

**EUROPEAN NETWORK FOR GASTROINTESTINAL
HEALTH RESEARCH (ENGIHR)**

Standing Committee for the Medical Sciences
(European Medical Research Councils, EMRC)



engiHR

The European Science Foundation (ESF) is an independent, non-governmental organisation, the members of which are 78 national funding agencies, research performing agencies, academies and learned societies from 30 countries.

The strength of ESF lies in the influential membership and in its ability to bring together the different domains of European science in order to meet the challenges of the future.

Since its establishment in 1974, ESF, which has its headquarters in Strasbourg with offices in Brussels and Ostend, has assembled a host of organisations that span all disciplines of science, to create a common platform for cross-border cooperation in Europe.

ESF is dedicated to promoting collaboration in scientific research, funding of research and science policy across Europe. Through its activities and instruments ESF has made major contributions to science in a global context. The ESF covers the following scientific domains:

- Humanities
- Life, Earth and Environmental Sciences
- Medical Sciences
- Physical and Engineering Sciences
- Social Sciences
- Marine Sciences
- Materials Science and Engineering
- Nuclear Physics
- Polar Sciences
- Radio Astronomy
- Space Sciences

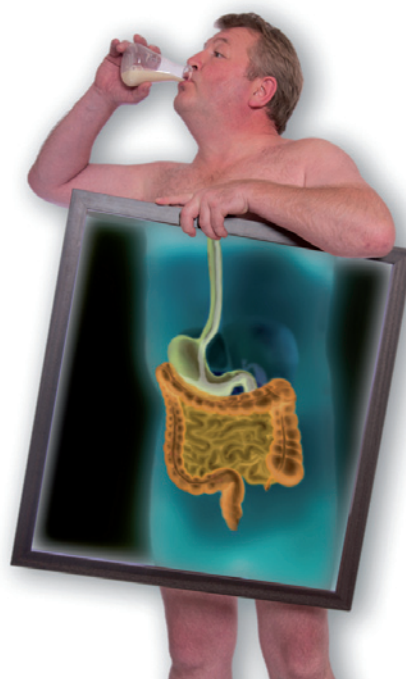
Introduction

Recent consumer awareness regarding food suggests that the primary role of a diet is not only to provide enough nutrients to fulfil metabolic requirements of the body but also to modulate various functions of the body. Considerable efforts have been made to influence the intestinal microbiota by dietary means in such a way that the health of the host is beneficially affected. There has been a strong growth in food products containing probiotics and/or prebiotics, though not in all cases supported by clinical studies. As an example, probiotics have been used therapeutically to treat inflammatory bowel disease (IBD), with mixed success. However, a recent research collaboration (the metaHIT project) has characterised the composition of the gut microbiota, identifying a pattern of microbial species in healthy versus diseased patients. It may be the case that future probiotic treatments can be tailored to meet the needs of the patient. Genetic modification of probiotics is a recent development which aims to deliver therapeutic agents directly to the gut, avoiding problems involved with systemic treatments. Such cutting-edge treatments hold much promise and it is prescient to discuss their development.

Uncovering how probiotic and prebiotic interventions function *in vivo* will make it possible to further expand applications that improve general health and provide anti-disease benefits. Recent changes in the way the EU regulates functional foods will bring new challenges in the development of functional products. The European Food Standards Authority holds public consultations to set the minimum scientific requirements needed for manufacturers of functional foods to make specific health claims. It is therefore an important time for researchers in industry and academia to interact and ensure that the correct work is carried out to a standard high enough to meet these requirements.

The European Network for Gastrointestinal Health Research (ENGIHR) aims to bring together a wide spectrum of scientists and professionals sharing their knowledge and expertise to address the current challenges and issues related to the production and validation of gut health promoting foods. This will be done through a series of scientific meetings organised within the framework of an ESF Research Networking Programme over a four-year period. An ENGIHR website will promote interaction between network collaborators and generally promote network activities. The network will have an interdisciplinary nature, encompassing food manufacturers, microbiologists, and clinicians. The Research Networking Programme will promote training and development of young scientists through short visit grants, and will encourage the integration of new partners. The Steering Committee and collaborators include a very broad range of disciplines and have the support of industrial partners. There is also a global dimension with collaborations in Japan, USA and Australia. Throughout the course of this Research Networking Programme, additional collaborators will be encouraged so that its knowledge-base constantly evolves.

The running period of the ESF ENGIHR Research Networking Programme is for four years from May 2010 to May 2014.



