Biofortis

20 years experience

BOOKLET

- Biofortis Innovation Day -

Special edition

July 7th 2022

Dear readers,

Biofortis Innovation Day 2022 was a real opportunity to share visions of the last evolutions in microbiome science from different perpectives, including academia, regulation agencies, pharma & biotech companies and CRO perspective. Thanks to all the speakers and the participants, the quality and content of all debates opened our eyes about the current and future challenges and opportunities associated to the diversity of human and animal microbiota and the new associated biomarkers. We will share in this booklet the essential of our discussions and conclusions. Enjoy your read!

Biofortis

20 years experience

A PRIVATE SYMPOSIUM...

...TO CELEBRATE OUR 20 YEARS

MICROBIOME FOR BETTER HEALTH

The aim of this premium event was to gather experts & professionals from the health and nutrition industries.

We were looking for answers and ideas to assess the current developments and future trends in the field of microbiome.

1996 - Atlangene Applications

A company specialized in molecular biology methods and sequencing for probiotics & prebiotics analyses for pharmaceutical and food industries.

2002 - Biofortis

An entrepreneur, Murielle Cazaubiel who gathered a clinical research team in Nantes, France. Her goal was to apply the standards of the pharmaceutical industry to the evaluation of food and dietary supplements.

2009 - Biofortis Merieux NutriSciences

ATLANGENE Applications, BIOFORTIS and ADRIANT merged under the name Biofortis and joined the Mérieux NutriSciences family.

Today And Tomorrow

Mérieux NutriSciences sells the activities of Biofortis to its managing director, Benoît Fouchaq who will continue its development alongside Institut Mérieux.
Biofortis is a unique full-service CRO providing Nutrition Clinical Trials, Microbiome Investigation and Data Science for Human and Animal Health.

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PROGRAMME

- BInD -
Biofortis' Innovation Day

July 7th 2022

NANTES - Espace Titan

MICROBIOME FOR BETTER HEALTH

Lita Proctor
PhD, [V] NHGRI/NIH

Tom Van de Wiele
Full Professor at Ghent University - Senior science advisor to

Philippe Marteau
Professeur, Sorbonne Université-APHP

Hugo Roume
Microbiome Scientist at Lesaffre

Manfred Ruthsatz
Executive Director, Nutrition+HealthCARE

Céline Druart
Microbiome Project Manager, PRI

AGENDA

Moderator: Françoise Le Vacon, CSO Biofortis

TIME		SPEAKERS
8:00	Welcome	
8:45	Welcome & Opening	Benoît Fouchaq, CEO Biofortis
9:15	**Keynote Presentation - Lita Proctor -**	Challenging the concept of the human microbiome as an organ system
10:00	**Presentation - Céline Druart -**	Microbiome-based products: an update on the current developments in the regulatory framework and regulatory science initiatives
10:30	Networking break	
11:00	**Presentation - Manfred Ruthsatz -**	Microbiome & Diet: NCD Prevention & Personalization *New Public Health Opportunities: are we Prepared to Adapt Current Regulatory & Policy Frames?*
11:30	**Panel Discussion - Vanessa Rouaud -**	How to boost market opportunities of functional food and LBPs?
12:15	Contest Presentation	
12:30	Lunch & Networking break	
13:50	**Presentation - Philippe Marteau -**	Are the Microbiome or Associated Products used in Medical Practice?
14:20	**Presentation - Hugo Roume -**	Multicenter evaluation study of gut microbiome profiling by next-generation sequencing
14:50	**Presentation - Tom Van De Wiele -**	Microbial metabolism and bioactivation of dietary polyphenols: connecting the dots between in silico, in vitro and in vivo data
15:20	Networking break	
15:35	**Panel Discussion - Thomas Carton -**	In silico <-> in vitro <-> in vivo: is the road safe for the microbiome?
16:15	Award Contest	
16:30	Closing session	

