5th Annual Forum

Better Foods for Better Health

MICROBIOTA & HEALTH: THE CHALLENGES OF A PROMISING APPROACH

APRIL 6th to 8th 2016

Fondation Mérieux Conference Centre ‘Les Pensières’
Veyrier-du-Lac - France

SUPPORTED BY

MERIEUX NutriSciences

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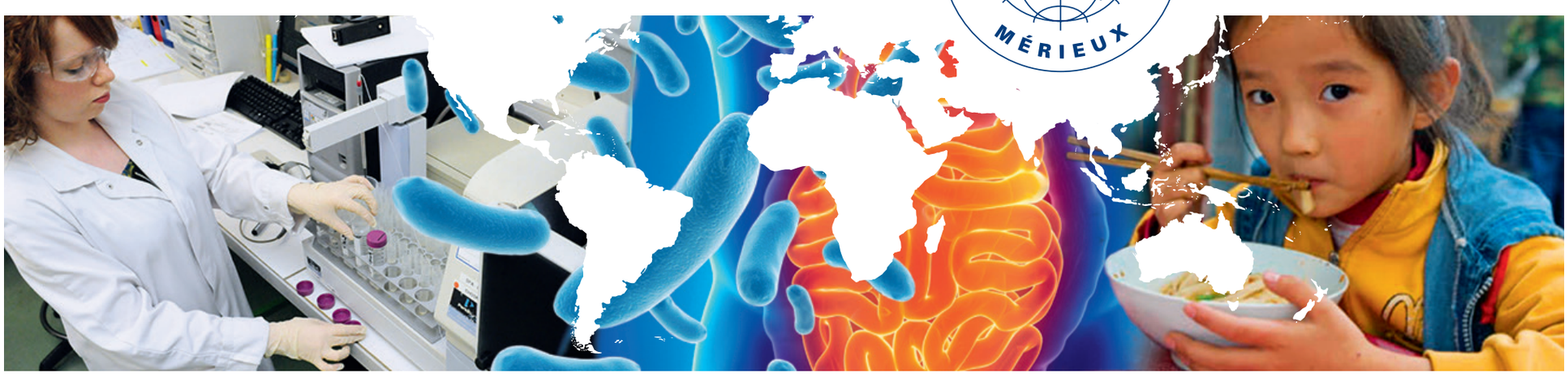


PREFACE

Improving nutrition for the burgeoning global population is one of today's major public challenges. Over the past six years, "**Better Foods for Better Health**", our international symposium dedicated to pursuing advances in nutrition, has brought together leading scientists, NGOs, policy stakeholders and key opinion leaders to exchange ideas and drive progress for this global cause.

Fondation Mérieux, the inaugurator of the Symposium, with the support of Mérieux NutriSciences, has sought new views on the fundamental link between health and nutrition form scientific, business and regulatory perspectives.

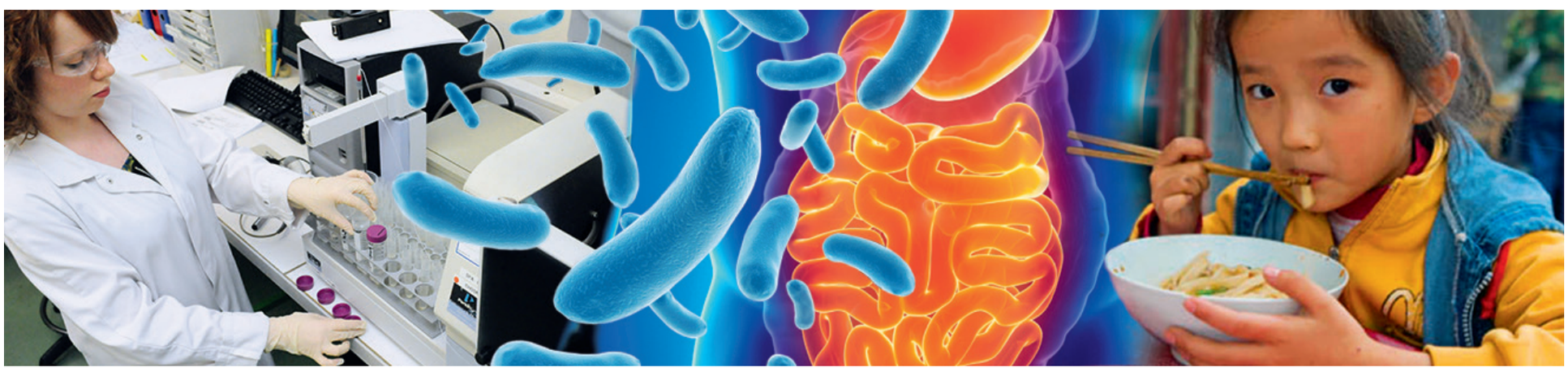
With health matters occupying a pressing dimension, the Symposium is dedicated to sharing the latest scientific developments in nutrition in both developed and developing countries. Valuable insight from industry is provided by esteemed moderators, placing the consumer at the centre of the dialogue between scientific evidence and public policy makers.

This year's symposium, "**Microbiota & Health: the challenges of a promising approach**", addressed the role of the gut microbiota in health and chronic diseases. New perspectives from the microbiota approach to prevent or cure disease were presented and opportunities offered by novel scientific models based on microbiota studies were discussed.

Increasing dialogue between the scientific community, regulatory, nutrition and industry stakeholders is a top priority. This White Book provides a summary and recommendations of the stellar cast of participants who took part in the Symposium, confirming their commitment to promoting "Better Foods for Better Health". We are proud to be part of to all-important discussion

Alexandre Mérieux
Vice President
Fondation Mérieux

Philippe Sans
President and CEO,
Mérieux NutriSciences



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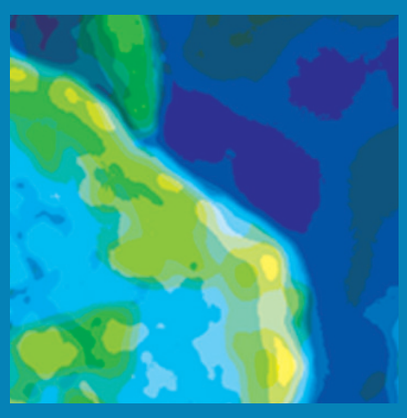

Better Foods for Better Health

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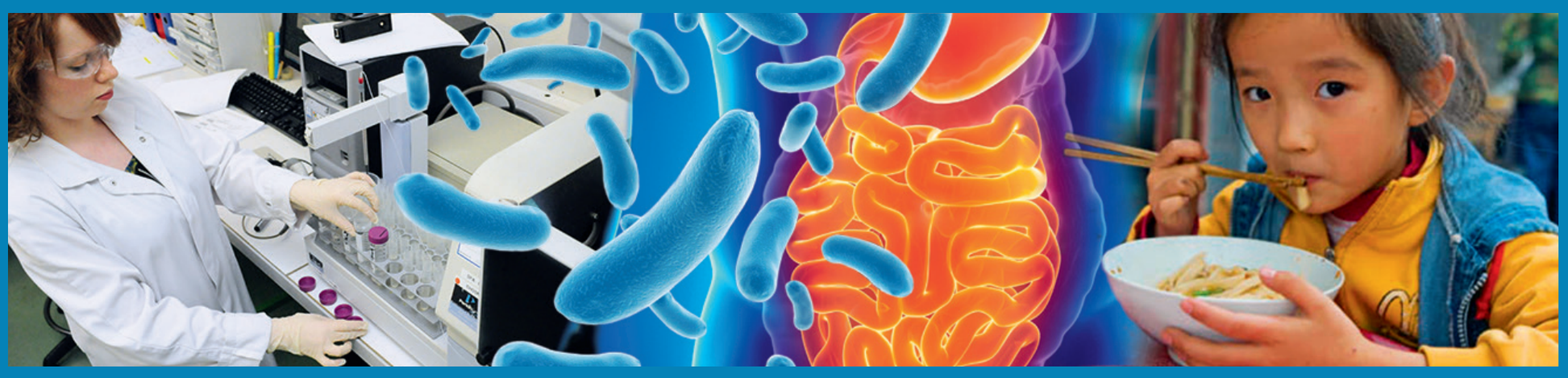

The fifth Better Foods for Better Health symposium, organized by the Fondation Mérieux with the support of Mérieux NutriSciences, was held from April 6th to 8th, 2016, at Les Pensières conference center in Veyrier-du-Lac, France.

The objective for the meeting was to create a platform that gathered experts from academia, international organizations, NGOs, regulatory authorities and industry to foster exchange between these groups. With the theme **'Microbiota & health: the challenges of a promising approach'**, discussions and presentations focused on exploring the relationship between the gut microbiota and metabolic syndromes, malnutrition and healthy living.

This year, the symposium sought to:

- present new perspectives in microbiota research to prevent or cure disease,
- evaluate the opportunities offered by novel scientific models based on microbiota studies,
- discuss the need for new, harmonized tools to assess nutrition efficiency and safety, and
- provide a platform for increased dialogue between regulators, academia, industry and sources of research funding.

The fifth Better Foods for Better Health symposium produced a number of messages:

- Due to the ongoing obesity epidemic, it is imperative to understand the complex interplay between diet, microbiota and host. Evidence suggests that the effects of different nutrients can be influenced by gut microbiota-diet interactions, which could determine the final energy yield of a diet. There is much promising clinical and preclinical data supporting the therapeutic potential of microbiota-based intervention.

EXECUTIVE SUMMARY

- Studies have also shown that food, notably broccoli and dietary fiber, can promote anti-inflammatory mechanisms, supporting the view that diet is the key environmental factor that modulates both gut microbiota and body weight. By broadening our knowledge of the interplay of diet, immunity and the microbiome, we might develop novel food-based approaches to prevent or treat many major diseases.