Aims and Objectives

Consumers worldwide are becoming increasingly aware of the relationship between diet and health and are better educated regarding nutrition. A large number of individual food constituents are known or suspected to have a direct positive or negative effect on human health, and new foods increasingly have associations to different aspects of health. Rapid advances in science and technology, increasing healthcare costs, changes in food laws affecting label and product claims, an ageing population, and rising interest in attaining wellness through diet are some of the factors driving the interest on functional foods worldwide. This has led to an increment in the number of foodstuffs in the market with references to health, sometimes at a relatively high retail value. In some cases good research and clinical trials support these health claims, but in others the success of the new products has been based more on marketing strategies than strong science, which has created certain confusion and scepticism in the consumer.

This is a particularly important time in the evolution of probiotic and prebiotic research. There has been a strong growth in food products with gut health associated claims, but it is important that these new formulations meet appropriate standards and have been shown to confer the defined health benefit in well-designed clinical studies. This is being addressed to some extent by the European Food Standards Agency which, following a public consultation, will assess health claims by manufacturers of functional foods to ensure substantiation of claims for foods related to gut and immune function.

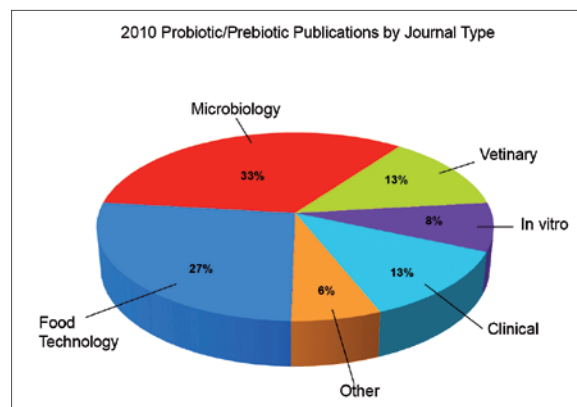
Some international associations on probiotics and prebiotics have been created and a number of meetings and conferences have been organised on the subject in the last decade, but a scientific debate on methods and techniques used to characterise and assess these products and their potential health benefits has not taken place at European level. It is timely to examine recent developments in this area since medical evidence will be key for the expansion of the use of probiotics and prebiotics in Europe.

The European Network for Gastrointestinal Health Research will bring together a diverse scientific community working to uncover some of the fundamental roles played by microbes in human (and animal) development and long-term wellbeing, and to develop novel ways to administer strains (probiotics) and nutrients (prebiotics) to counter adverse conditions. The network will create an interdisciplinary arena where knowledge and new ideas will be exchanged and scientists can interact with colleagues from complementary disciplines. It will be open to newcomers and young scientists and will encourage the participation of private organisations, large companies and SMEs, together with national and European food agencies and legal authorities.

Probiotics and Prebiotics

In recent times there has been a growing appreciation for the important role of commensal microbes in human and animal health through mediation of intestinal development and innate immunity, or digestion of foods for protection of the host against disease. This has led to attempts to manipulate or enhance the microbiota through the use of probiotics and/or prebiotics.

Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit on the host. Prebiotics are nondigestible substances that provide a beneficial physiological effect by selectively stimulating the favourable growth or activity of a limited number of indigenous bacteria. A combination of probiotic microorganisms and prebiotic carbohydrates is called symbiotic food. Functional foods targeting gut health constitute one of the largest and fastest growing sectors within functional foods. In the last two decades research related to probiotics, prebiotics and gut health in general has dramatically increased, although in recent years, publication numbers have fallen. In 2010, almost half the total publications on pro- or prebiotics were from the European Union, indicating that the European Union has at present the largest potential for gut health research in the world.



Disease Treatment and Prevention

Probiotics and prebiotics have been investigated extensively in clinical trials over recent years for the treatment of many diseases ranging from those affecting the gut itself to those that may be indirectly affected by changes in the gut microbiota. Below are examples of such research.

Inflammatory Bowel Disease (IBD)

IBD is a chronic inflammatory condition comprising ulcerative colitis and Crohn's disease. Researchers have found that probiotics and prebiotics were able to successfully ameliorate disease activity in various animal models of IBD, and this finding led to several clinical trials¹. However, results from the majority of these trials have been disappointing; only pouchitis (a disorder affecting ulcerative colitis patients) was shown to benefit from probiotic treatment. It may be the case that optimisation of probiotic dose and disease strain will lead to the achievement of better clinical results.