Lita M. Proctor

PhD, [V] National Human Genome Research Institute, US National Institutes of Health

Presentation: Challenging the concept of the human microbiome as an organ system

At the US National Institutes of Health, Dr. Lita Proctor served as the Coordinator of the Common Fund's Human Microbiome Project, a ten-year (2007-2016) $215M community resource program to create a widely distributed research toolbox of human microbiome reference datasets, multi-omic computational and analytical tools and clinical protocols for this emerging field of biomedical research. Prior to this, she served as Program Director in the US National Science Foundation's Geosciences and Biosciences Directorates, where she managed microbiological, bioinformatics and research resource programs and for the Marine Microbiology Initiative at the Gordon and Betty Moore Foundation. She is formally trained in microbial ecology with a Ph.D. in Oceanography from Stony Brook University and in molecular microbial genetics through an NSF Marine Biotechnology postdoctoral fellowship at UCLA. She held appointments at Florida State University and at UC-Santa Cruz. Dr. Proctor retired in 2018, currently has NIH emerita status and serves as an advisor to the National Microbiome Data Collaborative, the Microbiome Center Consortium, the American Gastroenterological Association, the American Society for Microbiology, and the World Microbiome Partnership and carries out public outreach activities about the microbiome. Her H index is 24.

Research on microbiome is quite a young discipline. This is a wide field of research sustained by large investments (NIH funded 1.5 billion US$/ lot of money spent on microbiome research). LP wonders whether it is time to think beyond the traditional model of the human microbiome, with its gastro-intestinal, nasal, oral, skin and urogenital components. Many diseases are associated with microbiome, affecting various systems or organs:

- Neurological / mental: epilepsy, Alzheimer's, psychiatric disorders
- Gastro-intestinal tract: irritable bowel disease, ulcerative colitis, Crohn's disease, gastroesophageal reflux disease, necrotizing enterocolitis
- Heart: cardiovascular diseases
- Lungs: asthma, cystic fibrosis
- Skin: eczema, psoriasis, acne, rheumatoid arthritis
- Vagina/uterus: bacterial vaginosis, preterm birth
- Liver: non-alcoholic liver disease, alcoholic steatosis
- Cancers: Hodgkins' lymphoma, liver, gastric, esophageal, colorectal, cervical, breast
- Systemic: obesity, type 1 and type 2 diabetes, lupus, multiple sclerosis, autism spectrum disorder

Beyond "traditional" microbiomes, other microbiomes are suspected to exist. Indeed, microbes and/or microbial metabolites have been found in unexpected body sites of healthy subjects. Many questions are still debated.

Placenta: does fetus / infant microbiome development begin at birth or during gestation? Do we identify microbiome, or microbiome products? Does the fetus receive transplacental signals from the maternal microbiota? Is it contamination (during labor / delivery, or sample collection / processing) or does it really exist?

Skin dermis: Is there a healthy subepidermal (i.e. dermal) microbiome? Particular microbial metabolic pathways are enriched in dermal microbiome, as compared to epidermal microbiome.

Blood: Is there a healthy blood microbiome? Phylogeny appears to correlate between gut and blood microbiomes. About 10^6 to 10^7 bacteria/mL were described in the blood of healthy donors.

Approximatively 95% of this microbiome is in the buffy coat fraction, including white blood cells and platelets, around 5% is associated with red blood cells. Gut-produced short-chain fatty acids, transported into blood, regulate blood pressure via G-protein coupled receptorsA brain microbiome may also exist, this is still debated.

Whatever the site, the existence of tissue microbiome is controversial. Pros argue that microbial number and diversity vary between tissue sites. Cons argue that contamination can never be excluded. There are many possibilities for microbes to filtrate in the blood (e.g. brushing teeth).

