

## Hot topics at a glance

From healthy diet and breast milk composition to autism, IBD, gastrointestinal cancer and probiotics – various exciting facets of current gut microbiota research formed the scientific program of the Barcelona Summit

Internationally-leading experts from all fields of gut microbiota research – including doctors, nutritionists and dieticians, as well as chemists and biologists – joined the 4th Gut Microbiota for Health World Summit (GMFH) in Barcelona, covering a broad range of basic, as well as applied, research and presenting their audience with cutting-edge studies. What follows is a short overview of selected "hot topics".

### GUT MICROBIOTA AND AUTISM: WHAT'S GOOD FOR THE GUT IS GOOD FOR THE BRAIN

At least one child in 160 suffers from an autism spectrum disorder (ASD), according to the World Health Organisation (WHO). Autism is often associated with gut impairment and changes of the intestinal microbiota. Therapeutical approaches have been limited so far, but recent findings indicate that novel pathways are opening up with



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the gut microbiota playing a key role. Some beneficial gut microbes offer the potential to restore the balance inside the gut and thus improve the psychiatric symptoms significantly.



The 4th GMFH World Summit took place in Barcelona

Prof. Elaine Y. Hsiao (California Institute of Technology, Pasadena CA / USA) presented the audience with studies that provide a large body of evidence in support of this promising approach. They point to a mechanism by which a human commensal bacterium can improve ASD-related deficits.

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### GUT MICROBIOTA AND CROHN'S DISEASE: MICROBIAL COLLABORATIONS TRIGGER INFLAMMATORY DISEASES

Over the past decades, inflammatory bowel diseases have become a major burden in many countries of the world. They are caused by a complex interplay of genetics, gut microbes and environmental factors, which to a large extent, have not been unravelled yet. This is a considerable obstacle for a fundamental improvement of diagnostic and therapeutic approaches. Now, recent findings presented by Prof.

**PROF. DIRK HALLER**

Technische Universität München  
Munich, Germany



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Dirk Haller (Technische Universität München, Munich, Germany) make it plain that community effects of the complex microbiota and gain of aggressive, or loss of protective mechanisms, rather than the selection of aggressive phylotypes as single agents, are core factors for the development of the disease, as well as for its treatment.

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## CONTENT

<b>Hot topics at a glance (continued) 2</b>	
<b>How healthy are weight-loss diets? ..... 3</b>	Gut metabolites shape GI health
<b>Unwanted sensations ..... 4</b>	IBS – the result of a detrimental interplay between gut, brain and microbiota?
<b>Redefining "healthy" gut microbiota ..... 5</b>	Paleolithic lifestyle provides fascinating insights
<b>Breast is best ..... 6</b>	Sugar-compounds in mother's milk essential for infant's intestinal health
<b>The field's leading international event ..... 7</b>	Participants from all gut microbiota-related specialities met in Barcelona to present and discuss latest research results
<b>Joining forces of excellence ..... 7</b>	Gut microbiota summit welcomes three new partner societies
<b>Rising stars ..... 8</b>	Research prize for two excellent young investigators

# Hot topics at a glance (continued)

## GUT MICROBIOTA AND INTESTINAL CANCER: FUTURE OPTIONS FOR COLORECTAL AND LIVER CANCER THERAPY THROUGH MICROBIOTA ANALYSIS

Every year, around 1.3 million patients die of liver cancer or colorectal cancer (CRC) worldwide, which places these diseases among the most life-threatening cancer types. Recent studies suggest that the gut microbiota is involved in the development of both conditions. The unveiling of the underlying processes provides promising starting points for creating novel diagnostic



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and therapeutic measures. This was demonstrated by the findings of Prof. Robert F. Schwabe (Columbia University, New York, USA) and Dr Peer Bork (University of Heidelberg, Germany): In liver cancer, the identification of interactions between intestinal bacteria and liver cell receptors might lead to novel treatments. Regarding CRC, fecal microbiota analysis offers a non-invasive way of detecting the disease at an early stage.