- Many disorders of circadian rhythm are associated with obesity and type 2 diabetes. Recent research also suggests that the gut microbiome is a key element in maintaining circadian rhythms, providing evidence that in addition to taking into account what and how much you eat, when you eat is also an important component.

- Like obesity, undernutrition is another serious manifestation of malnutrition, with studies indicating an interrelationship between diet, gut microbiota and health, with the gut microbiota acting as a link between environmental factors (such as diet) and the host. Nutritional deprivation may lead to a "disease-promoting" microbiota. Further research is necessary to investigate possible probiotic or prebiotic approaches to address undernutrition, whether the result of disease or deprivation.

- The intestinal microbiome is an organ with an enormous potential to be explored using new technologies. More than ever before, methods and technological procedures must also be standardized such as: sample identification, collection and extraction, as well as sequencing, complex data integration and biostatistical analysis. Yet there are a number of confounding factors in this area that might be difficult to solve.

- Discussions from a societal and public health standpoint about tackling stubborn health issues yielded important insights. It is important to keep in mind that we must rely not only on "hard" science but we should also take into account behavioral and societal components, such as social barriers to seeking treatment. We must have a transdisciplinary approach to address healthcare problems in an efficient manner.

- The financial perspective of microbiome-based businesses appears very healthy, with both public and private stakeholders invested to varying extents. If countries hope to keep up in this market, it is imperative that sufficient public funds be allocated and regulation keep up with innovation. Researchers were also encouraged to avail themselves of funds from industry, which is willing to invest in promising, practical technologies.

Going forward in this field, it will be important to keep up open, ongoing discussions between all of the stakeholders in the healthcare field in order to reap the benefits of promising microbiotic approaches.

FOOD FOR HEALTH

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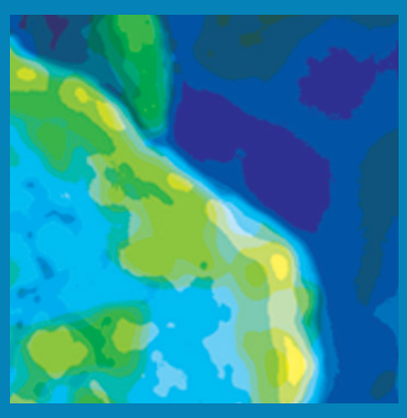

Better Foods for Better Health

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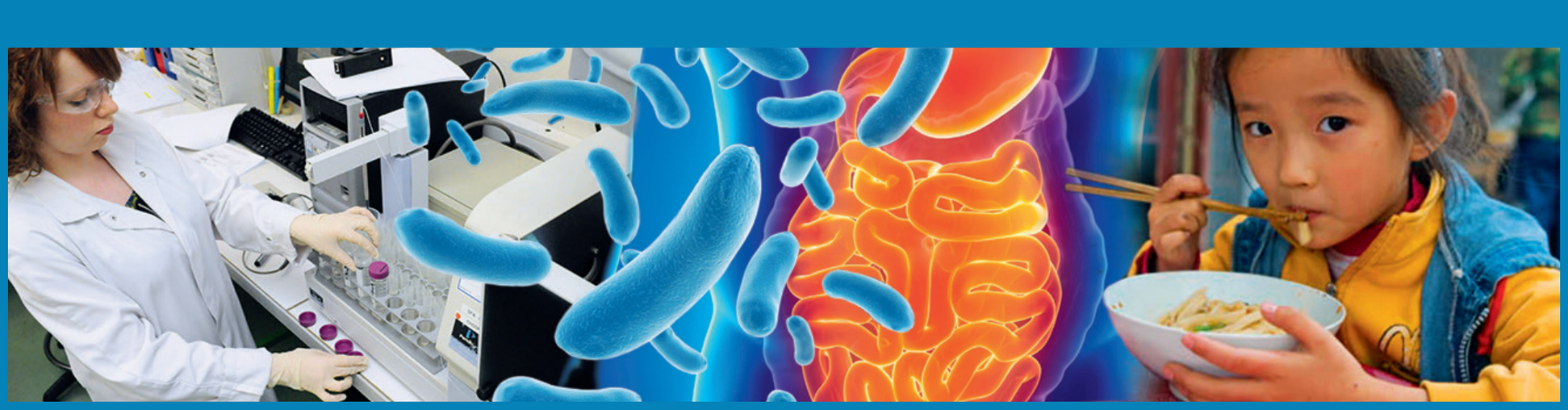
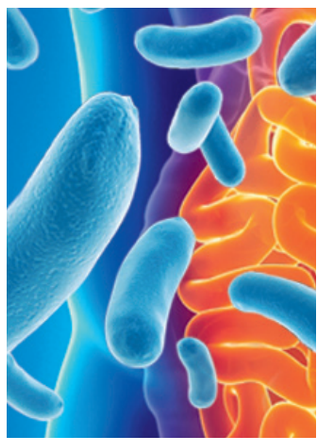


Introductory lecture: nutrition, microbiota and metabolic diseases



Alexander Moschen, M.D., Ph.D. Associate Professor, Medical University Innsbruck

Obesity is a worldwide epidemic, which has been rising since the 80s. Particularly alarming is that the prevalence is rising dramatically in children and adolescents, meaning the epidemic will continue to worsen.

Obesity is associated with numerous health conditions, including diabetes, hypertension and cardiovascular disease, and this translates into decreased life expectancy, poor quality of life and increasing healthcare costs.

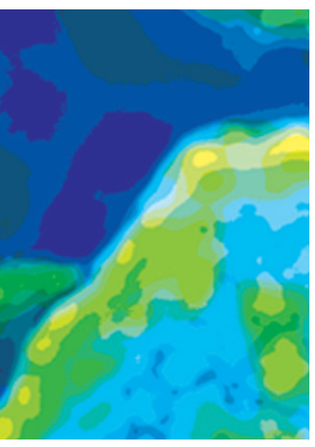
In trying to explain this epidemic, we should keep in mind that the human body evolved in a context for a struggle for food and against infection. With food shortage as the norm, our bodies evolved to include finely regulated mechanisms regulating body weight and energy balance. Today, however, we can obtain palatable, calorie-rich food without expending energy. In short, today our bodies are not suited for the time we're living in.

Obesity is associated with dysbiosis, or the disturbance of the mutualistic relation between host and microbiota. The microbiota and its metabolic machinery produce a myriad of metabolites that serve as important mediators in the complex interplay between diet, microbiota and host.

Mice studies have shown that the microbiota regulates energy balance mechanisms and that transferring microbiota can transfer the propensity for obesity, demonstrating the microbiota's key role in the condition. Furthermore, mice studies have shown that interactions between gut microbiota and food elements such as animal fat or dietary emulsifiers can promote metabolic inflammation, weight gain and insulin resistance.

Studies have also shown that food, notably broccoli and dietary fiber, can promote anti-inflammatory mechanisms. In sum, diet is the key environmental factor that modulates both gut microbiota and body weight.

By identifying and expanding our knowledge about the underlying mechanisms of the interplay of diet, immunity and the microbiome, we might develop novel food-based approaches to prevent or treat many major diseases.



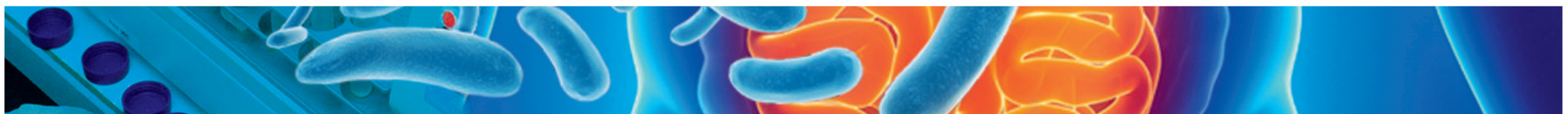
The gut microbiota and obesity: the role of “tall-tree species” and “guilds”

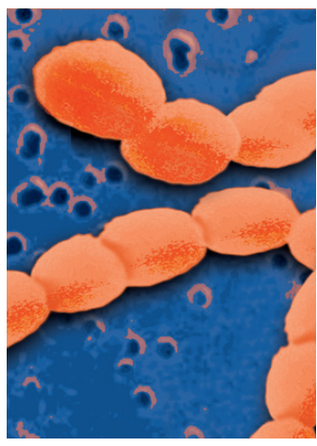
Liping Zhao, Professor of Microbiology and Associate dean for School of Life Sciences and Biotechnology, Shanghai Jiao Tong University Rutgers University

For a microbiologist interested in understanding the role of gut bacteria in diet-related obesity, critical questions include: which bacteria exist in the gut, what do they do there, what do they interact with and how? To answer these questions researchers must consider several important general principles of ecosystems. First, bacteria live as a population in an ecosystem and differences between bacteria make it important to do research at the bacteria strain level. Second, not all bacteria species are equal, some are more important in some hosts (ecosystems) than others and can be considered “tall tree species” or “keystone species”. Third, in any ecosystem — including the human gut — different species work together as a functional groups or a guilds, where some bacteria mutually exclude each other and others co-exist and even interact.

Given preliminary work in understanding that dysbiosis (disturbance or imbalance of gut microbiota) may work as a contributing factor in diet-related obesity and that a diet based on whole-grains, traditional Chinese medicinal foods and prebiotics (WTP diet), has led to significant alleviation of inflammation, obesity and insulin resistance, Zhao and his collaborators set out to find compelling evidence that the gut microbiota serves as a pivotal contributing factor in the development of diet-related obesity in both mice and humans.

