GUT MICROBIOTA FOR HEALTH
2nd World Summit

Madrid, Spain
Summit Report
2nd World Summit "Gut Microbiota for Health" 24-26 February 2013

Looking for causal chains

Gut microbiota abnormalities involved in functional bowel disorders

The precise genesis of the various functional bowel disorders (FBD) is still to be unravelled. Looking into the relations between gut microbiota and host has opened a research avenue that will very likely lead to results that offer interesting answers with a remarkable potential for clinical applications.

From left to right: moderator Dr Mark Porter (UK) in discussion with Prof. Fernando Azpiroz (Spain), Prof. Magnus Simrén (Sweden) and Prof. Giovanni Barbara (Italy)

FBD, such as irritable bowel syndrome (IBS) or dyspepsia, form a considerable burden for the individual quality of life, as well as for the public health systems. FBD have a global prevalence of 11.2 per cent, with a wide regional range from 1.1 to 45 per cent, as Professor Giovanni Barbara (University of Bologna, Italy) pointed out. In countries such as Germany, Portugal and Switzerland, the annual costs per patient range between 700 and 1,600 €. According to Prof. Barbara, there is increasing evidence that the gut microbiota is involved in the onset of FBD. He named several bidirectional mechanisms between the host and the intestinal microbiota, by which the latter can modulate gut motor functions. These mechanisms are related, for example, to the release of neurotransmitters or proteases, to the activation of toll-like receptors and to the production of short chain fatty acids (SCFA).

Every second patient consulting a gastroenterologist complains of symptoms typical of FBD, said Professor Fernando Azpiroz (University of Barcelona, Spain), Chair of the Gut Microbiota & Health Section of the ESNM (European Society of Neurogastroenterology and Motility). He confirmed the strong possibility of the gut microbiota to play an important role in FBD. He pointed to animal trials which demonstrate that the sensory pathways between gut and brain are affected by the microbial composition, as germ-free rats exhibit visceral hypersensitivity. Not only the absence of the gut microbiota, but also its abnormal composition might induce FBD. However, it is still unclear what such results, encouraging as they are, imply for the clinical practice. To fill these gaps, Prof. Azpiroz asked for thorough physiological tests in order to better define the various subgroups of FBD and then assign them to different microbial compositions.

SOME PROBIOTICS CAN ALLEVIATE IBS

One microbiota-related factor that has frequently been held responsible for certain FBD, such as IBS, is small intestinal bacterial overgrowth (SIBO). But as Professor Magnus Simrén (University of Gothenburg, Sweden) pointed out, it is still unclear to which extent SIBO is really involved in the pathogenesis, as the methodological validity of the breath tests that have been used to establish its causal role is questionable. As regards possible treatments, Prof. Simrén presented studies which show that some probiotics can alleviate IBS symptoms, particularly gas-related ones, such as bloating. While meta-analyses confirm the beneficial potential of probiotics, the evidence for the effects of particular strains is limited. This calls, as Prof. Simrén said, for more in-depth trials concerning mechanisms explaining probiotic efficacy in IBS.

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Gut Microbiota & Health
A section of the ESNM European Society of Neurogastroenterology & Motility Member of UEG
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Leading experts in Madrid

Wider attendance at 2nd Gut Microbiota for Health World Summit

270 researchers and clinicians from 25 nations attended the conference, which was hosted by the Gut Microbiota & Health Section of the ESNM (European Society of Neurogastroenterology and Motility) — a member of UEG (United European Gastroenterology) — and the AGA (American Gastroenterological Association). Over the course of three days, the speakers offered cutting-edge science, presented as a well-balanced mixture of lectures, workshops and posters.

Poster exhibition at the 2nd World Summit "Gut Microbiota for Health"

The summit's topics, all related to the gut microbiota, ranged from various GI diseases to effects of pre- and probiotics, from the intestinal microbiota's interplay with brain functions to molecular biology research methods. The programme covered basic scientific and translational aspects of the field. The six workshops, which provided continuing education presented by world-leading experts, were very well attended. Summaries can be found here. Pre- and probiotics turned out to be the most popular topic, as the corresponding workshop attracted the largest audience with over 100 participants. The summit's attendees particularly welcomed that ample time for discussion had been allocated, so that a lively exchange of information, opinions and experiences accompanied the event from the start. The summit's digital communication means were widely used, which demonstrated the ever-rising interest that gut microbiota research is provoking inside the scientific community. More than 300 tweets communicated event-related messages via the summit's twitter account (@GMFHx). Almost 50 new followers joined during the event. More than 180 experts from all over the world followed the live coverage of the plenary sessions on the Experts Exchange website gutmicrobiotaforhealth.com (available here). Not to forget an online press conference with journalists from all over the world, which can be viewed here.