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Various exciting research results were presented in fifteen lectures and seven workshops

## GUT MICROBIOTA AND BREAST MILK: MOTHER'S INTESTINAL BACTERIA IMPACT MICROBIAL COMPOSITION OF HER BREAST MILK

Breast milk can provide the infant's gut with beneficial bacteria that induce protective effects against a number of conditions. As Dr Esther Jiménez (Complutense University of Madrid, Spain) pointed out, the mother's gut microbiota has an important impact upon the microbial composition of the milk and its health-supporting qualities. Her findings suggest that there is a pathway linking the mother's gut with the mammary gland during the lactation period and that various cells serve as transport vehicles that carry these live intestinal bacteria via this pathway. This



**DR ESTHER JIMÉNEZ**  
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opens up promising avenues for the application of breast milk bacteria as beneficial microbes in the management of infectious and immune diseases in mothers and infants.

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**PROF. COLIN HILL**  
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Ireland

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## HEALTHY DIET INCLUDING PROBIOTICS PROMOTES A BALANCED GUT MICROBIOTA COMPOSITION

Diet is a key issue when it comes to preserving gastrointestinal health, because by eating and digesting, we also partly feed our gut microbiota and thus influence its diversity and composition. If this balance is disturbed, a number of disorders, including metabolic conditions, as well as functional and inflammatory bowel disorders and other immune-mediated diseases, might result. One way to maintain or improve intestinal health is by consuming probiotics. Prof. Colin Hill presented a number of studies, which aim at specifying the effects of probiotics on several conditions. These findings make it plain that certain specific probiotics can alleviate a number of lower gastrointestinal symptoms in adults. But, this requires that the probiotic is carefully chosen and taken in adequate doses and at regular intervals.

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# How healthy are weight-loss diets?

## Gut metabolites shape GI health

The metabolic products of gut bacteria play an important role for colonic health. Though many of the complex pathways involved still need to be unravelled, the potentially adverse effects of certain weight-loss diets have already been established.

Most important contribution to the host's health made by the gut microbiota is the production of beneficial metabolites, among them short chain fatty acids (SCFA), such as butyrate, propionate and acetate. These SCFAs, which result from carbohydrate fermentation, provide energy sources and exert anti-inflammatory, as well as cell protective effects, that help to prevent intestinal diseases, such as colorectal cancer and ulcerative colitis. Apart from this, SCFAs are involved in the regulation of hormones that affect satiety and they influence pH values, gut transit, gas production and the overall gut microbial balance.



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*Salsify is one of the nutrients that contain prebiotic components, which stimulate the production of SCFAs*

### COMPLEX INTERPLAY

Since it is well known that diet can influence the gut microbiota, the idea of specific diets tailored to individual health needs in order to induce beneficial metabolic outputs in the gut seems only logical. This, however, is not quite easy to achieve, as Prof. Harry J. Flint (University of Aberdeen, Scotland) made clear. The different groups of bacteria that colonize the gut vary widely in their

ability to make use of carbohydrate and other nutritional sources. This is due to differences in their uptake and enzyme systems and their energy metabolism. Moreover, some bacteria that are specialized, for example, in the production of butyrate, are able to change to propionate production if there is a change in the substrates available. What makes the situation even more complicated is the matter of cross-feeding: Certain microbes do not feed directly on nutrients, but instead make use of breakdown-products of other bacteria. Thus

not only single bacterial species, but their interplay in relation to varying intestinal environments has to be accounted for.

### HEALTH RELEVANT FINDINGS

"What we are facing here is a very complex and multifariously interactive system, which at our present state of knowledge, makes it difficult to precisely predict the outcome with regard to dietary interventions,

including prebiotics. Further research is urgently required," says Prof. Flint. However, as he pointed out, certain findings that are highly relevant for the gut's health have already been made.

### LOW CARBOHYDRATE – HIGH RISK

A study performed by Prof. Flint and his colleagues demonstrates the potentially detrimental impact of certain weight-loss-diets: 17 obese men were provided with an initial diet with balanced proportions of protein and carbohydrate. This was followed by a HPMC (High-protein and moderate carbohydrate) and a HPLC (High-protein and low carbohydrate) diet. Compared to the initial diet, both the HPMC and the HPLC diet resulted – among other things – in increased proportions of N-nitroso compounds (NOCs), which are known to be potential carcinogens. The HPLC diet also induced a significant decrease in the amount of butyrate, as well as beneficial phenolic acids, such as ferulate, which help to defend the host against cardiovascular and cancer diseases. "We have to conclude that weight-loss diets that are high in protein, but reduced in carbohydrates promote metabolite profiles that pose a risk to intestinal health," says Prof. Flint.