In a hospitalized intervention trial with patients with Prader Willi Syndrome (a rare genetic disease that includes the most common form of human genetic obesity) and patients with simple obesity, a dietary intervention rich in non-digestible carbohydrates induced significant weight loss and structural changes of the gut microbiota together with reduction of serum antigen load and alleviation of inflammation. Further analysis suggested functional groups (guilds) and “tall-tree species” at play in morbidly obese children with either genetically predisposed or simple obesity. In summary, similar dietary modulation of gut microbiota may become a promising strategy to be integrated into the management of metabolic diseases upon further research in mouse models and humans.





The Equilibrium model of immunity

Gérard Eberl, Head of Microenvironment and Immunity Unit, Institut Pasteur

Immunity is a complex system of organs, tissues, cells and molecules that protect from disease. For some time a dualistic view of microbes has been accepted in which the immune system reacts to pathogenic microbes and tolerates mutualistic microbes. Given our proximity with so many microbes, how does the human immune system differentiate between "good" and "bad" microbes? It turns out the question is as difficult to resolve as differentiating between a "good" and "bad" person.

Eberl proposes a more modern view of immunology in which three if not four types of immune responses exist. Intracellular threats include, for example, viruses and tumors, and induce type 1 responses. Extracellular microbial threats include bacteria or fungi that induce type 3 responses. In the case of large threats, such as worms, the immune system resorts to type 2 (tissue repair) responses to reinforce tissues and prevent invasion. A fourth type of response aims at keeping the threat at a safe distance from sensitive tissues, such as the eye, which cannot tolerate inflammation.

These four types of immune responses stay in equilibrium in health, during which the four types of responses regulate each other. As a consequence, if one of these four responses is missing, the others deviate from equilibrium and may be exacerbated as a result and drive pathology. Eberl's lab has shown that activation of type 3 immunity occurs in the presence of intestinal symbiotic bacteria. In the absence of this activation, type 2 (pro-allergic) responses are exacerbated. This has been demonstrated as particularly important before and during weaning (the ending of breast feeding), where the activation of type 3 immunity by microbiota prevents the long term exacerbation of type 2 immune responses (e.g., allergy) into adulthood.

It is not only important what we eat, but when we eat it!

Eugene B. Chang, Martin Boyer Professor of Medicine, Knapp Center for Biomedical Discovery, University of Chicago

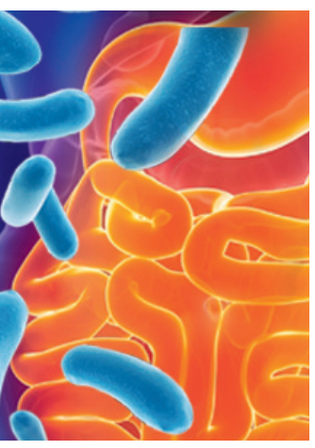
Obesity has become a global epidemic over a short period of time, pointing to the fact that it is not genetic drift but environmental factors that are largely responsible. A shift in the collective microbiome has also been proposed as a major factor,

given the well-established fact that microbes can regulate our metabolism. Also well established is the fact that circadian rhythms are essential to providing living things with the ability to react to external cues and adapt metabolically to changes in the environment.

Many disorders of circadian rhythms (e.g., sleep apnea, jet lag) are highly associated with obesity and type 2 diabetes. Chang's research demonstrates yet an additional component to this complex system: the gut microbiome is a key element in maintaining circadian rhythms (CR). There are genes that are induced by light (via the eye) that turn on our metabolic switch. Through a negative feedback loop, an oscillation of on and off metabolic signals occurs.

This work has found that mouse gut microbiota produce metabolites (specifically short-chain fatty acids) in daily patterns and these can influence the expression of circadian clock genes in the hypothalamus and liver. The results provide additional support for the idea that the gut microbiome is dynamic and that gut microbes are integral in CR in a way that in their absence normal oscillation cannot occur. This work also provides a scientific basis for many of the dietary recommendations that have been based on empirical observation, such as the importance of when, how much and what you eat, in additional to lifestyle changes.

In terms of future research, this finding strongly suggests that studies must be standardized in terms of being sensitive to the time when samples are taken.



The use of fecal microbiota transplantation: a potential treatment but above all a powerful search tool

Guido J. Bakker, M.D., Academisch Medisch Centrum, University of Amsterdam

Recently, gut microbiota has been identified as having an important role in disease and health and more specifically as a critical regulator of metabolism, playing a role in the development of obesity and progression to type 2 diabetes. Previous research has created a foundation of knowledge around bacterial translocation (microbiota crossing tissues and ultimately ending up in the bloodstream to cause inflammatory response) and functional changes (shifts in gut bacteria composition) that accompany metabolic disorders such as obesity and insulin resistance.

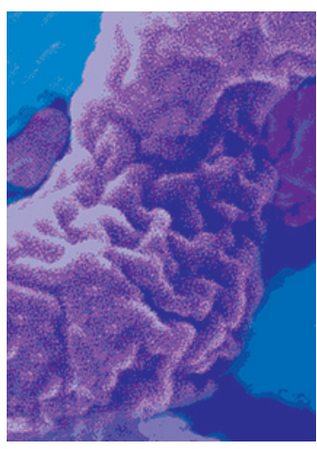
This new understanding further supports fecal microbiota transplantation (FMT) as a way to alter the gut microbiota composition in humans — specifically *Clostridium difficile*. This technique has been used since the 16th century by

Li Shizhen in the form of "yellow soup" and more recently by Dr. Eiseman in 1958 to cure patients of pseudomembraneous colitis by enemas containing feces from healthy colons and successfully replenishing good digestive bacteria.

A recent study has showed an improvement in peripheral and hepatic insulin resistance and microbial diversity in patients with metabolic syndrome after FMT from lean donors. It is suspected that enhanced microbial diversity may result in decreased bacterial translocation, which in turn improves inflammation and insulin sensitivity. In addition to the therapeutic potential of FMT in a range of diseases, the technique is also a powerful research tool as it creates extreme shifts in gut bacteria composition, making it easier to associate clinical outcomes with changes in the microbiome as opposed to other factors.

Therapy: nutritional intervention in metabolic diseases via modulation of gut microbiota

Ellen Blaak, Professor, Department of Human Biology, Maastricht University

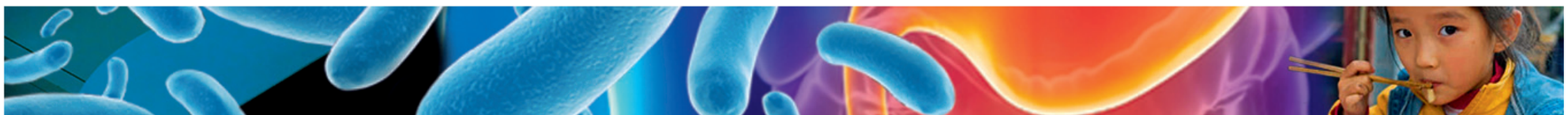


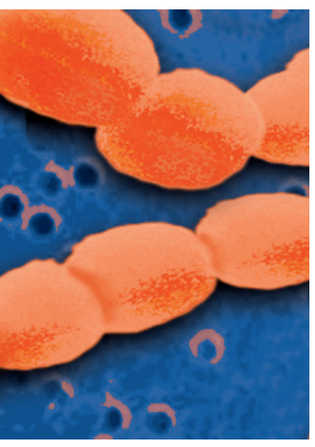
The prevalence of obesity and diabetes is increasing worldwide. Disturbances in fatty acid metabolism in adipose tissue, liver, skeletal muscle, gut and pancreas play an important role in the development of insulin resistance. Adipose tissue dysfunction, characterized by an altered capacity to store dietary lipids, may result in systemic lipid overflow. This overflow may be one of the drivers of peripheral insulin resistance through interference with insulin signaling.

A study conducted by Blaak and her team attempted to gain insight into the interaction of gut microbial levels, insulin sensitivity and energy levels. An intervention the team conducted studied microbial modulation with antibiotics, in which 56 subjects at high risk for diabetes were divided into three groups: placebo, amoxicillin and vancomycin. Subjects were studied before, during the one-week intervention and eight weeks afterward.

The most pronounced changes in microbial composition occurred in the vancomycin group, though this did not translate into effects on adipose tissue insulin sensitivity.

Additionally, the team studied the effect of adding gut-derived microbial products like short chain fatty acids to the colon, with the conclusion that the site of administration and fermentation was an important factor, with administration in the distal colon resulting in a marked increase in fat oxidation compared to the proximal colon.





Optimizing the host-microbiota partnership to tackle obesity: the EU MyNewGut project

Yolanda Sanz, Professor of Research, Institute of Agrochemistry and Food Technology, Spanish National Research Council; MyNewGut Project Coordinator

The human gut microbiome is known to affect our body's ability to extract energy from our diet and to influence brain functions. There is currently a lack of general understanding about the importance of the gut microbiome's role in health and well-being. Finding out more could lead to the development of dietary interventions allowing for more control if its functions, therefore preventing diet-related and behavioral disorders.

There are various approaches to explaining the obesity epidemic and its relation to the gut microbiota. One is that gut microbiota "causes" obesity, in that it increases the host's ability to extract and store energy. Studies have suggested that there may be key bacteria involved in human obesity, with "obesogenic" microbiota and "lean" microbiota. Further, a study by Gauffin *et al*. indicated that the introduction of *Bacteroides uniformis* reduces weight gain in obese mice.

Other approaches suggest that certain "obesogenic" (high-fat, high-sugar) diets favor the dominance of Gram-negative bacteria, leading to an obese phenotype. Meanwhile, changes in diet have been shown to be beneficial. A two-year intervention with the so-called Mediterranean diet has shown that it restores "beneficial" bacteria, with parallel improvements in metabolic markers.

