milk drink, eventually sold as a probiotic product. This reached the UK in 1996, starting the rapid expansion and popularity of the category with products now available as fermented milk drinks, yoghurt drinks, yoghurts, capsules, tablets or powders – from supermarkets, pharmacies, health food shops and the internet. In 2008, it was estimated that the retail value of probiotic supplements in the EU was €380m (26% of the global total) and €5 billion for probiotic yoghurts (32% of the global total)[1].

WHAT ARE PROBIOTICS?

Back in the 1990s, it was a real challenge to persuade people that it was beneficial to eat live bacteria. Remember ads featuring a 'geeky guy' pontificating about 'friendly bacteria' and the importance of digestive health? By 2001, two United Nation bodies (the World Health Organisation and the Food and Agriculture

Organisation) recognised the need for guidelines for this category, and agreed the probiotic definition as: 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host'[2].

Thus probiotics should have evidence of health benefit from human intervention studies conducted either with the product or the strain given at an equivalent level. They must be safe for their intended use: most strains are lactobacilli or bifidobacteria, types of bacteria associated with food for centuries and normally found in the gut of humans. Further advice can be found on the International Association for Probiotics and Prebiotics website (www.isapp.net), which emphasises that products should show the probiotic strain name and number of live microorganisms.

HOW DO PROBIOTICS WORK?

To understand this, one must appreciate the importance of the mutually beneficial relationship between humans and their personal collection of 100 trillion (10^{14}) gut bacteria, key to many of the body's developmental, immunological and nutritional functions. Disruption of this microbial community, perhaps because of antibiotic use, infection, stress, poor diet or ageing, can increase risk of infection or other disease.

Several mechanisms of probiotic activity are based on their ability to reach the lower colon alive and persist in the gut for a short period of time. Here, they can help strengthen different aspects of the gut defences by competing with pathogens for nutrients and adhesion sites in the gut, strengthening the gut barrier and suppressing harmful products of other microbes. Their generally carbohydrate-fermenting metabolism helps maintain a low gut pH, producing metabolites such as short chain fatty acids, some of which are antimicrobial and important for the regulation of the gut cells. One reason why probiotics effects can go beyond the gut and become systemic, is their ability to modulate the immune response. Over 70% of immune cells are located in the gut; our gut bacteria can 'talk' to the immune system through specialised cells and receptors, starting a chain of instructions to the rest of the body via various cells and chemical messengers.

WHAT HEALTH BENEFITS HAVE BEEN SHOWN FOR PROBIOTICS?

An indication of the their strength of scientific evidence and range of benefit can be gauged by searching the medical database PubMed[3], which will find about 9,000 probiotic papers, about 10% of which describe human trials (see Table). Systematic reviews have also reached positive conclusions for probiotic use in a range of areas, recently for example to prevent antibiotic-associated diarrhoea[4]; to treat acute infectious diarrhoea[5]; to prevent upper respiratory tract infections[6]; and to prevent necrotizing colitis[7].

Many people rely on a daily probiotic for relief of irritable bowel syndrome symptoms. Current guidelines from NICE and the British Dietetic Association[8] advise that in these cases, people should take the probiotic daily for at least one month at the recommended dose and monitor if this helps. If it does not, they suggest trying another.

THE REGULATORY SITUATION

Commercial health and nutrition claims now come under EC Regulation 1924/2006, requiring assessment of evidence by the European Food Safety Authority NDA panel. By 2008, approximately 350 probiotic claims were submitted via the Article 13.1 route for 'generally accepted scientific evidence', with the majority relating to the gut flora, digestive health or

The main areas of human study research where positive effects have been demonstrated*.

Investigation area	Outcomes
Intestinal microbiota	• Survival of the probiotic through the gut
	• Increase in 'beneficial' species (eg lactobacilli, bifidobacteria)
	• Reduction in pathogens
	• Reduction in harmful microbial metabolites
Infections (Gut-related)	• Reduction in diarrhoea (rotavirus, travellers', children)
	• Reduction in antibiotic-associated diarrhoea and *Clostridium difficile* infection
	• Reduction in necrotising enterocolitis in preterm babies
	• Reduction in post-operative infections
Gut function	• Improvement of irritable bowel syndrome symptoms
	• Improvement of constipation symptoms
	• Benefit for inflammatory bowel disease
Immune function	• Reduction of allergic and atopic disease incidence
	• Enhancing antibody response to vaccination
	• Reduction of common infectious diseases (eg colds)
	• Downregulation of inflammation in the gut
Other areas of research	• Cancer; children's colic; gut-brain axis (mood, anxiety); obesity-related disease (metabolic syndrome, etc.) ; urogenital health

*Probiotic effects are considered strain specific; not all effects have been demonstrated for all strains.