An alternative approach to disease treatment in IBD has been the use of genetically-modified *Lactococcus lactis*². A strain of this bacteria has been generated which produces human interleukin 10 (IL-10). Recombinant IL-10, an anti-inflammatory cytokine, has been used in clinical trials for IBD with little success, mainly due to its short half-life when administered systemically. The potential benefit of using a genetically-modified bacterial strain to express IL-10 at the site of inflammatory disease is enticing. Phase I clinical trials have shown the safety of this system and the results of further trials will show whether this technology provides clinical benefit to patients. This technology could also be used to deliver other biologically active compounds in the treatment of IBD. Moreover, animal studies have shown that this technology can also be used to vaccinate against a range of infections.

Obesity and Metabolic Disease

The role of the gut microbiota in energy metabolism has recently become apparent³. Approximately 30% of energy intake occurs through the bacterial metabolism of non-digestible polysaccharides, releasing fatty acids such as butyrate which can be metabolised by the host epithelium. Mice raised in germ-free conditions have significantly less body fat than those with a normal gut microbiota and it has also been shown that particular species of bacteria may play a role in energy metabolism, leading to weight gain and obesity. Indeed, higher levels of *Bacteroidetes* and lower levels of *Firmicutes* have been shown in obese patients versus healthy controls, with these levels changing to a healthy profile following dieting. It remains to be seen whether the findings in animal models can be extrapolated to human health.

A high-fat diet is associated with obesity as well as low-grade inflammation. This low-level inflammation in turn

is associated with atherosclerosis and type 2 diabetes. There is accumulating evidence that bacterial lipopolysaccharide (LPS, released in the gut by Gram negative bacteria) is responsible for driving low-level inflammation associated with a high-fat diet. Feeding mice a high-fat diet increases plasma LPS levels and it has been shown that injecting LPS to mimic high-fat diet induced LPS levels also leads to obesity. *Bifidobacteria* have been shown to reduce intestinal LPS levels, and increasing *Bifidobacteria* levels via prebiotic treatment of mice fed a high-fat diet led to a reduction in inflammation (and associated glucose intolerance). These studies suggest that probiotic or prebiotic strategies which aim to decrease LPS production may help protect against the harmful effects of a high-fat diet. In humans, LPS levels are also associated with food intake. Large-scale studies have yet to be performed to investigate any possible health benefit of probiotics or prebiotics in the treatment of obesity and other metabolic diseases such as atherosclerosis.

Infection

The potential for probiotics and prebiotics to reduce infection rates as well as treating infections has been widely studied⁴. Probiotic bacteria inhibit the effects of pathogenic bacteria via several mechanisms. Probiotic bacteria adhere to the colonic epithelia, stimulating the release of defensive molecules and promoting gut barrier function. They interact with the host immune system, providing a constant stimulation necessary for efficient response to harmful microbes. They also compete for space and nutrients with harmful bacteria, preventing their outgrowth.

In mice, prior treatment with a probiotic inhibits the colonisation of *Helicobacter pylori*, and probiotics can be used to clear an established *H. pylori* infection. In humans, probiotic treatment reduces the side-effect of conventional antibiotic treatment for *H. pylori* infections. Children in developing countries treated with probiotics have a reduced risk of contracting diarrhoea and reduced disease duration. Similar results have been found in hospitalised patients at risk of contracting diarrhoea. Also, the incidence of antibiotic-associated diarrhoea has been shown to be reduced by the use of probiotics. Therefore probiotics may provide an important adjuvant to current therapies used to fight infections.

The evidence which has emerged from such clinical trials has led proponents of probiotics and prebiotics to propose that regular consumption of these foods could have a long-term prophylactic effect, maintaining a 'healthy gut', and preventing the development of inflammatory diseases, infections and conditions such as irritable bowel syndrome. Further research is required to determine if this view can be substantiated.

Current Challenges

There are a number of challenges that the scientific community in Europe will face in the future to further develop functional foods targeting gut health. Probiotics and prebiotics have to be safe for human and animal consumption, and provide the expected functional benefit. In addition to all desired safety and functional characteristics, industrial production must ensure that products maintain and convey the expected functionality to the consumer through the food chain.