The MyNewGut Project, which receives funding from the European Union's Seventh Framework Program, encompasses 30 partners in 15 EU and non-EU countries. It is researching how the human gut microbiota and its genome (microbiome) influence obesity, behavioral and lifestyle-related disorders and vice versa. The project is investigating diet-microbiota-host metabolic cross-talk to identify the bacteria and pathways involved in the metabolism of different nutrients and their health effects.

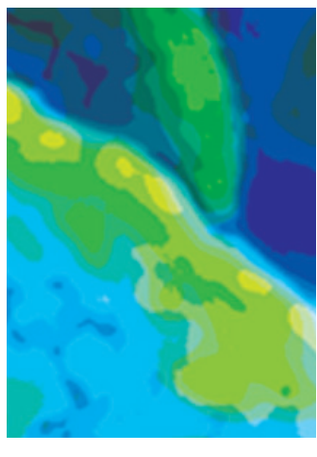
The specific objectives of the MyNewGut Project are to:

- identify the role of specific components of the gut microbiome in nutrient metabolism and in energy balance;
- identify microbiome-related features that predict obesity;
- identify the role of the gut microbiota and its metabolites in regulation of reward mechanisms and eating behavior;
- understand the influence of environmental factors on the gut microbiome in

pregnancy and the offspring and its impact on brain, immune system and metabolic development and health programming;

- develop new food and food ingredients that target the gut ecosystem, which could reduce the risk of metabolic and behavioral disorders.

The five-year project, now in its third year, is applying a multidisciplinary research approach in well-controlled human epidemiological and intervention studies and humanized mouse models. This information will be used for the design of innovative foods/ingredients and intervention strategies, targeting the gut ecosystem, to ultimately contribute to reducing the socioeconomic burden of diet-related disorders.

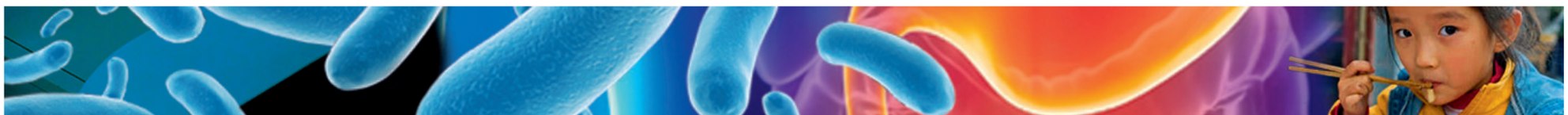


Technical and conceptual challenges linked to microbiota studies roundtable

Joël Dore, Director of Research INRA, French National Institute for Agricultural Research (INRA); Scientific Advisor, MaaT Pharma

A detailed understanding of human-microbe symbiosis requires a precise characterization of the human microbiome. We now have the ability to extract genetic information from microbiota and then to use shotgun sequencing for the assembly, annotation of genes and reconstruction of a reference gene catalogue. These techniques have already led to a number of observations. But in order for the microbiome to become a source of innovation, whether as a stratification tool, a source of novel drugs and targets, a target for modulation or a treatment of its own, the data generated in metagenome research must be optimally comparable. The IHMS has proposed standards for sample identification, collection and extraction as well as sequencing, complex data integration and biostatistical analysis to make this possible.

It should also be recognized that the research and health community is slowly moving to the recognition that humans are a mix of host and microbes with symbiosis and cross talk between them. Triggers, such as genetic predisposition, infection, diet, lifestyle and the environment push the balance towards either reversible imbalance of the gut microbiota (dysbiosis) or transient low-grade inflammation. New research suggests that by pushing the system beyond a point of resistance, you may actually enter into an alternative stable pathological state in which sustained low-grade overt inflammation signals sustain alteration of gut microbiota and this vicious cycle may be underlying many of the pathologies discussed in this forum. Today's medicine only addresses the symptoms and the rest of the system should be considered in order to make progress.



Scott Parkinson, Head of Gastrointestinal Health and Microbiome, Nestlé Institute of Health Sciences

The field is currently at a crossroads where it has produced considerable material in describing microbiome composition, but has much to learn in understanding what the composition means in terms of functionality and applications. For each current and future research observation, conclusion, technique and potential therapy we must ask ourselves the following questions:

- Where are we (are we accurate, precise, both)?
- When is it important (descriptive or functional)?
- What do we need (what limitations or bias can we work with)?
- Why do we need it (what application)?
- How should it be done (standards)?

These are the questions we must ask ourselves in order to take the knowledge we have gathered on the microbiome and extract value from it.

Françoise Le Vacon, Head of Biofortis Research, Mérieux NutriSciences

The Biofortis business unit of Mérieux NutriSciences offers research services for innovation in nutrition, microbiota and health helping translate academic knowledge and scientific evidence on a number of chronic diseases into application from study design to biological analysis to data management, etc.

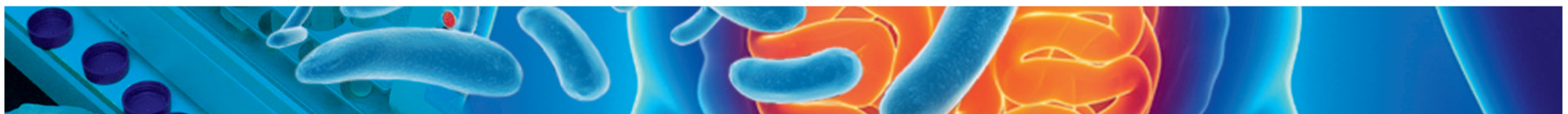
It is well known that bias in each step of the process of microbiota testing (including sampling, shipment and storage, sample preparation, sequencing, quality control and data analysis integration) makes it very difficult to perform meta-analysis. Recommendations from the Human Biome Project (HMP) and IHMS are crucial, but more studies are needed to ease conditions, sampling and others steps.

It is also well established that dysbiosis is involved in many pathologies. It is possible now to go so far as to define "normal" values for dysbiosis as biological parameters?

These are two technical challenges that industry faces and where academia can help contribute to consensus.

Bruno Pot, Director of Business Development, Applied Maths

Challenges in the field of bioinformatics can be described as falling under one of three categories: reliability issues, complexity issues and practical hurdles. The quality of a bioinformatics analysis will depend the quality of sample preparation

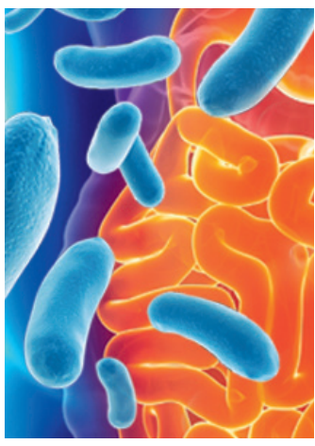


(e.g. soil, stool, sputum, swaps, blood), wet lab protocols (DNA preparation, library preparation currently very unstandardized) and sequencing equipment (quality, read length, sequencing depth).

Bioinformatics analysis will also depend on the sample origin (and its complexity) and on the availably of sufficiently "complete" and "reliable" reference databases for proper identification of all relevant microorganisms and functionalities. Such databases on not yet available, for example, for full-blown metagenomics analysis. Validating results of analysis using bioinformatics will require inter- and intra-run controls.

Another obstacle in the field of bioinformatics is the amount of data generated by current research. High-throughput data processing will imply some mind shifts. These mind shifts will happen on the hardware level where the use of cloud technology will need to be accepted despite potential confidentiality issues, extended memory may introduce higher costs, and faster data transfer must be used. On the software level, the research community must reach consensus on advanced (fast) algorithms, read analysis strategies and advanced visualization tools. Finally more user-friendly applications must be developed shifting dependency on specialized informaticians to for non-specialized research users.

The viscous cycle of undernutrition: towards a microbial basis of therapy for undernourished children



G. Balakrish Nair, Communicable Diseases Department, South East Asia Regional Office, World Health Organization - New Delhi

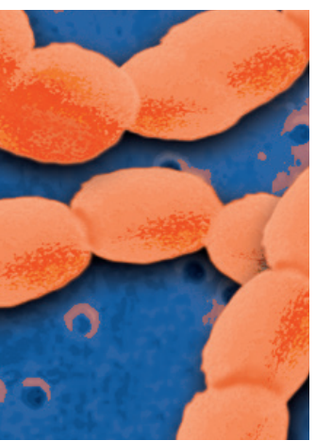
Undernutrition is defined as the outcome of inadequate dietary intake as a result of a variety of factors such as insufficient food intake, impaired immune response, repeated infections and impaired regulation in gut lining. It is a viscous cycle in which each of the conditions worsen and perpetuate each other as a result of impaired innate and adaptive immune responses.

The global hunger map as of 2015 showed Africa and much of Southern Asia bearing much of this disease that affects 793 million people worldwide. A large percentage of those suffering are children, especially in India. Several studies in these areas comparing the intestinal microbiota of children with severe acute malnutrition (SAM) to healthy children have helped extend the understanding of the basis of malnutrition beyond simple nutrition deprivation.

To further understand the relationship between diet, gut microbiota, and health and its involvement in SAM, Nair and colleagues conducted a recent study in West Bengal, India, examining the metagenomes of 20 children with varying nutritional status. The study findings suggest interrelationships between the pattern of gut microbiome and the nutritional status of children. Several key messages from the study include:

- Undernutrition is associated with lower diversity of the gut microbiota.
- SAM was associated with a more prolonged delay in gut microbiota maturation that was only partially corrected by food interventions.
- The gut microbiota under nutritional deprivation conditions appears to develop towards a "disease-promoting microbiota".
- The promotion of a beneficial microbiota by certain diets resulted in marked changes in the microbiota, with prominent increase in certain species.
- Antibiotic therapy might modify the microbiota and affect the potential for energy extraction.