Studying microbes and microbial metabolites outside traditional body sites addresses practical issues, such as understanding microbiome function and discovering potential microbial therapeutics. Microbiome research relies on omics technology, and provides information on the community composition, microbial pathways, virome profiles, antibody profiles, host genomes, epigenome profiles, cytokine profiles, metatranscriptomics, metaproteomics and metabolomics. Analysis of the microbiome composition is not enough, we must explore what is produced. Many gut microbiota metabolites are found in blood, with physiological actions (mostly putative for the moment). Microbiome research also addresses scientific questions: do microbiomes communicate with each other? what is the human microbiome? To this last question, one can assume that human microbiome is intermediate between free-living microbes (e.g. marine bacterioplankton or hydrothermal spring archaea) and strict symbioses (e.g. squid light organ bacteria or termite gut wood-digesting protits).

Is the human microbiome an organ, a part of the immune system, a part of a superorganism, a holobiont, or an ecosystem? Hereafter are the definitions and pro/con arguments:

MICROBIOME ?	DEFINITION	YES / NO
Organ	Composed of 2+ tissue types that perform one or more common functions	Y: FMT to replace microbiome gut «organ» N: microbial exchange with environment
Immune System	Set-up an inside-out, to provide a defensive mechanism for a self-contained system	Y: directly and indirectly exclude pathogens N: pathobionts; more functions than immunity
Superorganism	Group of organisms with emergent properties not found in individuals	Y: host-microbes function as a whole; other Wheeler (1911) criteria N: not all microbes are heritable; other limits
Holobiont	Evolutionary unit which coevolves to increase fitness of both (host + microbe)	Y: positive interactions of unit support co-evolution of unit N: microbes are not strictly heritable
Ecosystem	Community of organisms interacting in an environment resulting in system-level functions	Y: dynamic movement of microbes in/out of host N: where does microbiome end and environment begin?

Credit: Lita Proctor, BiND presentation, October, 6th

Céline Druart

Microbiome Project Manager, PRI

Presentation: Microbiome-based products: an update on the current developments in the regulatory framework and regulatory science initiatives

Céline Druart obtained her PhD degree in biomedical and pharmaceutical sciences from UCLouvain (Belgium) in 2014. She then joined the research group of Patrice Cani to lead a 3-year project devoted to the development and exploitation of the promising results regarding the beneficial effects of Akkermansia muciniphila, a commensal gut bacterium. Taking advantage of her Master's in Management, she worked for 3 years as Scientific and Business Project Manager at A-Mansia Biotech, an innovative microbiome company developing health products based on the unique properties of A. muciniphila. Her main duties there were the implementation and coordination of their preclinical and clinical programs, regulatory affairs and IP dossiers, and grant applications. In July 2021, she joined the Pharmabiotic Research Institute (PRI) as Microbiome Project Manager. She is in charge of the Regulatory Science activities of the organization; coordinating Task Group work, focusing on the emergence of new scientific and technological standards, and supporting PRI Regulatory Members in their development efforts.

Pharmabiotic Research Institute (PRI) is a financially-independent corporate entity (non-profit organization) founded in 2010, whose mission is to identify and confirm the Regulatory and Scientific requirements for the development of microbiome-based medicinal products (MMPs) for the European Market. Once gathered, this knowledge is made available to stakeholders in order to support and de-risk pharmaceutical development – for the ultimate benefit of patients, many of whom suffer from high unmet medical needs. The unique and innovative collaborative approach is called "share & learn".

MMPs cover a wide spectrum of products: they can be whole ecosystem-derived products (donor stool or vaginal microbiota, substantially manipulated and prepared industrially), synthetic ecosystems (rationally-designed microbial ecosystem, often co-cultured), live biotherapeutic products (single-strain or consortia-based), non-living biotherapeutic products (inanimate microbes and/or microbial lysates), or bacteriophage therapy (wild-type or genetically modified organisms).