In our Olympic year: an example probiotic trial with athletes[9]

Athletes' heavy schedules of training and competition can affect their immune response and gut function, increasing their risk of infection and gastrointestinal problems. A double-blind, placebo-controlled randomised trial conducted at Loughborough University by Professor Mike Gleeson investigated the effects of a probiotic (*Lactobacillus casei* Shirota) who recruited 84 people engaged in endurance-based physical activity during four months' winter training. At the end of the trial, the average number of colds was 50% lower in the probiotic group, a benefit associated with better maintenance of levels of salivary IgA. The probiotic group also experienced significantly fewer days with digestive discomfort symptoms.

function, or immune system. Further claims have been submitted via other routes.

At the time of writing, however, no probiotic claims have been approved. So we have a situation where products that fit the WHO definition cannot be called probiotic – this is a health claim. This has come as a surprise to industry and scientists alike. Whilst some strains may well have insufficient evidence, others were considered to have good evidence of health benefit, with well-designed human studies published in peer-reviewed journals.

So what are the problems? Many claims (260) were rejected for lack of strain characterisation data, a requirement not realised at the time of submission. Evidence from even major studies was rejected for a variety of reasons, including use of disease endpoints or unvalidated biomarkers (there are few validated biomarkers that measure health maintenance). There was also a lack of acceptance that certain gut bacteria, such as lactobacilli or bifidobacteria, are beneficial to health.

Concern has been expressed by scientific and medical experts about the appropriateness of the current assessment procedure for probiotics [10, 11]. In April 2011, guidance for scientific requirements for claims relating to gut and immune health was published. A lack of clarity still remains, making it difficult for companies to invest in large, costly studies that could still be rejected as evidence even with positive results and peer approval. Rejection of claims also incurs negative media attention.

A scientific platform is needed to agree the criteria for probiotic claims that will satisfy the requirements of all stakeholders: regulators, manufacturers and researchers. This would enable this innovative functional food sector to demonstrate and communicate substantiated health benefits that are relevant to the general public, and for the EU to remain active in probiotic research.

An electron micrograph of a probiotic strain (*Lactobacillus casei* Shirota)

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FOOD AND GUT HEALTH

MANIPULATING THE MICROBIOME FOR LIFELONG HEALTH

The third speaker on 15th May was Professor Simon Carding, from the Institute of Food Research in Norwich.

Here are some of the key points he raised :

Manipulating the microbiota composition and/or function has enormous potential for improving gut health.

There are several strategies

1. Pharmaceutical, involving antimicrobial therapy
2. Biotics, involving both probiotics and prebiotics
3. Altering the activity and behaviour of the microbiota and the response to it in patients using modified commensal bacteria and food

This last requires the production of smart bacteria able to deliver, in a controlled manner, biologically active therapeutic agents to the gastro intestinal tract.

There are many benefits to this approach

a. Increased safety
b. Delivery is targeted to inductive mucosal sites
c. Protection is afforded against both disease and infection
d. Systemic and mucosal responses are stimulated
e. There is usually high acceptance, and increased compliance
f. Administration is easy
g. It is cheaper than conventional therapies

Tests have shown that genetically modified probiotic organisms (Lactococcus lactis) can cure Inflammatory Bowel Disease – a chronic lifelong autoimmune disease.

Another organism, bacteroides ovatus, has been altered to enable it to treat ulcerative colitis.

The second half of his talk described work by his colleagues, Richard Mithen and Cathie Martin, to produce new varieties of broccoli with enhanced levels of glucoraphanin, and tomatoes with elevated levels of several antioxidants. The tomatoes are purple and have the added advantage that they look pretty in salads. This increases the likelihood of consumer acceptance. This is no small matter when introducing novel foods, although it should be emphasised that both these are the products of conventional plant breeding.

Alan Malcolm
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