Though the cause of the interrelationships between the pattern of gut microbiome and the nutritional status of children requires further exploration through additional functional studies in a larger population of children, results of this study point to key microbial groups that may one day be used for formulating a microbial basis of therapy for SAM in children in India and beyond.



The potential for prebiotics and probiotics in the treatment of malnutrition and wasting in cancer patients

Nathalie Delzenne, Professor, Faculté de pharmacie et des sciences biomédicales (FASB), Louvain Drug Research Institute (LDRI), Université Catholique de Louvain

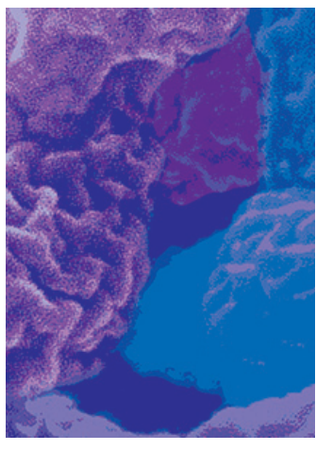
When investigating of the role of gut microbiota in cancer-related malnutrition, several points must be kept in mind: (1) the gut microbiota is an internal organ we feed every day; its significant size has been determined but there are still many details to be determined regarding its composition; (2) gut microbiota has two faces — both positive and negative roles that must be kept balanced and "at bay"; and (3) dysbiosis may be linked to changes in the gut lining.

Cancer-related cachexia is defined as the loss of muscle and fat mass with consequences on life span and quality of life. Recent studies suggest that cachexia is not only due to radiotherapy, chemotherapy or appetite loss but also

inflammation. Results of Delzenne's research demonstrate that a drop in bacterial diversity and specific lactobacilli as well as a bloom in *Enterobacteriaceae* are related to changes in gut barrier function, muscle wasting and inflammation in several mouse models.

Further clinical studies are planned to investigate a probiotic (live bacteria and yeasts that are "good" for health) and prebiotic (nondigestible carbohydrates that act as food for probiotics) approaches. Better knowledge of a potential therapy to improve the nutritional status of cancer patients can also have important overall implications by prolonging opportunities for radiotherapy and/or chemotherapy.

The role of antibiotics in malnutrition: prevention and treatment



Andrew Prendergast, Senior Lecturer in Paediatric Infection and Immunity, Queen Mary, University of London; Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe

There is an urgent need for new approaches to malnutrition to sustain gains in child survival of the previous 100 years with sanitation, vaccines, etc. Although malnutrition does not appear as such in global health mortality statistics, it is underlies 45% of deaths due to infectious diseases. There are two major presentations of undernutrition: stunting and wasting. Stunting (low height-for-age) is often a hidden presentation of undernutrition (children may look healthy to both parents and clinicians) occurring in the first 1000 days of life with no recovery thereafter. The challenge of stunting is that it is cyclical processes where stunted girls become short mothers and have low birth weight babies who go on to become stunted children making it difficult to know where to intervene to stop this cycle. The problem with both types of malnutrition is that they cannot be "fixed" with food alone, as demonstrated by an extensive review of intervention programs. This review concluded that no nutrition program or intervention trial has ever been shown to normalize linear growth among children in developing countries.

It is well established that infections contribute to malnutrition. Repeated infections impair normal growth — so much so that malnutrition is sometimes considered an enteric infectious disease with effects on long-term child development. More recently, it has become obvious that clinically apparent infections (such as diarrhea) represent just a small percentage of the burden of infection that affects people in developing countries. Finally, research has also demonstrated that feeding interventions can partially restore the maturity of the gut microbiome, but only

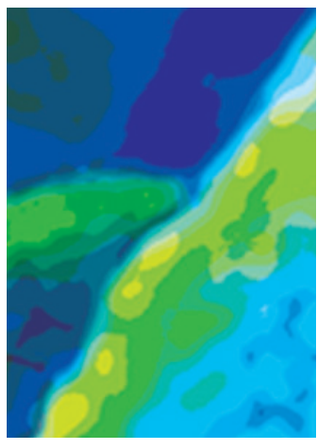
temporarily, as when interventions end the gut microbiome maturity declines again. There is clearly a complex cycle of pathology underlying malnutrition and intestinal pathogens likely to be key in this cycle whereby epithelial breaches lead to malnutrition, dysbiosis and inflammation, which only cause more epithelial breaches and may also lead to reduced tissue accretion, anorexia and sepsis.

It has been known for decades that antibiotics improve growth in animals and they are used in great quantity in this industry. And we know now that antibiotics improve growth in humans. A meta-analysis of existing randomized trials performed over the last 50 years in which antibiotics were introduced and growth was measured (at least as a secondary outcome), and despite heterogeneity in the studies, an overall affect was observed of an average 30g of weight gain per month in prepubescent children as compared to placebo. This data suggest that antibiotics may have a role in preventing malnutrition. Despite this mounting evidence, questions remain about which groups to target, when in the life-cycle to intervene, what specific agents to use and whether risks outweigh the benefits in terms of cost, side effects and public health consequences, such as antimicrobial resistance and impact on microbiota.

In terms of antibiotics as a treatment for malnutrition, one must again consider that malnourished children most often die from common infections. This risk of mortality lies across the nutritional spectrum. Children with severe stunting (who may appear less unstable than children with wasting) actually have greater risk of mortality than children with moderate wasting. Given that one in three children are stunted in developed countries, this represents a huge potential increased burden of death due to infection. Unfortunately, the immunodeficiency of malnutrition is still largely under-researched, thus knowledge of how to intervene is lacking. Although infections are common in malnourished children and it is safe to say that when they are admitted into a hospital they are likely to have an infection, it is hard to diagnose clinically. The other complication is that organisms isolated from children in hospital are often resistant to the antibiotics that are currently used first line for children with malnutrition (for example, Cotrimoxizol is still recommended in WHO guidelines), suggesting that our current regimens may not be the most effective, especially in developing settings.

There is no doubt that antibiotics are essential for children who are hospitalized for severe acute malnutrition (SAM), but in the last decade we have moved towards community management of SAM, during which children are fed high-nutrient diets (e.g., Plumpy'Nut). What is the role of antibiotics in this new approach to SAM management? Several studies are currently addressing this question in uncomplicated SAM, and some have demonstrated significant recovery

in clinical groups treated with antibiotics while others studies have not. More studies are required to understand the impact of different settings and different regimens on the role of antibiotics in malnutrition.



Targeting muscle in malnutrition-related disorders

Johan de Vogel-van den Bosch, Senior Scientist, Danone Nutricia Research

There is both a hidden and visible problem of malnutrition, which encompasses undernutrition and overnutrition. About 29% of the world population is obese, which is visible in the streets. Undernutrition, largely a problem of the elderly, on the other hand, is hidden in hospitals and homecare.

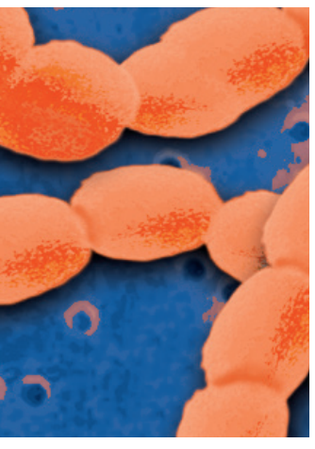
An estimated 33 million people in Europe are undernourished. Hospital stays for this population is 1.4 days longer than for the well nourished, with the geriatric population having the highest percentage of undernutrition among hospitalized patients, at 37%, according to one study.

Undernutrition is nevertheless a neglected issue, with healthcare professionals exhibiting a lack of awareness. There is therefore a need for the education of healthcare workers.

Use of medical nutrition, which occupies a place between food and pharmaceuticals, contributes to improved effectiveness of medicine, strengthened physiological processes, reduced risk of complications, positive influence on recovery and avoidance of specific food components. It can be useful in cases of cancer, surgery and inborn errors of metabolism (PKU). In a 2003 meta-analysis by Stratton *et al*., oral nutritional supplements reduced mortality in hospitalized liver disease, orthopedic and surgical patients, as well as older people by 24% *versus* the control, and complications by 56%.

A 2015 multicenter double-blind study of the effect of vitamin D and leucine-enriched whey protein supplementation on older people by Bauer *et al.* showed that muscle mass and lower extremity function improved significantly. Another study showed that such supplementation preserved muscle mass during a weight-loss regime in obese older adults. These studies suggest that targeted nutritional supplementation might benefit geriatric patients.

These represent promising approaches to improved patient outcome and quality of life through management of nutritional deficiencies and the preservation of muscle mass.



Microbiota and *Lactobacillus plantarum* strains maintain growth of infant mice during chronic undernutrition by interacting with the hormonal somatotropic axis activity

François Leulier, Research Group Director, Institut de Génomique Fonctionnelle de Lyon, Ecole Normale Supérieure de Lyon

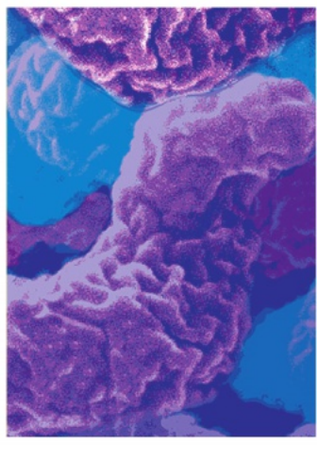
Leulier presented his collaborations investigating how the microbiome environment shapes the nutritional input and thus host physiology using several host models. Using the "pre-pre-clinical" model of *Drosophila melanogaster* it was demonstrated that strains of *Lactobacillus plantarum* promote larval growth by modulating TOR (target of rapamycin, a signaling pathway controlling metabolism and lifespan) and hormonal growth signaling pathways. This work provided an ideal duo for study of host-microbe interactions.