There is no unique regulatory status for these products, and no unique regulatory pathway to follow. The regulatory status is based on the intended use of the product, and never on the nature of the product/substance, depending on the product's action, its mechanism of action and the target population (consumer or patient). MMPs can be assimilated to medicinal products, intended to prevent or treat a disease, restoring, correcting or modifying physiological functions. They require a marketing authorization based on evaluation of quality, safety, efficacy and benefit / risk balance in the targeted population. Within medicinal products, the closest categories to MMPs are biological medicinal products and Advanced Therapy Medicinal Product (ATMP), even they are not perfectly within the scope of specific legislations / guidelines (ICH, EMA, FDA, EUCAST).

MMPs require proposing innovative solutions and rationales through regulatory science. There is a need to develop / adapt methods, models, approaches, practices and tools to assess safety, efficacy and quality of those products.

Regulatory affairs are reactive, whereas regulatory science is proactive. Transversal work is needed between food and drug on methods and models.

Probable future evolution of legislation is expected between blood, tissues and cell (BTC) legislation (currently under revision) and the general pharma legislation, which interplay. MMP can be regarded as a new BTC requiring substantial manipulation, and/or as substance of human origin (SoHO) industrially manufactured, borderline with medicinal product and medical device legislation.
Currently, feces and maternal milk are included in the proposed SoHO regulation, they could be integrated in BTC, with impacts on donation, procurement and testing of SoHO.
The revision of EU pharmaceutical regulation is concomitant to the work on MMPs, and to be considered within the future pharmaceutical framework.

Manfred Ruthsatz

Executive Director, Nutrition + HealthCARE

Presentation: Nutrition & diet: non-communicable disease prevention & personalization

Executive Director, Nutrition + HealthCARE (Connecting Advocacy, Regulatory, Empathy): created global advisory services to share the passion for healthy aging, consumer and patient care. Making personalized/ specialized/ clinical nutrition, microbiome & product profiling, development, advocacy strategies sustainable
Past lead roles in healthcare advocacy, regulatory, safety, quality, health economics/reimbursement (Nestlé Health Science, L'Oréal, Abbott, Roche); NIH Visiting Fellow (molecular cancer virology), US-FDA pharmacologist
Long-standing recognition leading global/ regional working groups; on management, governing (ISDI; MNI), scientific advisory (IS_MIRRI 21), editorial boards (RAPS, EAC) & faculty (RAPS Convergence)
Publishing and presenting frequently across the globe: healthy longevity, disease-related malnutrition, microbiome, food-drug continuum, global convergence, multi-stakeholders & policymaking
Board Certifications in Pharmacy, Toxicology (PhD, DABT), Regulatory Affairs (RAC). Distinguished Regulatory Affairs Professionals Society (RAPS) Fellow

We are experiencing societal and healthcare paradigm shifts, from growing to aging population, from infectious to non-communicable diseases (NCDs). Market and patient access imply growing healthcare costs. Disruptive technologies (omics, diagnostics...), social media, globalized e-commerce, etc. change the game. Healthy aging is the greatest progress of last decades.

Regulatory framework and policy concepts also evolve, in terms of disease prevention, nutrition therapy, personalized nutrition, microbiome personalization, and multiple continua (food-drug, health-disease, consumer-patient, population based-personalized, human-microbiome genomics...).
New approaches involve multi-stakeholders: public-private partnerships and regulators / academics (ONCA/ENHA, ILSI, OECD/Flemish government, US national microbiome initiative, NASEM).

The association of microbiome and diet in NCD prevention represents new public health opportunities. Are we prepared to adapt current regulatory and policy frames?
Microbiome in health and disease requires strategic options for regulatory science and healthcare policy. Many sustainable development goals (SDGs) defined by the United Nations are linked to nutrition and disease prevention. Microbiome based innovations can contribute to achieve these SDGs. Guidelines should consider diet-changing microbiome mechanisms.
Microbiome is inherently personalized, with a similarity rate between humans of under 10%. The NIH Project – Nutrition for Precision Health was proposed for several reasons:

- Poor diet is a leading cause of preventable death and disease and preventable healthcare costs in the US
- Current dietary recommendations provide a one-size-fits all approach
- Interactions between dietary intake, microbiome ecology, metabolism, nutritional status, genetics, and the environment are still poorly understood.