**PROF. HARRY J. FLINT**

University of Aberdeen, Scotland



# Unwanted sensations

## IBS – the result of a detrimental interplay between gut, brain and microbiota?

The relevance of the gut microbiota and the gut-brain axis for IBS was the topic that Prof. Emeran A. Mayer (University of California, Los Angeles, USA) addressed. He presented his audience with current research results that shed light on the complex signaling networks that connect these organs and help to induce "bad gut feelings."

In IBS (Irritable Bowel Syndrome) the close relationship between the gut and brain is quite obvious: Patients often suffer from consciously perceived bowel movements that are accompanied by discomfort and visceral pain. These symptoms result from a complex network of multidirectional pathways connecting not only the gut and brain with each other, but also with the gut microbiota. Several of these communication routes have already been explored and include – among others – the vagus nerve, spinal pathways, bacterial metabolites, cytokines, and the hypothalamic-pituitary-adrenal axis, which is part of the neuroendocrine system, thus influencing many physiological, as well as psychological, processes. Probable channels between gut microbiota and the brain comprise neuroactive and bile acid metabolites, SCFAs, cytokines and peripheral blood mononuclear cells (such as lymphocytes) that are important for immune responses.

### PUTTING THE PIECES TOGETHER

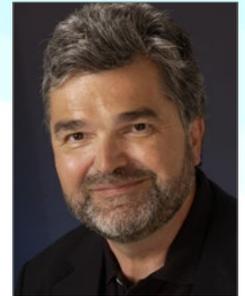
Several links connect the gut with emotional, sensorimotor and cognitive centers of the brain. Due to this, intestinal processes such as bowel movements and gas production, which we normally are not aware of, can become so salient that they are being

perceived as conscious "gut feelings," taking the form of disease symptoms. As the gut microbiota is an integral part of the gut-brain-axis, it is to be expected that it is involved in the development of IBS. Although researchers have only just started to reveal these relationships and many pieces of the puzzle are still missing, several findings already point to a broad variety of roles the microbial community seems to play. With regard to the gut bacterial composition, there is evidence that in IBS patients, the proportions of the genera *Bifidobacterium* and *Lactobacillus* are decreased compared to healthy individuals. "However,

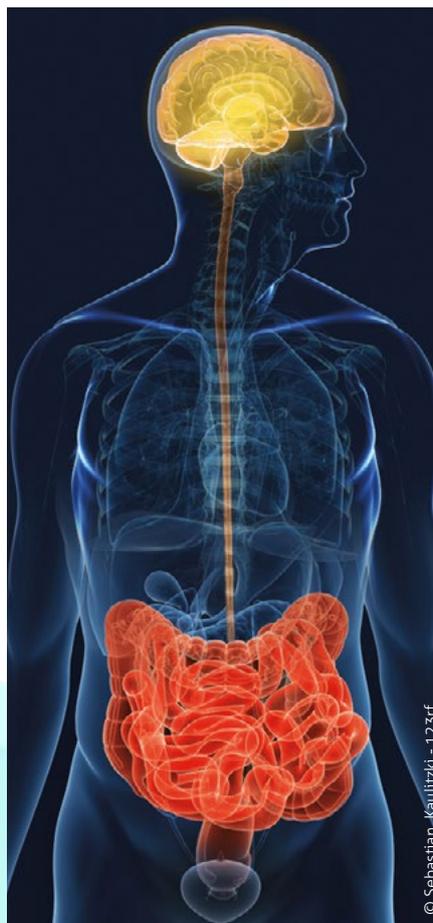
consistent alterations in the gut microbiota of IBS patients in general have not been reported so far, which may be a consequence of existing IBS subpopulations," said Prof. Mayer.