When translated and transferred to a mouse model, it was observed that the microbiota of infant mice sustain both weight gain and longitudinal growth when mice are fed a standard laboratory mouse diet or a nutritionally depleted diet. Leulier and his collaborators found that the intestinal microbiota interacts with the somatotropic hormone axis to drive systemic growth. Using monocolonized mouse models, they showed that strains of *Lactobacillus plantarum* promoted juvenile growth in a strain-dependent manner that recapitulated the microbiota's effect on growth and the somatotropic axis. These findings show that the host's microbiota supports juvenile growth. Moreover, they discovered this lactobacilli strain buffered the adverse effects of chronic undernutrition on the postnatal growth of germ-free mice.

Together these studies suggest that specific beneficial microbes should be further explored in preclinical and clinical studies to investigate the potential of this *Lactobacillus* strain in promoting healthy growth in malnourished conventional animals and when used in tandem with nutritional intervention in children at risk of chronic undernutrtion.

Evidence-based solutions proposed by the Global Alliance for Improved Nutrition (GAIN) to address malnutrition

Greg Garrett, Director of Food Fortification, The Global Alliance for Improved Nutrition



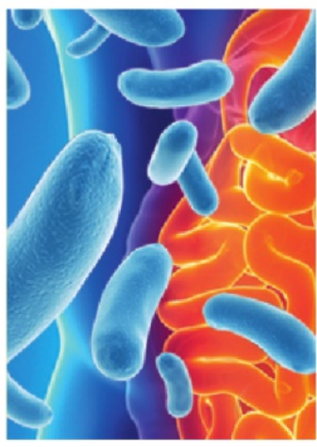
The GAIN foundation aims to implement programs to reach the estimated 795 million hungry people worldwide (source: State of Food Insecurity [SOFI]) with programs that provide more nutritious foods. With poor nutrition as the underlying cause of death for an estimated 45% of all child deaths, and 160 million children worldwide stunted with lifelong effects on their health, education and ability to earn a living, GAIN has its work cut out for them.

The foundation supports four types of interventional program to address hunger (and hidden hunger such as stunting), reduce and eliminate micronutrient deficiencies and improve nutrition. These include (1) exclusive breastfeeding up to six months of age with complementary foods from six months on, (2) improving dietary diversity by working with local business, e.g., agribusiness, (3) vitamin and mineral supplementation and (4) food fortification such as iodine, iron, folic acid and vitamin A fortification.

Evidence-based solutions are having an impact. However, there is still much potential in rolling out these interventions more efficiently and in unison to help end malnutrition more quickly. All programs include a key element of education to combat the mistaken notion that fortified foods replace a balanced diet.

The social and ethical issues impacting caregivers' access to treatment for severe acute malnutrition

Elizabeth Fox, Ph.D. candidate, Division of Nutritional Sciences, Cornell University



About 11% of children under the age of five are affected by acute malnutrition, but only 15% of the affected children have access to treatment through community-based management of acute malnutrition (CMAM). This represents a huge gap in implementation.

To design CMAM programs, often a technical frame is used that takes into account such considerations as cause and effect, dose and response, and efficacy. However, different analytical frames can yield different insights. Here Fox focused on a social

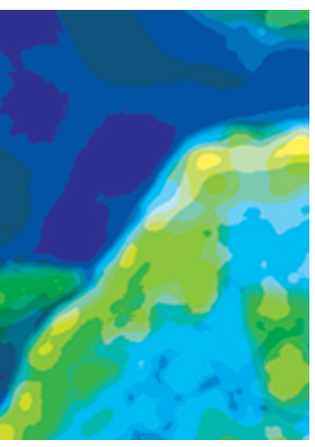
and normative frame, which considers fairness, rights, beneficence, values, consent and participation.

If programs focus on the survival of a malnourished child, for example, they may not also consider the mother's or siblings' health. What might keep a mother from participating in a program? What are the tradeoffs we are asking people to make, and what is the value of these tradeoffs for those people?

A 2015 study in Kenya showed that the main barrier to accessing child health services was that caregivers did not have enough time. It might be harvest time, or the caregiver might also be charged with taking care of elderly family members, for example. This was followed by social barriers. Shame was greatest among caregivers of children with severe acute malnutrition; there was a stigma associated with going to a clinic because mothers felt this showed they were not doing a good job.

Additionally, problems may arise when the ethical frame of a health center is not aligned with the ethical frame of caregivers. Healthcare workers may wrongly assume that people are rational, that social systems are adaptable and that "giving the answer" is enough.

Instead, health programs should be designed to account for the ethical frame of the people it to treat by, for example, looking for positive behaviors and strengths in the community that can be built upon. Programs should take into account caregivers' multiple and often competing goals, and acknowledge the social complexity of nutrition and health programs.



Gut microbes and pediatric asthma

Marie-Claire Arrieta, Postdoctoral Fellow, University of British Columbia

Over the past 50 years there has been an explosive increase in the prevalence of asthma, during which time there has been a shift in our understanding of the disease. The "hygiene hypothesis" suggests that children's environment is too clean in developed countries, so there is a lack of early-life exposure to microbes. Children therefore develop an over-responsive immune system.

It is interesting to note that asthma is not increasing at the same rate in developing countries, highlighting the influence of environmental factors. Similarly, children born and raised on farms have a decreased risk of developing asthma, as do breastfed children. Children born by C section, on the other hand, who thereby bypass a site rich in microbes, have an increased risk of developing asthma, as do

children whose mothers used antibiotics during pregnancy and who themselves took antibiotics during the first year of life.

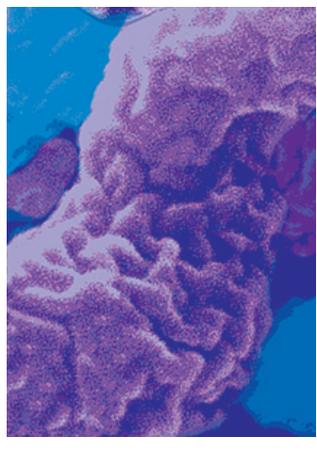
Recent studies in mice have identified a critical window early in life during which the effects of gut microbial changes (dysbiosis) are most influential in immune development and asthma. Shifts in the gut microbiome and in gut microbe-derived compounds, including short-chain fatty acids (SCFA), have been implicated in a number of diseases, including asthma.

However, current research has yet to establish whether these changes precede asthma and if they are involved in human asthma. Arrieta's lab compared the gut microbiota of children enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) Study. This work provided evidence that infants at risk of active asthma at school age exhibit gut microbial dysbiosis during the first 100 days of life, which is no longer evident at one year of age. The relative abundance of four bacterial genera was strikingly low in infants who developed atopy and wheezing. This early-infancy dysbiosis was associated with reduced production of SCFA acetate in the gut and dysregulation of enterohepatic metabolites.

Partnering with another team, the lab performed a similar analysis in Ecuador, which suggested that different bacterial species are associated with asthma risk in three-month-old Ecuadoran babies. Among other conclusions, the lab's work suggests that the first 100 days of life are critical for intervention, and that microbial alterations depend on the geographic region.

Gut microbial metabolism of plant-food bioactives: impact on dietary exposure and cancer risk

Johanna Lampe, Associate Division Director, Public Health Sciences Division, Fred Hutchinson Cancer Research Center



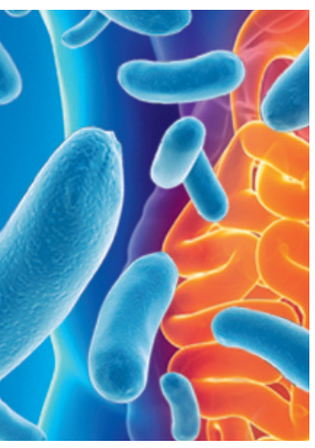
Several classes of phytochemicals — glucosinolates, isoflavones and lignans — have been extensively studied for their potential role in cancer prevention. Cruciferous vegetable intake, for example, shows a consistent association with lower risk of lung, colorectal, breast, prostate and pancreatic cancer.

Isothiocyanates and indoles from glucosinolates in cruciferous vegetables have been found to be chemopreventive in animal models, decrease inflammation and oxidative stress, induce cell differentiation and apoptosis and improve carcinogen metabolizing capacity.

Many of the bioactives in plant foods associated with lower cancer risk are metabolized by gut microbes.

In the context of host microbiome-diet interactions, a major focus of Lampe's research focus has been the investigation of how biomarkers of cancer susceptibility are modulated by constituents of diet.

Using dietary interventions, her work has shown that differences in gut microbial metabolism can substantially affect circulating levels of the bioactive metabolites and biomarkers of cancer risk. Generally, her work suggests that the gut microbial community plays an important role in exposure to bioactives from plant foods and therefore possibly cancer risk. Gut microbes modify a variety of dietary constituents to bioactive compounds not found in the diet. Understanding the impact of diet-microbial community interactions on cancer risk may help guide future prevention strategies.



Impact of diet upon intestinal microbiota and microbial metabolites

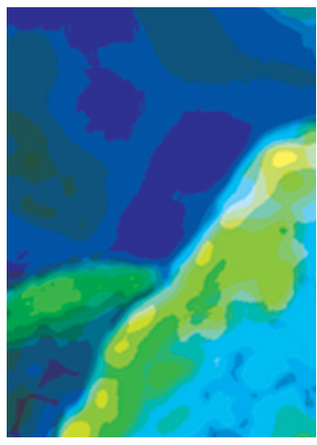
Harry Flint, Professor, Rowett Institute of Nutrition and Health, University of Aberdeen

Scientific evidence has shown that both the species composition of our gut microbiota and its metabolic outputs are influenced by diet. *In vitro* studies carried out by Flint's lab (Chung *et al*., 2016), where pH and substrate supply can be precisely controlled, suggest that the modulation of human gut microbiota by isolated dietary fibers (prebiotics) is highly species-specific. This reflects the fact that many species (perhaps especially Firmicutes) are highly specialized in their substrate utilization.