The IS21 project (Implementation and Sustainability for the 21st century of the Microbial Resource Research Infrastructure [MIRRI]) intends to meet several goals: develop and launch of the collaborative work environment, establish a transnational access program, establish an education and training program, and extend the number of MIRRI memberships.

The project intends to involve several stakeholders: policy makers, potential members of MIRRI, citizens, microbial resource providers and scientific and industrial microbial raw material users.

Can regulatory healthcare categories and concepts keep pace with science and uncertainty? The study of host-microbiome symbiosis is complex, and requires to integrate parameters for disease prevention and cure. Innovative, novel trial designs and methodologies (using artificial intelligence, in-silico experiments…) are to be developed. The regulatory landscape for microbiome products must evolve from food to drug standards, on pre-pro-post-biotics, novel foods / claims, ATMP, life biotherapeutic products, fecal microbiota transfers, human tissue, bacterial cells… Toxicological assessments on microbiome products must evolve, with new assessment models, case-by-case strategies (biodistribution, colonization, immunogenicity, tumorigenicity, genotoxicity, reprotoxicity…). A bench to bedside translation is required.

Regulatory needs:

- Ensure the science base, and try to fulfil regulatory requirements of safety and efficacy.
- Harmonization and flexibility of frameworks, with cross-border solutions and a common language. Quality / safety / efficacy cover the same concepts for food and drug, but different procedures and levels of proof are required for a food, a drug or a cosmetic product.
- Address the reality of the continuum
- Allow for an acceptable level of scientific uncertainty on outcome benefits in decision making, despite authorities expecting certainty from industry. Most aspects of nutrition and microbiome are low risk fields: even if there is some uncertainty, we need to move on. We should not block neither science nor action.

Creating value:

- Cost and reimbursement mechanisms must evolve to support development of personalized nutrition for health and disease prevention, and as part of preventive medicine. Prevention is only 3% of NCD budgets: it must be increased, and the message must be spread: it's never too late to do something. Current business, regulatory and policy frameworks still favor treatment. Let's anticipate and prevent the problem with preventive nutrition instead of solving it.

- We need to raise the awareness of population, either patients or consumers, about nutrition / microbiome, to get the right message to the public and healthcare providers, to move from hype to reality, agree on opportunities, translate and disseminate knowledge via experts / consensus, implement policies and solutions rapidly, provide dedicated training for healthcare professionals. SDGs are mainly linked to nutrition, therefore to microbiome. . We are still lacking clear cause–and-effect relationships between diet, optimal microbiome and health from randomized controlled trials. However, we have convergent data from "blue zones" (areas where people grow older than elsewhere). All information should be valuated, even if not regulatory-validated. The best population approaches are not fully developed yet.

Can consumer education includes microbiome-based analysis as an element of personalized public health concepts?

There is a trend towards "tailored to fit" demands. Consumers expect personalized products, although science is not yet there:

- Growing awareness of long-term ownership of health and wellness via natural diet, nutrition and lifestyle interventions.
- Change from rule-based reactive, one-size-fits-all sick care to personally proactive health span optimization.
- Motivated consumers seek trusted, science-based guidance, tailored solutions
- Democratization of "biohacking" measuring and monitoring.

Multiple microbiome commercial tests are already available. Their interpretation raises many opportunities but also permanent challenges:

- Science and tools getting better, quicker, cheaper, more precise
- Analysis resolution until genus, species or strain
- Microbiome / human genome interactions, with responders to drugs or nutrients

Food associations stay complex Reports include statistical charts, dietary recommendations and claim conclusive information. Rapid and affordable new diagnostic technologies open new personalized healthcare pathways. The microbiome should be one key element in preventative healthcare policy approaches. Population-based policy approaches can co-exist with personalized concepts. Individualized healthcare concepts are a great way to take verifiable responsible actions.