The 3rd Gut Microbiota for Health World Summit will be held on 8 and 9 March 2014 in Miami, USA.

New AGA research center

A virtual "home" for scientific exchange and education

The American Gastroenterological Association (AGA), co-organiser of the 2nd Gut Microbiota for Health World Summit in Madrid, recently founded the AGA Center for Gut Microbiome Research and Education. Its mission is "to advance research and education on the gut microbiome in human health and disease". The foundation of the center, which will serve as a virtual "home" for research activities and exchange, is based on the AGA Governing Board's conviction that "the gut microbiome is among the most exciting and promising areas of science today" and should be a top priority for gastroenterology and the organisation as a whole. "This is an incredibly exciting time in science, where technological advances provide an unprecedented opportunity to explore not only the composition, but also the function of the microbial communities that live in our intestinal tract," said Prof. Wu, chair of the center's scientific advisory board, comprising distinguished experts in all subspecialties of the field. "It is hoped that the knowledge gained will provide new insights into disease pathogenesis and innovative therapeutic modalities."

"To me, personally, to meet the world leaders, who have published extensively on the field of the gut microbiota, all at one meeting is a bonus."

Infusion of diluted donor faeces through the colon

Curing by faeces

Stool transplants are highly effective for treating GI conditions

Faecal microbiota transplantation (FMT) is a rapidly acting treatment for recurrent *C. difficile* infection (RCDI). It also offers a promising outlook regarding other GI diseases. While a large part of the knowledge about FMT so far has been gained through practical experience, the systematic exploration of its potential is now under way.

The basic principle of FMT is the infusion of diluted donor faeces through the colon or the nasoduodenal route in order to restore the lack of diversity of the gut microbiota, which is assumed to play a major role in the onset of many GI diseases. Dr Anne Vrieze (Academic Medical Center, Amsterdam, The Netherlands) and Professor Lawrence Brandt (Montefiore Medical Center, New York, USA) presented the audience with results of clinical trials, as well as with case studies and reports based on their own clinical experience that impressively demonstrated the potential of this treatment. As RCDI is a major field of application, Dr Vrieze presented a study on the effect of donor faeces in patients with this condition, the conventional treatment of which with antibiotics often fails. Dr Vrieze described the safety procedures, which make sure that the potential donor's microbiota is healthy and matches the recipient's therapeutic needs. She reported that 94 per cent of the patients who had received donor faeces were cured, compared to much lower cure rates in the control groups who had received conventional antibiotic treatment.

TREATMENT WITH PROMISING FUTURE

The high benefit of this comparatively low-cost therapy was confirmed by Prof. Brandt — one of the FMT pioneers — who provided an overview of the development of FMT during the last decades, as well as a follow-up study on the long-term effects of the treatment, both of which showed success rates of well over 90 per cent. Apart from RCDI, cases in which FMT has been shown to be helpful include IBD, IBS and metabolic syndrome. Concerning the latter, Dr Vrieze presented a study that showed how faecal transplants of lean donors improved the insulin sensitivity of obese patients, as well as their gut microbial diversity. As Prof. Brandt pointed out, even in a number of non-GI-related diseases, such as Parkinson's, chronic fatigue syndrome and autism, FMT has been helpful.

However, as both experts made clear, there is still a whole range of questions waiting to be answered. These concern practical aspects (such as the right amount of stool), the causative role of the gut microbiota in the different diseases, the need to further establish the efficacy of FMT, and the development of novel treatments that could replace FMT in the long run. One way might be the culturing of beneficial microorganisms that could be used for novel probiotics.

PROF. LAWRENCE BRANDT, *Montefiore Medical Center, New York, USA*

"I was particularly interested in the faecal microbiota transplant discussions. I think this has a very interesting future. The microbiota in general is the future in understanding many of the diseases."

DR ANNE VRIEZE, *Academic Medical Center, Amsterdam, The Netherlands*

Weapons against GI diseases

Evidence for medical efficacy of pre- and probiotics

Over the past years, an ever-growing number of studies on the clinical relevance of pre- and probiotics have been performed. Although several aspects still require clarification, a large body of evidence in favour of their beneficial impact has already been gathered.