In vivo, comparing the effect of various diets, Flint's group found that certain bacterial species are promoted by nondigestible carbohydrates. Yet individual variations still outweighed dietary change in influencing the bacterial community. Nevertheless, very extreme dietary changes — a 70% fat-based diet, for example — can lead to tremendous shifts (David LA *et al*., 2014), changing practically the whole human gut bacterial community.

The *in vivo* work of Flint's lab has further suggested the presence of "keystone species", or to borrow from George Orwell, "some species are more equal than others". They have proposed *Ruminococcus bromii* as such a keystone species, as it appeared that in its absence, starch is not fully fermented in the large intestine and therefore that potential energy is not available to the community.

Broadening his discussion, Flint noted that many metabolites have a beneficial effect on health. New areas of study such as metagenomics, genomics and microbiology have allowed for the identification of bacterial species with specific metabolites. Using this information, Flint's team has devised functional bacterial groups (similar to Liping Zhao's "guilds") to build a theoretical model to help predict some of the outcomes of their *in vitro* and *in vivo* work.



Gut microbes, food and cardiovascular disease

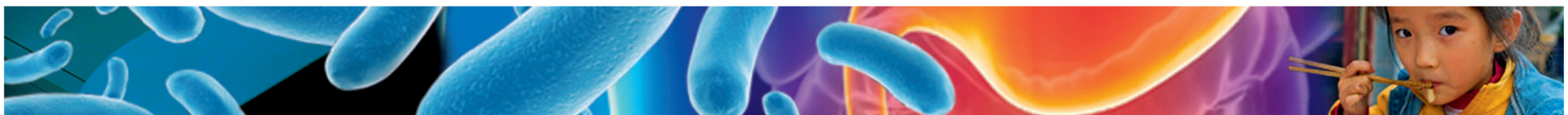
Federico Eugenio Rey, Assistant Professor, Department of Bacteriology, University of Wisconsin – Madison

Even if you served the same meal to a group of people, each individual person would extract different amounts of nutrients from each food. Microbial differences between individuals modulate the nutrients we get from the food we consume. But how does this ultimately affect our health?

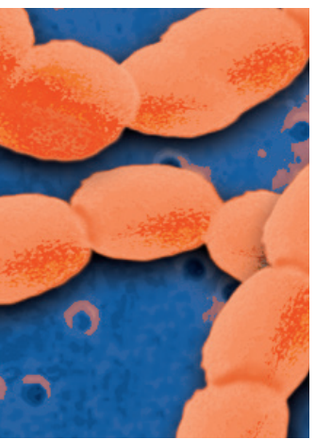
The central focus of Rey's lab is the understanding of how interpersonal or disease-associated differences in gut microbial composition and thus metabolism impact the nutritional value of food. Identifying biomarkers for these processes will help nutritionists formulate dietary recommendations that are matched by the metabolic potential of a person's gut microbiota.

To do this Rey and his colleagues used mouse models with defined human gut microbial communities, housed in controlled environments and fed diets of defined compositions. They employed cutting-edge research techniques to study how microbes metabolize nutrients, how they interact with each other as a function of diet and host genotype and how these interactions impact health.

Rey demonstrates a proposed framework for diet-microbe interaction and its impact on health using the example of choline. Choline, an essential nutrient for human health, was recently brought to the research spotlight after studies published in 2013 indicated that high levels of TMAO (trimethylamine-oxide, a metabolite of choline) in the blood are associated with an increased risk of major adverse cardiovascular events. TMA (trimethylamine) is a product of the metabolism of dietary choline by intestinal bacteria. Most TMA formed in the intestinal tract is later oxidized and excreted as trimethylamine oxide (TMAO). TMAO has since been linked to many other chronic diseases. Rey's research results highlight the specific multiple factors, i.e., microbial, host and environmental factors, that modulate metabolism of choline to TMAO.



Future studies aimed at understanding how to manipulate the representation of choline-consuming, TMA-producing bacteria in the gut microbiota or at identifying species that influence conversion of TMA to TMAO might lead to new interventions for preventing or treating atherosclerosis and/or choline deficiency-associated diseases. In other words, you may be able to modify your metabolism of choline depending on what you eat with it.



Industry Roundtable

Harro Timmerman, Principal Scientist – Metagenomics, Nizo Food Research

Nizo Food Research is an independent private contract research company, doing work for infant nutrition, food, personal care and pharmaceutical products. The company has conducted research on host-microbe interactions in the gastrointestinal tract, oral cavity, upper respiratory tract and the skin.

Two clinical studies Timmerman participated in looked at iron supplementation and fecal microbiota composition in anemic Kenyan infants, which suggested that iron fortification adversely affects the gut microbiome, increasing pathogen abundance and causing intestinal inflammation. The next research question Timmerman would like to answer is, Can we prevent this phenomena by making iron more available to the host with prebiotics?

Timmerman discussed the widespread use of fecal samples for studies of the microbiome, which he noted reflects the inaccessibility of the small intestine. His lab joined forces with Medimetrics to develop the IntelliCap, a noninvasive way to sample and map content from the small intestine. The cap is swallowed and makes its way through the digestive tract. The remote-controlled capsule is able to "freeze" each sample to avoid deterioration as it moves through the system, measuring its transit time, pH levels and temperature.

A current study he is participating in compares a high-protein diet with a high-carbohydrate diet and their effect on the microbiome. Preliminary results indicate differences in both fecal and small intestinal samples.

He sees a current challenge in how to prove a microbiome-mediated health benefit in humans. His work on strep pneumonia colonization of the nose suggests there may be certain "cornerstone" species that protect against such colonization. These may be the next-generation probiotics, he suggests.

Douwina Bosscher, Global Nutrition Leader, Cargill Global Food Ingredients and Systems Research

Cargill is a multinational organization, founded in 1865, with 142,000 employees in 65 countries, and $130 billion in annual revenue. There are 1,300 R&D specialists around the globe; the main research center is in Brussels, with others in Minneapolis, Los Angeles and Asia Pacific. The company supports such EU-funded projects as MyNewGut and Metacardis.

Bosscher discussed a number of challenges that industry faces as regulatory bodies enact more stringent criteria for health and function claims while the science and technology of microbiota research is rapidly evolving:

- current uncertainty about previous research as understanding evolves;
- complexity as different disciplines interface;
- new scientific concepts quickly become outdated.

Therefore the risk of investment is high. Risks include:

- uncertainty of valorizing research, as there are issues of intellectual property and ownership of big data;
- health claims criteria differ across the globe, requiring different studies;
- data deposition on public databases raises the question of how to conserve the competitiveness of the investment;
- scientific substantiation becomes a large R&D investment, heavily impacting product cost.

She also noted the need the need for scientific consensus on a number of issues:

- standardization of protocols;
- which animal models to use;
- standardization of clinical trials;
- consensus on gut biomarkers.

Patrice Malard, Chief Technology Officer, Biostime Inc.

Biostime, a 15-year-old China-based company, focuses on pediatric nutrition and care. It is number one for infant formula in China — a market where 20 million babies are born annually — with 728 regional distributors and 40,684 points of sale.

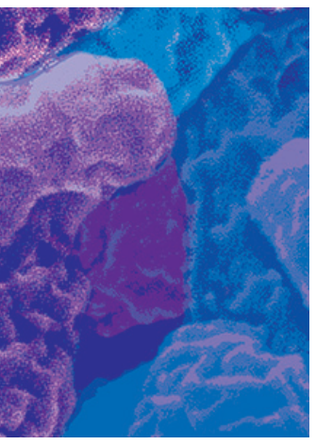
Other pertinent factors in the Chinese market include the fact that there is both a high percentage of C-sections and low level of breastfeeding, both of which have an effect on infant immunity. These factors are among those considered when the company manufactures its infant formulas for this population.

In terms of product development, the company has an interest in probiotics, both for gut flora and for breast milk. Biostime is also investigating human-milk oligosaccharides, which have a variety of beneficial benefits for infants, including resistance to disease. However, as not all women produce them equally, this area could be a target for personalized nutrition.

Keith Garleb, Director, R&D Programs, Abbott Nutrition

Abbott Nutrition is the largest of four divisions of Abbott, a global pharmaceutical company. It has pediatric products, such as infant formula; adult products, such as supplemental nutrition (its best-known product is Ensure), disease-specific products (diabetes, cancer, renal disease); and sports and fitness performance.

He encouraged scientist to seek investment from industry if they were pursuing research that could lead to an advance in the health and well-being of the patient population. As the emphasis turns more and more toward prevention in healthcare, he feels that nutrition will increasingly become an area for investment.



Regulatory affairs roundtable

Stephanie Bodenbach, Policy Officer, Unit Nutrition and Nutrition Related Aspects of Labeling, DG Health and Food Safety EU

In the European Union, Member States had much authority over nutrition and health. But today, health status as it relates to nutrition is a public health issue. The European Commission's authority in this area, however, remains restricted to soft strategies and actions that involve the voluntary participation of member states, NGOs, academics, consumer groups and other stakeholders. The new Dutch EU presidency has cited improvement of food in the EU as a priority.