If we feed our microbiome, we feed ourselves. Nutrition and microbiome are partners.
What is missing?:

- Innovation (omics, microbiome, personalization, speed)
- Food-medicine continuum between health and disease
- Citizen and societal aspects: disease prevention and low health costs.

ROUND TABLE

How to boost market opportunities of functional food and Life Biotherapeutic Products?

“During this first round table moderated by Vanessa Rouaud (Head of Central lab & Microbiome Business Unit at Biofortis), our experts exchanged with the attendees on the evolution of the different market segments linked to the growing scientific knowledge on microbiome. The development of functional foods and life biotherapeutic products faces many challenges, as their place and related practices are still poorly defined : the game’s rules need to be reinvented.”

Philippe Marteau

Professor, Sorbonne Université-APHP,
Hôpital Tenon

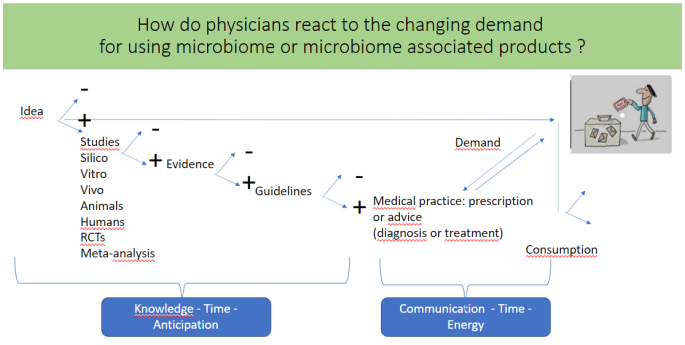
Presentation: Are the microbiome or associated products used in medical practice

Professor Philippe MARTEAU, MD, PhD is a specialist of gastroenterology and intestinal ecology. He trained mainly at St Lazare hospital, Paris with JC Rambaud and at INSERM U270 "Fonctions Intestinales et Nutrition" before a sabbatical at TNO Nutrition and Food Research in 1992-1993.
His main research focuses on inflammatory bowel disease and the pathophysiology of the human intestinal ecosystem (intestinal microbiota in health and disease). The aim is to understand the role of the ecosystem in the development of intestinal diseases and to try to influence it (especially using probiotics) in order to treat or prevent these diseases.
His studies included descriptive studies in healthy subjects and patients with inflammatory bowel disease and randomised controlled trials of probiotics in various gastrointestinal disorders (Crohn's disease, irritable bowel syndrome, abdominal discomfort). He was member of the GETAID (Groupe d'Etude des Traitements des Affections Inflammatoires Digestives) for 20 years (scientific secretary for 8 years), member of the IOIBD (International Organization for Inflammatory Bowel Disease) for 15 years, member of the CNU-HGE (Conseil National Universitaire d'Hépato-gastroentérologie) for 6 years and president of the CDU-HGE (Collégiale des Universitaires en Hépato-gastroentérologie) for 3 years. He was president of the French Society of Gastroenterology (Société Nationale Française de Gastro-Entérologie SNFGE).
He is professor of gastroenterology since 1997 (since 2016 at Sorbonne Université-APHP). He is chief Editor of the Journal "Clinics and Research in Hepatology and Gastroenterology". He published more than 250 original articles and book chapters including the book "Intestinal Microbiota in Health and Disease".

New microbiome associated products are intended to be used for diagnostics (microbiome profiles), theranostics (microbiome profile linked to response rate), and therapeutics (fecal microbiota transfer [FMT], probiotics, prebiotics). But actual uses are limited. For the moment, the scientific society SNFGE (Société Nationale Française de Gastro-Entérologie) recognizes no diagnostic test and no prebiotics. FMT is only indicated for recurrent Clostridioides difficile infection, and probiotics for irritable bowel syndrome. A minority of physicians prescribe microbiome associated products, but the majority follow the official position and disagree with their practice (at least partly). It becomes problematic when a patient seeks a confirmation, comment or adaptation by another physician.