### MICROBIOTA AFFECTS BRAIN STRUCTURES

Other studies show that intake of probiotics can be associated with a blunted reactivity of sensory brain regions, which in the case of IBS, might lead to a dimming of the "gut consciousness." According to Prof. Mayer, not only brain functions, but also brain structures, are likely to be affected by the gut microbiota: In individuals whose gut microbial composition was characterized by a predominance of *Prevotella*, a greater fiber density between brain regions that are involved in sensory modulation and emotional regulation was found. At the same time, these individuals showed a higher negative affect after looking at disgusting images. "Which consequences all these scientific approaches are going to have for diagnosis and treatment of IBS remains to be seen. Prerequisite is the elucidation of the causal relationship between brain and gut microbiota in general. With regard to IBS, longitudinal and interventional studies are needed to evaluate the precise role of the microbiota," said Prof. Mayer.



**PROF. EMERAN A. MAYER**  
University of California, Los Angeles, USA



Complex signaling networks connect the gut and the brain

# Redefining "healthy" gut microbiota

## Paleolithic lifestyle provides fascinating insights

What characterizes a well-balanced microbiota? The example of the Hadza, an East African hunting and gathering community, shows that the range of possibilities is by far wider than what is to be expected under a western lifestyle perspective.

The Hadza, a small community living in north western Tanzania along the Rift Valley, have attracted the attention of gut microbiota researchers. This interest arises from the Hadza's lifestyle, which resembles that of paleolithic hunter and gatherer communities. The Hadza neither cultivate plants nor do they keep farm animals. Their diet almost completely consists of wild foods, such as honey, baobab, berries, tubers and game. This makes for a daily diet that is rich in simple sugars, starch and protein, while



The Hadza live as hunters and gatherers in northwestern Tanzania

and typically mediterranean with high amounts of plant food, fresh fruit, pasta, bread and olive-oil and a low to moderate proportion of dairy, poultry, fish and red meat. The analysis of the participants' faecal samples showed a higher diversity in the Hadza's gut microbial composition compared to the Italian cohort.

generally good health status of the population shows. Instead, the Hadza gut microbiota is obviously well adapted to the environment of this community. Prof. Brigidi: "The complete absence of *Bifidobacteria*, at least in adult Hadza, for example, is probably a consequence of the post-weaning gut microbiota composition in the absence of agro-pastoral-derived foods." The gut microbial distinctions also correspond with differences in the production of SCFAs.

### STRIKING DIFFERENCES

But, most striking were the differences with regard to the dominating bacterial species: By contrast with the Italian controls, the Hadza gut microbiota composition was characterized – among many other specifics – by a complete absence of *Bifidobacteria* combined with an enrichment in bacteria such as *Proteobacteria* and *Spirochaetes*. *Bifidobacteria* are associated with breastfeeding and regarded as beneficial. *Proteobacteria* and *Spirochaetes*, on the other hand, have the reputation of being potentially harmful – "opportunistic" – microorganisms. This might lead to the conclusion that the Hadza have an unfavourable, disease-promoting gut microbiota composition. However, this is not the case, as the

The Italian samples are characterized by a significantly greater abundance of butyrate, which helps stabilizing the gut barrier. Hadza samples, by contrast, are enriched in propionate, which is an important energy contributor. According to Prof. Brigidi, this might provide nutritional support for the Hadza, whose diet contains high amounts of fiber, but is seasonally lean in lipids. "A main conclusion to be drawn from our research is that we have to revise our standards by which we define whether a gut microbiota is healthy or not and take the respective contexts into account," says Prof. Brigidi.

PROF.

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lean in fat. "By investigating the Hadza's gut microbiota, we can look back into the past and see what the gut microbiota was like before the majority of the human population became farmers, which fundamentally changed dietary patterns and caused the intestinal microbial population to adapt," says Prof. Patrizia Brigidi (University of Bologna, Italy). She and her team conducted a study including 27 Hadza, aged 8-70, and 16 Italians, aged 20-40, as a western lifestyle control group. The Italians' diet was agriculturally shaped

# Breast is best

## Sugar-compounds in mother's milk essential for infant's intestinal health

Breast milk has two consumers: It not only nourishes the baby but also the infant gut microbiota. By fostering the growth of beneficial micro-organisms and helping to protect the gut against pathogens, breast milk contributes largely to the infant's health and well-being.