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Prebiotics can be found, for example, in chicory, probiotics in fermented dairy products

Prebiotics are 'food' for beneficial intestinal bacteria!" This catchy definition, presented by Dr Karen Scott (University of Aberdeen, UK), stressed the clinical importance of prebiotics, such as resistant starch and oligosaccharides. In her talk, Dr Scott outlined the role of these prebiotics — which occur, for example, in chicory — as ingredients that are fermented by gut bacteria, thus changing the composition or activity of the microbiota in a positive way. The main underlying process consists of the fermentation that results in different types of beneficial SCFA. These can help to protect the host against

PROF. KAREN SCOTT, *University of Aberdeen, UK*

bowel cancer, IBD, diarrhoea and constipation, or to moderate the course of disease. Other positive effects are the decrease of cholesterol and the increase of calcium absorption.

SUFFICIENT EVIDENCE

The clinical potential of some probiotics was at the centre of Professor Colin Hill's talk (University College Cork, Ireland). He pointed out that between 2000 and 2011, more than 1,000 publications on human clinical trials with different probiotics had appeared. The most commonly targeted conditions for probiotics are IBS, diarrhoea, pouchitis, necrotising enterocolitis and ulcerative colitis. Although not all of these studies have passed uncriticised, there is sufficient evidence, according to Prof. Hill, for the health benefit

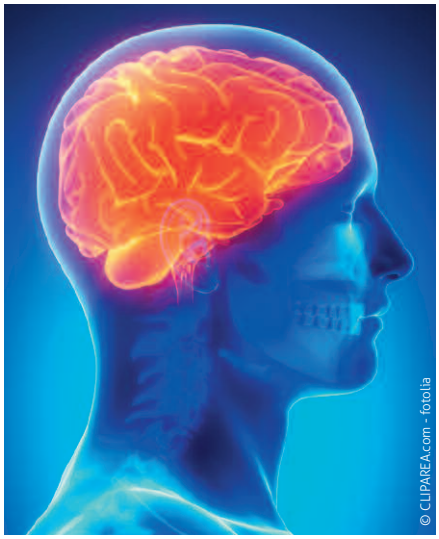
PROF. COLIN HILL, *University College Cork, Ireland*

of some probiotics. What remains to be clarified is, among other things, which therapeutic outcomes are to be assigned to which bacterial strains. Prof. Hill predicted a promising future: "Probiotics have the potential to offer the clinician another weapon against GI conditions."

While research on probiotics has so far mostly focused on the large intestine, Professor Michiel Kleerebezem (Wageningen University, The Netherlands) presented findings that concern the interaction of probiotics with the microbiota of the small intestine, which forms the part of the gut where the initial interactions between food and microbes occur and which is a highly important region for controlling metabolic and immune functions. Prof. Kleerebezem demonstrated that some probiotics exert

PROF. MICHIEL KLEEREBEZEM, *Wageningen University, The Netherlands*

significant influence over genes involved in regulating the metabolism of cells lining the small intestine. Some of the observed effects may be clinically significant and may lead to the use of specific probiotic strains for treatment.



There is a tight interplay between the brain, the gut and the intestinal microbiota

Probiotics and brain activities

The underlying reality of "gut feelings"

A widely ramified network of signalling paths enables a smooth and efficient communication between brain, gut and intestinal microbiota. Disturbance of this exchange, however, can severely affect the psychological balance. A growing number of findings elucidate how strong the interdependence between these areas is.

GI disorders are often accompanied by psychological symptoms, such as anxiety or depression. This is due to the tight interplay between the nervous system, the gut and the intestinal microbiota. Communication between these three "players" runs bottom-up as well as top-down through a diverse network of signalling pathways, among which the vagus nerve and the spinal chord are two important roads. Professor Premysl Bercik (McMaster University, Hamilton, Canada) presented a large number of mice trials that demonstrated how closely emotional states depend on the communication between the intestine and the nervous system. Animals with different kinds of GI infection showed anxiety- or depression-related behaviour, accompanied by corresponding changes in neuroregulatory and immunomodulatory processes. Also, Prof. Bercik could show how an induced disturbance of the microbial composition, often combined with inflammation, goes hand in hand with depression- or anxiety-related behaviour. On the other hand, probiotics such as *B. longum, L. farciminis* and *L. rhamnosus* can exert a beneficial effect, mediated through the gut microbiota, by reducing specific neuronal activities and thus inducing a normalisation of behaviour.