The patient / consumer wants to be confirmed by the physician that he does the right thing, and wants to be prescribed what he thinks is good for him. The physician can't dedicate much time and energy to collect the information individually. So he expects scientific societies to provide guidelines, but they say NO on the basis of science and expert consensus, ie what is believed to be true for most people.

Personalized medicine is therefore a modern concept, but currently impossible to implement. Physicians need the help of algorithms to define the individualized outline of treatment for each patient; and the patient will have to accept not having what he wants, but only what suits him. The mass of information provided by microbiome analysis is hardly exploitable for the moment in clinical practice, especially since it must be crossed with data on physical activity, drug intake, etc. At best, the physician takes into account the diversity and richness of the microbiome.



Credit: Philippe Marteau, BiND presentation, October, 6th

Hugo Roume

Microbiome Scientist, Lesaffre

Presentation: Multicenter evaluation study of gut microbiome profiling by next-generation sequencing

Hugo pursues his thesis in systems biology applied to microbial ecology in Systems Ecology group (Wilmes lab) at the LCSB (Luxembourg). During his doctoral thesis, he developed methodologies and models to integrate multi-omics data from complex microbial consortia applied to the treatment of wastewater to optimize the microbial production of biofuel from sewage sludge lipids. Following the obtention of his PhD thesis from the University of Luxembourg in 2013, he chooses to pursue a postdoctoral fellowship at the Center for Microbial Ecology and Technology in Ghent (Belgium), where he developed methodologies for the characterization of microbial communities using metagenomic, to optimize resources biorecovery through fermentation processes. Hugo chooses then to redirect his career in France, towards the characterization of human and animal microbiome in association with diet and health. In 2016, he obtains a permanent position as research engineer in France National Research Institute for Agriculture, Food and Environment (INRAE). For four years, he managed the quantitative metagenomics platform at the MetaGenoPolis Unit, center of metagenomics expertise in human and animal gut microbiome research in Paris area (France). Working through various project in close collaboration with industrial partners, in 2020 Hugo chooses to quite his position to reach the industrial leader in fermentation, Lesaffre, as senior microbiome scientist in the group Discovery lead team dedicate to research and innovation in human, animal and plant nutrition and health using microorganisms and derivatives.

In 2014 a same gut microbiota sample sent to two companies brought very different microbiota analyses, highlighting a huge need for protocol standardization.

This motivated the initiation of the international human microbiome standards (IHMS) project, which coordinated the development of standard operating procedures (SOPs) designed to optimize data quality and comparability in the human microbiome field. IHMS is promoted by 8 partners and 15 contributors across 12 different countries, including Biofortis. The IHMS SOPs were published in Nature, and data are available via open access since April 2015. They describe samples identification, collection, DNA extraction and sequencing and bioinformatics processing in metagenomics studies.

Today, 16S metabarcoding is the most frequently used (and published) assay for studying the microbiome. A first inter-laboratory study has been conducted, in which similar DNA aliquots extracted from human stool and mock community samples have been used to characterize specific biases due to sequence production and bioinformatic pipeline. We reveal major biases due to library preparation and databases used for taxonomic annotation in the bioinformatic pipeline in metabarcoding. None of the partners provide bacterial genus profiles with enough similarity to the one obtained by shotgun metagenomic sequencing to allow a lower inter-individual variance than inter-laboratory variance and thus even with the use of a single bioinformatic pipeline.

In the near future, similar ring test and benchmarking need to be done to measure variability brought by shotgun metagenomic sequencing and data analysis.

What are the solutions for labs?