**B**reast milk contains a huge number of complex sugar compounds, called human milk oligosaccharides (HMO). Although the baby cannot digest these components, they are immensely useful for the maintenance of the infant's intestinal health, as Prof. David A. Mills (University of California, Davis, USA) illustrated. He and his colleagues are investigating

into their structures and functions. Around 200 different HMOs have been identified. Among the most important of their functions is promoting the growth of one particularly beneficial bacterium: *Bifidobacterium longum* subspecies *infantis*, a micro-organism that produces SCFAs, which serve as food for other beneficial bacteria and also help the cells that line the infant intestine to mount an immune defense.

### OUTCOMPETING BAD BUGS

By consuming oligosaccharides that reside on the cell walls of the infant's intestine, *B. infantis* exerts another helpful effect: It outcompetes harmful microbes that would otherwise be

baby's microbiota, making up as much as 90 per cent of it. After weaning, its proportion drops considerably. The analysis of fecal samples shows that the microbial composition in formula-fed infants is different from that in breast-fed ones.

**PROF.**  
**DAVID A. MILLS**  
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Apart from fostering the growth of *B. infantis*, the HMOs themselves can ward off harmful microbes: As they closely resemble carbohydrate structures on the infant's intestinal cells, they attract many pathogens that bind to these structures, thus serving as decoys that keep these pathogens off the intestinal wall and prevent them from infiltrating the gut.

Researchers are currently investigating the potential of HMOs and *B. infantis* as nutritional supplements that might help prevent severe intestinal diseases in infants, such as necrotizing enterocolitis (NEC). It has been shown that the risk of NEC drops if pre-term infants are given breast milk instead of formula. However, it has to be taken into account that there are different types of breast milk: Recent studies suggest that milk of mothers who are secretors protects better than that of non-secretors by promoting a more favourable microbial composition through the selection of HMOs and other sugar-comprising compounds present in their milk.



Breast milk fosters the growth of beneficial bacteria

the multifarious components of breast milk in order to translate this knowledge into clinical applications and the development of nutritional supplements.

Due to the chemical complexity of HMOs, it was not until elaborate analytical techniques were available that scientists could look deeper

attracted by these compounds and prevents them from colonizing the gut. *B. infantis* and the HMOs are made for each other as the bacterium disposes of all the enzymes that are needed to digest these oligosaccharides. Other bacteria, even closely related ones, lack this biochemical equipment. As this bacterium specializes in feeding on HMOs, it dominates the breast-fed

# The field's leading international event

Participants from all gut microbiota-related specialities met in Barcelona to present and discuss latest research results

**300** gut microbiota experts, including gastroenterologists, paediatricians, nutritionists, dietitians and general practitioners coming from 13 countries, as well as 17 journalists, attended the GMFH World Summit 2015 in Barcelona. The event was hosted by the Gut Microbiota & Health Section of the European Society of Neurogastroenterology and Motility (ESNM) and the American Gastroenterological Association (AGA) together with three new partner societies (see article below) and with the support of Danone. Fifteen talks and seven workshops covered all the exiting facets that constitute this expanding research area. The program spanned a broad range of scientific and health care topics, from maternal imprinting of the gut microbiota to practical dietary recommendations for gut microbiota



300 experts attended the World Summit on-site - a further 360 followed the plenary talks via video live stream

modulation and from microbial impact on GI diseases to the definition of standards for the application of probiotics. A live video stream of the plenary talks was followed by 360 experts from all over the world. The **replay** is still available on the website [gutmicrobiotaforhealth.com](http://gutmicrobiotaforhealth.com). The discussions at the venue were accompanied by an equally

lively exchange via twitter. More than 2400 tweets communicated event-related messages via the summit's twitter accounts ([@GMFHx](https://twitter.com/GMFHx)) ([@GutMicrobiotaWW](https://twitter.com/GutMicrobiotaWW)). 186 new followers – experts and students from all relevant specialities – joined during the event. Fact sheets on the most important topics of the Summit are online available [here](#).