An important challenge is the delivery of probiotics and prebiotics to the gut and this is being addressed by the food industry. The areas of knowledge involved in the production of gut health promoting foods and ingredients is extremely diverse and cannot often be found in a single institution or sometimes even in one country. This complexity poses a challenge and it is likely to hold back the advance of science in this field in the EU. A multidisciplinary approach across Europe bringing together all this knowledge and know-how is essential. ENGIHR will create a vehicle for scientists and industrialists to exchange information, knowledge and experience that can lead to future projects and collaborations at European level in different aspects of gastrointestinal health.

Though consumer acceptance of probiotics and prebiotics is recognised, recent changes in legislation will affect the way functional foods are labelled and marketed in Europe, and health claims attributed to new foods will have to be verified with scientific evidence. As described above, some of the health effects currently associated with probiotics and prebiotics include prevention and treatment of infections, treatment of food allergies, prevention of colon cancer and coronary heart disease, treatment of inflammatory bowel disease and lactose intolerance, and prevention of diarrhoea. This research is still ongoing, with important questions remaining unanswered. The next generation of functional foods targeting gastrointestinal health may have other associated health benefits and may even be used to prevent obesity.

EU Regulation 1924/2006 on Nutrition and Health claims made on foods became law in July 2007. This is the first piece of scientific legislation to deal with nutrition and health claims and aims to provide a higher level of consumer protection as well as to harmonise legislation across the EU. Only approved health claims listed in the Community Register (published in 2010) can be used on food, and only if the product meets with the requirements of the Regulation. This decision will strongly impact on future functional food development in the EU as more evidence regarding safety and efficacy will be required to assure market success while keeping consumer confidence. More research and collaboration across Europe will be necessary in the future to develop new probiotics and prebiotics, and ENGIHR aims to facilitate this.

Activities

The network includes research institutions in most ESF-supporting European countries. ENGIHR will bring together scientists with expertise in biochemistry and physiology, microbiology, functional biology, food biosciences and engineering, chemical engineering, analytical science, biotechnology, biomedical and life sciences, gastroenterology, pharmaceutical science and animal physiology. It has also attracted the interest of private companies, experts working in food authorities and researchers studying the social acceptance of functional foods.

The activities of the network include:

Scientific workshops: ENGIHR will organise several workshops which will gather experts from various fields together to discuss new developments and current challenges and to identify areas of research which require special attention. Travel grants will be available for these meetings.

Short exchange visits: Funds will be available for short exchange visit grants which will promote collaboration between research groups and facilitate knowledge transfer.

Website: A dedicated website will provide up-to-date information on ENGIHR activities as well as providing contact details and research interests of collaborators so that collaborations can more easily be established. This website will be an important tool for networking activities.

References

1. Guarner, F. (2009) Prebiotics, probiotics and helminths: the 'natural' solution? *Digestive Diseases* 27(3), 412-417.
2. Steidler, L. and Rottiers, P. (2006) Therapeutic drug delivery by genetically modified *Lactococcus lactis*. *Annals of the New York Academy of Sciences* 1072, 176-186.
3. Cani, P.D. and Delzenne, N.M. (2009) The role of the gut microbiota in energy metabolism and metabolic disease. *Current Pharmaceutical Design* 15(13), 1546-1558.
4. Sanz, Y., Santacruz, A. and Gauffin, P. (2010) Gut microbiota in obesity and metabolic disorders. *Proceedings of the Nutrition Society* 69(3), 434-441.

Funding

ESF Research Networking Programmes are principally funded by the Foundation's Member Organisations on an *à la carte* basis. ENGIHR is supported by:

- **Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (FWF)**
Austrian Science Fund, Austria
- **Eesti Teadusfond (ETF)**
Estonian Science Foundation, Estonia
- **Suomen Akatemia/Finlands Akademi**
Academy of Finland, Finland
- **Deutsche Forschungsgemeinschaft (DFG)**
German Research Foundation, Germany
- **Lietuvos Mokslo Taryba (LMT)**
Research Council of Lithuania, Lithuania
- **Norges Forskningsråd**
Research Council of Norway, Norway
- **Fundação para a Ciência e a Tecnológica (FCT)**
Foundation for Science and Technology, Portugal
- **Slovenská Akadémia Vied (SAV)**
Slovak Academy of Sciences, Slovakia
- **Consejo Superior de Investigaciones Científicas (CSIC)**
Council for Scientific Research, Spain
- **Forskningsrådet för miljö, areella näringar och samhällsbyggande (FORMAS)**
Swedish Council for Environment, Agricultural Sciences & Spatial Planning, Sweden
- **Schweizerischer Nationalfonds (SNF)**
Swiss National Science Foundation, Switzerland
- **Biotechnology and Biological Sciences Research Council (BBSRC)**
United Kingdom