PROF. PREMYSL BERCIK, *McMaster University, Hamilton, Canada*

PROF. EMERAN MAYER, *University of Califonia, Los Angeles, USA*

STUDY IN HUMANS CONFIRMS HYPOTHESIS GENERATED IN ANIMAL MODELS

By contrast with the abundance of animal data, comparably few controlled study results have so far been provided on the connections between gut, microbiota and psychological conditions in humans. This lends particular significance to an investigation that Professor Emeran Mayer (University of California, Los Angeles, USA) reported on: his team demonstrated that some probiotics affect evoked brain responses, in a measurable way, through change of the gut microbial composition. The trial group consisted of 45 women who underwent an emotional reactivity task that included viewing faces expressing negative emotions, thereby activating task-related brain circuits concerned with the central processing of afferent signals from the gut. Brain imaging showed that in those participants who had consumed a fermented milk product with probiotics, the neuronal response to the task was reduced, compared to two control groups without intake of probiotics. While Prof. Mayer cautioned against premature extrapolations from the study to complex human emotions, such as anxiety, he emphasised the importance of having been able to observe effects of some probiotics on the human brain.

"The gut microbiota plays important roles in metabolism, in the regulation of the immune system, and not only in the function of the brain, but actually in the development of the brain in the first years of life."

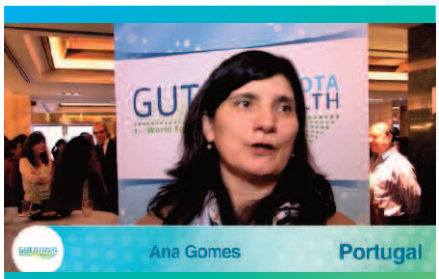
Detecting roots of obesity

Microbiota composition and gut barrier leaks involved in disease onset

The gut microbial composition responds quickly to change of food, but only long-term diet can alter the enterotype state. Another important mechanism underlying obesity and metabolic syndrome is the strong interplay of the gut microbiota, the body's own cannabinoid system and leaks in the gut barrier.

A low-fat/high-fibre diet already changes the gut microbial composition within 24 hours

How does the gut microbiota composition influence the development of obesity-related diseases? Professor Gary Wu (University of Pennsylvania, Philadelphia, USA) and his team investigated the gut microbiota composition and its correlation with food intake in 98 individuals, associating diet inventories with the outcome of the analysis of faecal samples. As a result, the individuals could be clustered into enterotype groups, distinguished primarily by levels of *Bacteroides* and *Prevotella*. Individuals who, over a long period of time, consumed more animal fat and less carbohydrates showed a dominating amount of *Bacteroides*, while a high level of *Prevotella* indicated the reverse. This coincides with the finding that *Prevotella* dominates in agrarian societies, while *Bacteroides* are associated with a Western diet. Based on another trial, Prof. Wu and his team could also demonstrate that the gut microbiobal composition already changed measurably within 24 hours of initiating a high-fat/low-fibre or a low-fat/high-fibre diet. However, the alterations during the ten-day study were too small to affect the enterotype identity. This suggests that a long-term diet is necessary to induce alternative enterotype states.



"I was particularly interested in the implications of diet and metabolic syndrome, and how the gut microbiota might modulate and influence the metabolic syndrome."

PROF. GARY WU, *University of Pennsylvania, Philadelphia, USA*

PREBIOTICS BENEFICIAL IN METABOLIC SYNDROME

To unveil the metabolic syndrome's underlying physiological mechanisms is the goal of investigations performed by Professor Patrice D. Cani (University of Louvain, Belgium) and his team. Their recent findings indicate that mutual interactions between the gut microbiota, the endocannabinoid (eCB) system and leaks in the gut barrier play an important causal role. The researchers found out that, in obese patients, the gut barrier is leaky as its otherwise very tight junctions are weakened. Hence, toxic molecules, so-called lipopolysaccharides (LPS) can permeate this wall and provoke inflammatory reactions of immune cells. This further weakens the tight junctions, consequently raising the LPS level and thus initiating a vicious circle. LPS are also associated with the onset of insulin resistance and type 2 diabetes. An important intermediary within this process is the intercellular network of the eCB system, which, among other things, is involved in appetite control. Based on several trials, Prof. Cani showed that the gut microbiota controls obesity symptoms via modulating the eCB system. Reversely, feeding prebiotics alters the microbial composition in a way that downregulates the eCB activity and reduces the symptoms.

PROF. PATRICE D. CANI, *University of Louvain, Belgium*

How to regain the balance?

Diversity loss in the gut microbiota is often associated with IBD

From antibiotics to faecal transplantation — there is a broad range of IBD treatment options that are based on altering the microbial composition. Improving their outcome and determining the most suitable approaches requires further research on the gut microbiota's role in disease onset.