## Joining forces of excellence

Gut Microbiota for Health Summit welcomes three new partner societies

The Gut Microbiota for Health World Summit is jointly organized by the Gut Microbiota & Health Section of ESNM and AGA. This year, the summit's base has been broadened by including additional excellence: Three other renowned societies – all of them members of United European Gastroenterology (UEG) – who share a common interest in the gut microbiota have joined the GMFH partnership in order to foster the event and present the audience with topics and findings related to their fields: the European Crohn's and Colitis Organisation

(ECCO [www.ecco-ibd.eu](http://www.ecco-ibd.eu) / [Click here for video interview with Julián Panés](#), President-elect), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition ([www.espghan.org](http://www.espghan.org)), and the European Association for the Study of the Liver (EASL [www.easl.eu](http://www.easl.eu)). "We are delighted to have all these distinguished associations joining forces in order to further advance gut microbiota research," said the section's president Prof. Fernando Azpiroz (Hospital General Vall d'Hebron, Barcelona, Spain). Representatives of all three

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partners are members of the board of directors of the ESNM Gut Microbiota & Health Section. "Looking at this year's GMFH World Summit, we can safely say that the input of our new partner societies has already resulted in a further increase of scientific quality and an extended range of topics," said Prof. Francisco Guarner (University Hospital Vall d'Hebron, Barcelona), chairman of the 4<sup>th</sup> GMFH World Summit.

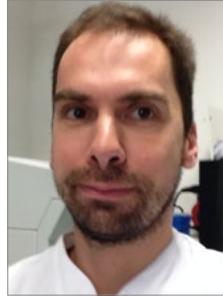
# Rising stars

## Research prizes for two excellent young investigators

Dr Guillaume Sarrabayrouse (University of Barcelona, Spain) and Dr Luca Pierri (University of Salerno, Italy) are the winners of the "Young Investigator Awards" set up by *Nature Reviews Gastroenterology & Hepatology* (@NatRevGastroHep) for the two best poster abstracts submitted to GMFH 2015. The two award winners, who were selected by the Scientific Committee, received a 500 Euros prize, plus one year's complimentary online subscription to NRGH, together with an award certificate.

**Dr** Guillaume Sarrabayrouse's poster presentation was entitled "Human CD4CD8 $\alpha\alpha$  regulatory T cell induced by *Faecalibacterium prausnitzii* and deficient in Inflammatory Bowel Disease" (Sarrabayrouse G. et al. PLOS Biology April 8, 2014). His starting point was the question of whether changes in the abundance of the fecal *Clostridium leptum* group, and in particular of *Faecalibacterium prausnitzii* in the gut microbiota, are cause or consequence of IBD and whether inflammation may arise from disturbed regulatory T cell (Treg) induction. "The findings of

**DR GUILLAUME SARRABAYROUSE**  
University of Barcelona, Spain



our group suggest that DP8 $\alpha$  colonic regulatory T cells are induced locally by *Faecalibacterium prausnitzii* and play a major role in the prevention or the control of colonic inflammation. This opens the road to new diagnostic and therapeutic strategies for IBD. Our data also uncover a divergence between mice and humans regarding the subset of IL-10-secreting Treg induced in the colonic mucosa by *Clostridium* species. Importantly, DP8 $\alpha$  Treg represent new tools to address the impact of the gut microbiota composition and of induced colonic Treg in human health and disease", says Dr Sarrabayrouse.

**A** pilot study of gut microbiota and gut-liver axis function in pediatric obesity" was the title of Dr Luca Pierri's poster presentation, which addressed the

**DR LUCA PIERRI**  
University of Salerno, Italy



role of gut microbiota and gut-liver axis malfunction in modulating body fat excess and obesity comorbidities. He and his team investigated the impact of the gut microbiota and of intestinal permeability (IP) in obese children with and without hepatometabolic comorbidities as compared to normal weight individuals. "What we found was that in pediatric obesity and Non Alcoholic Fatty Liver Disease, there is a low gut microbial diversity with a peculiar gut dysbiosis showing relationships with sleep and dietary habits, as well as with IP abnormalities. Microbial data we have gained possibly suggest that hydrogen gas (H<sub>2</sub>) transfer between bacterial and archaeal species reflects increased energy harvesting. This might serve as a target in future studies of tailored therapies," says Dr Pierri.



GMFH's poster exhibition attracted plenty of attention

For both scientists, this was the first time they attended a GMFH summit. "It was a great opportunity to listen to so many outstanding speakers," said Dr Sarrabayrouse. And, Dr Pierri added: "For me, it was a perfect GMFH summit."

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