There is another side to nutrition, however, over which the European Commission has more authority — and that is harmonization of nutrition and health claims. An independent European Food Safety Authority (EFSA) was put in place to provide scientific advice and communication on risks associated with food — specifically foods with nutritional and health claims submitted for authorization.

There are many current applications, although none have received authorization to date. Boenbach emphasized that more work was needed for applicants to understand what data and what format EFSA is looking for when evaluating applications.

There is much criticism from applicants about its stringent approach. Many applicants (companies) feel Europe has invested much in early science on the microbiota and is in danger of not having an adapted regulatory system to bear the fruits of these labors. Regulatory standards are seen as too stringent, outdated, not transparent and inconsistent. There are some other applicants, however, who appreciate this strict approach, which avoids the risk of approving applications with weak claims.

Carlos Eduardo Gouvea, Executive President, Associação Brasileira da Indústria de Alimentos para Fins Especiais e Congêneres (ABIAD)

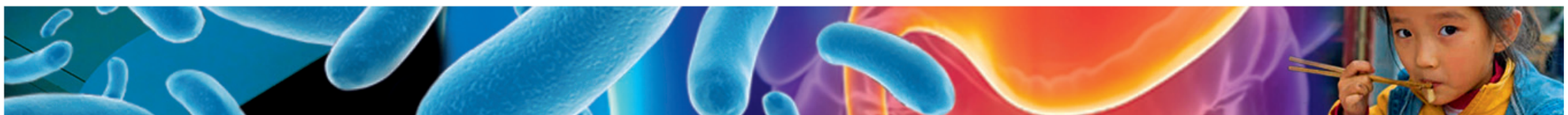
ABIAD is the umbrella association for special-purpose food products in Brazil. It was created to defend the interests of diet products, which were originally going to be considered as drugs instead of food products, potentially making the process for their approval much longer and more tedious than necessary. The organization has become more aware of global recommendations in nutrition as the Brazilian population is changing its eating habits and nutrition-related health states are becoming a major health issue in Brazil. Today the association's mission is to advocate for legislation for different categories of special foods (e.g., infant nutrition, clinical nutrition, sports nutrition, diet foods), creating and fostering markets for innovative products, some of which are imported from outside of Brazil.

The national authority for the approval and supervision of food (as well as cosmetics, tobacco, pharmaceuticals, medical devices, etc.) in Brazil is ANVISA, the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária). It is active in regulating, controlling and inspecting products on the market as well as creating public and industry policy on nutrition.

Products in Brazil fall into two categories of approval: "notification" and "registration".

Some products, such as sports nutrition and vitamin and mineral supplements, require only "notification" — communication on the beginning of production or import of a product.

Other products (such as food with health/functional claims, novel foods, infant food, enteral nutrition) have mandatory "registration" — a thorough approval process for which ANVISA has published guidelines for companies. Although legislation mandates 60 days for the process, in reality the process for this authorization is 1 to 1.5 years. A new protocol is currently being put forward by ANVISA for the review of probiotics.



Manfred Ruthsatz, Global Head Regulatory Advocacy, Nestlé Health Science

New, disruptive technologies (such as -omics, microbiome, next-generation sequencing, 3D printing, nanotechnologies) are allowing for a better understanding of genetics, nutrition, medical treatment and lifestyle interconnections. As with many healthcare paradigm shifts, regulation has not yet caught up with new technologies.

The current regulatory framework sufficiently requires products

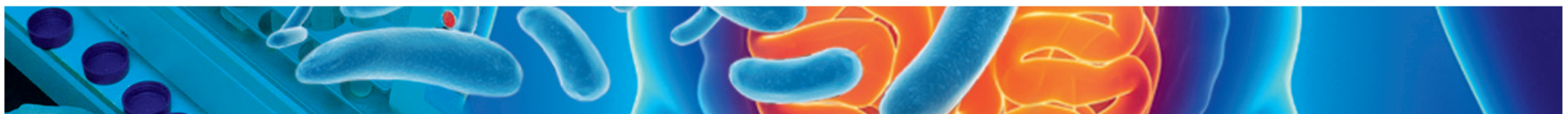
- to meet "intended use" and to be safe for this intended use;
- to not mislead the consumer/patient;
- to be defined as a drug if it is presented as treating or preventing disease.

Ruthsatz argues, however, that the current regulatory landscape is inadequate in that it is missing the role of decomplexifying the process and incentivizing the development of compliant food or products for patients in need. An ideal regulatory framework would also facilitate bringing (food) products to market in a timely manner, define acceptable levels of "uncertainty" in evidence and consider nutrition as a part of disease prevention, therapy and holistic approaches.

The new framework should include bridges in the food-to-drug continuum between regulated product categories to address these disruptive innovations, create incentives including market access (reimbursement) and address gaps concerning dietary disease management and disease prevention. For the moment, regulatory processes for foods vs. drugs, for example, are very different. Moving from one category to the other would imply beginning the approval process all over again. Disruptive technologies are creating new gray zones in regulation, and we must decide the scientific, clinical, financial and social framework for the approval of foods. Discussions on this issue must seek answers to such questions as:

- Where does health end and disease start in terms of regulating a product as a food or drug?
- What does these technologies mean for early interventions and regulations?
- To what extent are developers ready to invest in complex nutrition?
- Are regulators and payers ready to accepting limited evidence and related uncertainty around products?

Actions to ensure innovation include recognizing the microbiome as a key ally for innovative disease management, improving any inconsistent or unprepared healthcare regulatory and policy frameworks, accelerating market access for products and providing incentives for investing in the development of these healthcare solutions. Several multi-stakeholder venues (WHO, European Commission) and platforms (Fondation Mérieux, OECD) are available to help build consensus and productive policy and legislation in this area.



Financial perspectives on the emergence of a microbiome-based business industry: sorting out the hype from the hope

Isabelle de Cremoux, President and CEO, Seventure Partners

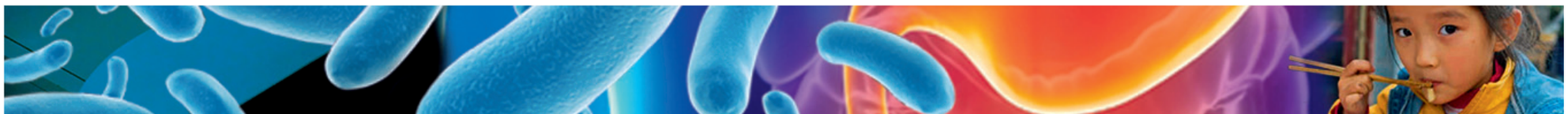
In 2013 Seventure Partners, a French venture capital firm, raised 160 million euros for Health for Life Capital, a fund dedicated to microbiome-based businesses. It was funded by institutional partners as well as partners such as Danone, Lesaffre and Novartis.

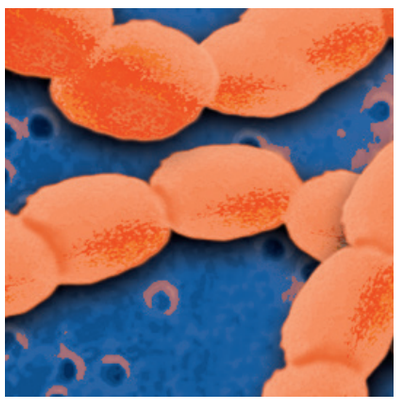
Cremoux sees three potential markets for microbiome-based business: human health and wellness, animal health, and industrial and agricultural biotech. For her talk, she concentrated on human health. She presented evidence that the field is growing rapidly, demonstrated by skyrocketing scientific literature (largely about gastrointestinal diseases, metabolic diseases and cancer), therapeutic products in development and the increasing number of trials underway.

The United States has invested much more money in the field than has Europe, even though there are currently more trials underway in Europe. Cremoux emphasized that there is a worldwide race in the microbiome market for the financial opportunities it represents. She expressed the fear that Europe will lose the race if it does not allocate more governmental funds.

Other than the small companies financed by venture capital firms, large industry players such as Johnson & Johnson, Pfizer, Nestlé Health Science, Danone, Genentech and others are jumping into the race. The private and public financial community is also increasingly implicated in the microbiome market.

Citing best-sellers, Google searches and Amazon titles containing the words "microbiome" or "gut flora", Cremoux noted that the public is showing strong and increasing interest in this topic. In terms of its future potential, she compared the microbiome industry with the biotechnology industry, and in conclusion suggested that in 15 years the microbiome industry would be as big as the biotechnology industry is today.





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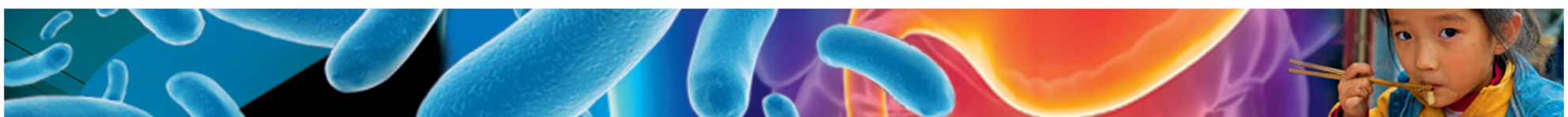

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Microbiota, nutrition and healthy living

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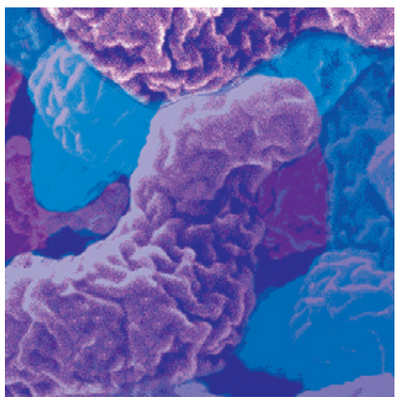

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