What constitutes a healthy microbial balance is unique in each individual

What exactly is a "normal" gut microbiota composition? This has not been defined yet, said Professor Dirk Haller (Technical University of Munich, Germany), pointing out that, at the same time, it is an established fact that many inflammatory bowel diseases are accompanied by a significant loss of bacterial diversity. The extent of this decrease can depend on the disease location: according to Prof. Haller, ileal Crohn's disease is connected with a heavier loss of bacterial richness than colonic Crohn's disease, although the amount of bacteria in the colon is larger. Another factor most likely to be involved in the intestinal microbial composition is genetic predisposition, which means that certain IBD patients might recruit a different microbiota from birth onwards. Environmental factors are not to be disregarded: for instance, repeated antibiotic treatments during adolescence appear to increase the risk to develop Crohn's disease by leaving an inerasable fingerprint in the gut microbiota. Nutrition also plays an important role, though, according to Prof. Haller, it still has to be examined how diet and gut microbiota interact precisely with regard to the onset and course of IBD.

PROF. DIRK HALLER, *Technical University of Munich, Germany*

CUSTOMISED TREATMENTS DESIRED

Additional clinical evidence for the gut microbiota's key role in IBD was provided by Professor Balfour Sartor (University of North Carolina, Chapel Hill, USA). He pointed to several studies showing that numerous Crohn's disease and ulcerative colitis patients have an imbalanced microbiota with an increase of detrimental and a decrease of protective strains. The exact proportions of this imbalance, however, differ between individuals, which corresponds to the fact that, on the other hand, what constitutes a healthy microbial balance is also unique in each individual. Prof. Sartor named several ways of "repairing" a disturbed microbiota composition, among them the intake of commensal bacteria, which, according to him, are more likely to have lasting therapeutic effects than traditional probiotic strains. As regards faecal microbiota transplantation, Prof. Sartor acknowledged its success in patients with recurrent *C. difficile* infection, while taking a more sceptical stance towards its potential for IBD, as there is a lack of trial results. In any case, every treatment should be guided by the insight that everyone's microbiota is different, thus requiring a customised instead of a uniform approach, said Prof. Sartor.

PROF. BALFOUR SARTOR, *University of North Carolina, USA*

"From this summit, I gained the insight that investigating the gut microbiota is much trickier than I had assumed."

Processing the genetic profile

Powerful techniques decipher the gut's metagenome

The gut microbiota includes far more genes than the human genome itself. Comprehensive analysis of this astounding diversity is crucial to improve the treatment of many GI diseases. Precise and efficient methods suitable for analysing and processing vast amounts of data are a prerequisite.

DNA analysing techniques are crucial for further progress in gut microbiota research

As Professor Paul O'Toole (University College Cork, Ireland) and Professor Joël Doré (INRA, Jouy-en-Josas, France) explained, the key to exploring the gut microbiota genes is metagenomics, a term denoting the investigation of the genes of all bacteria, viruses and fungi that form the intestinal microbiota. Bacteria, which are currently at the centre of gut microbiota research, can be classified, in descending order, by phylum, class, order, family, genus, species and strain. The human gut microbiota harbours four major phyla: *Bacteroidetes, Firmicutes, Actinobacteria* and *Proteobacteria*. The main metagenomic questions to be answered are precisely which kinds of microbes exist in the gut and what functions they have. A technique particularly suited to answer the first question is the microbiota 16S gene profiling (also called 16S barcode profiling), which is based on the analysis of the 16S rRNA gene, a fundamental molecule of the bacterial machinery. The procedure consists of studying phylogenetic markers using 16 rRNA gene amplification by pyrosequencing.

PROF. PAUL O'TOOLE, *University College Cork, Ireland*

PROF. JOËL DORÉ, *INRA, Jouy-en-Josas, France*

INVESTIGATING BY SHOTGUN SEQUENCING

A second, particularly fast method is shotgun sequencing, which is frequently used to analyse the whole of the microbiota in order to establish the functional repertoire and the abundance of microbial genes. This approach is based on analysing short and randomly fragmentised DNA strands. Bioinformatics helps to put the resulting pieces together until the genetic picture is complete. The application of these methods in the field of gut microbiota research has led, among other things, to the detection of three gut enterotypes — bacterial communities, into which humans can be subclassified, as Professor Stanislav Dusko Ehrlich (INRA, Jouy-en-Josas, France) indicated. In his opinion, the enterotypes will be key in linking diseases with certain microbial communities. A reference catalogue of the intestinal microbial genes, in which the results of microbial DNA analyses of individuals are mapped, is a crucial element to obtain individual microbiota profiles. Studies that compared obese to lean individuals and IBD patients to healthy controls demonstrated considerable differences in the microbiota composition and diversity. According to Prof. Ehrlich, this opens up promising paths to better understand the involvement of the microbiota in a broad range of clinical issues.

PROF. S. DUSKO EHRLICH, *INRA, Jouy-en-Josas, France*

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