Dr Severino Pandiella (Chair)
School of Chemical Engineering and
Analytical Science (C74/The Mill)
The University of Manchester
Oxford Road
Manchester M13 9PL
United Kingdom
Tel: +44 161 306 44 29
Fax: +44 161 306 43 99
Email: s.pandiella@manchester.ac.uk

Dr José Maria Lagarón
Novel Materials and Nanotechnology
Group
Institute of Agrochemistry and Food
Technology (IATA)
Spanish National Research Council
(CSIC)
Av. Agustín Escardino 7
46980 Paterna, Valencia • Spain
Tel: +34 627 337 247
Fax: +34 963 392 025
Email: lagaron@iata.csic.es

Dr Andrea Lauková
Institute of Animal Physiology
Slovak Academy of Sciences
Košice • Slovakia
Tel: +421 255 633 0283
Fax: +421 255 728 7842
Email: laukova@saske.sk

Professor Andrew MacPherson
Universitätsklinik für Viszerale
Chirurgie und Medizin
Leiter Gastroenterologie
Inselspital Bern
3010 Bern • Switzerland
Tel: +41 31 632 36 60
Fax: +41 31 632 97 65
Email: andrew.macpherson@insel.ch

Dr Reet Mändar
Department of Microbiology
Faculty of Medicine
University of Tartu
Ravila 19
50411 Tartu • Estonia
Tel: +372 73 74 174
Fax: +372 73 74 172
Email: Reet.Mandar@ut.ee

Professor Ingolf F. Nes
Department of Chemistry,
Biotechnology and Food Science
Norwegian University of Life Sciences
PO Box 50003
1432 Ås, Oslo • Norway
Tel: +47 649 458 78
Tel: +47 926 452 79
Email: ingolf.nes@umb.no

Professor Margareta Nyman
Lund University
Applied Nutrition and Food
Chemistry, Centre of Chemical
Engineering and Chemistry
Getingevägen 60
PO Box 124
221 00 Lund • Sweden
Tel: +46 46 222 4567
Fax: +46 46 222 4532
Email: Margareta.Nyman@
appliednutrition.lth.se

Dr Maria Saarela
VTT Technical Research Centre of
Finland
PO Box 1000 (Tietotie 2)
02044 VTT
Espoo • Finland
Tel: +358 405 760 913
Fax: +358 207 227 071
Email: maria.saarela@vtt.fi

**Professor José António Couto
Teixeira**
Department of Biological Engineering
Institute for Biotechnology and
Bioengineering
University of Minho
Campus de Gualtar
4710-057 Braga • Portugal
Tel: +351 253 604 406
Fax: +351 253 678 986
Email: jateixeira@deb.uminho.pt

Dr Herbert Tilg
Klinische Abteilung für
Gastroenterologie und Hepatologie
Medizinische Universität Innsbruck
Anichstrasse 35
6020 Innsbruck • Austria
Tel: +43 5223 502 2116
Fax: +43 512 504 67 23374
Email: Herbert.tilg@i-med.ac.at

Professor Bernhard Watzl
Department of Physiology and
Biochemistry of Nutrition
Max Rubner-Institute
Federal Research Institute of Nutrition
and Food
Haid-und-Neu-Str. 9
76131 Karlsruhe • Germany
Tel: +49 721 662 54 10
Fax: +49 721 662 54 04
Email: bernhard.watzl@mri.bund.de

Lithuania

The Research Council of Lithuania
has not yet nominated their
representative.

External Coordinator

Dr Nick Chadwick
European Network for
Gastrointestinal Health Research
School of Chemical Engineering and
Analytical Science
The Mill, University of Manchester
Oxford Road
Manchester M13 9PL
United Kingdom
Tel: +44 161 306 2354
Fax: +44 161 306 43 99
Email: n.chadwick@manchester.ac.uk

ESF Liaison

Dr Kirsten Steinhausen
Science

Ms Blanche Facchini
Administration
Medical Sciences Unit
European Science Foundation
1 quai Lezay-Marnésia
BP 90015
67080 Strasbourg cedex • France
Tel: +33 (0)3 88 76 71 18
Fax: +33 (0)3 88 37 05 32
Email: bfacchini@esf.org

For the latest information on this
Research Networking Programme
consult the ENGIHR website:
www.esf.org/engihrr