- Use reference bio specimens, cell and DNA reagent publicly and commercially available to challenge methodologies;
- Use the “Strengthening The Organization and Reporting of Microbiome Studies“ (STORMS) to report laboratory, bioinformatic and statistical methods, reproducible research and discuss interpretation, limitations and bias.

Tom Van de Wiele

Full Professor at Ghent University -
Senior science advisor to ProDigest

Presentation: Microbial metabolism and bioactivation of dietary polyphenols: connecting the dots between *in silico, in vitro* and *in vivo* data

Tom Van de Wiele is a full professor at the Center for Microbial Ecology and Technology from Ghent University, Belgium. The core expertise of his research group is the creation and application of enabling in vitro technologies that mimic the host-microbe interphase with particular focus on mucosal microenvironments. Model systems such as M-SHIME (a mucosa containing dynamic gut model) can be used to generate mechanistic insight in host-microbe interactions and complement in vivo observations. This is particularly important to increase our understanding of how the microbiome can modulate host health, either through production of specific metabolites, establishing colonization resistance against pathogens, modulating immunity, triggering local inflammation etc.... Such dynamic human gut models allow the screening of a wide variety of candidate drugs, functional foods and/or feeds before a more narrow selection enters the stage of in vivo trials. The research of Tom Van de Wiele has resulted in a scientific output of more than 250 peer-reviewed international publications and the yearly participation as invited and keynote speaker in around 5-10 international conferences and academic symposia. His research is picked up by his scientific peers: in 2021 he was a Highly-Cited Researcher in the Cross-field discipline.

Novel food ingredients have a health impact on the human body, such as reduction of blood pressure, increase of anti-inflammatory capabilities, regulation of the defense gene expression, reduction of menopausal symptoms in women, protection against diabetes, cancers, CVDs, neurodegenerative diseases, endothelial function maintenance, improvement of physical performance or stimulation of nitric oxide synthesis. However, inter-individual variability prevails among humans and yield to different effects, sometimes depending on unique functional microbiome, which defines a metabolic phenotype, or metabotype. Pharmaco-microbiomic strategies are emerging, stratifying people into responders and non-responders, and using microbial therapeutics to change an individual's metabotype. Microbiome helps stratify patients and make better predictions on who will respond to which drugs.

Isoxanthohumol found in hops can be transformed to 8-prenylnaringenin (8-PN) that has affinities with the 17-beta estradiol receptor. It presents a biological efficacy as a pseudo-estrogen to restore bone building after menopause. Conversion of Isoxanthohumol to 8-PN is a unique metabolic trait, dependent on the individual's microbiome, observed in vivo. The 8-PN producing phenotype is preserved in a dynamic gut in vitro model, called SHIME. The in vitro model provides mechanistic insight: 8-PN is primarily produced in the distal colon, which presents a more diverse metabolic potency than the proximal colon.

In silico exploration shows that bioactivation of isoxanthohumol requires O-demethylation. This crucial microbial metabolic step drives to identification of involved enzymes (O-demethylase) and corresponding encoding genes (methyltransferase I and II, corrinoid protein...). It is then possible to explore microbial genomes for gene presence, or query microbial metagenome databases for the functional gene of interest, then visualize microbial phylotypes whose genomes are positive for this gene, and stratify human individuals based on gene presence in microbial metagenome (influence of ethnicity, health status, age...).

The last step is an in vivo validation of the use of Eubacterium limosum as a precision probiotic or live biotherapeutic product, to transform an isoxanthohumol non-converting microbiome phenotype to a 8-PN producing microbiome phenotype.

In gnotobiotic rats, the 8-PN producing phenotype is preserved in vivo after inoculation of E. limosum. Paradigm shift in pharmaco-microbiomics emerge:

- Microbiome can modulate pharmacokinetics / pharmacodynamics of drugs,
- Microbiome can modify the drug vehicle or adjuvant

- Drug can kill microbiome
- Microbiome can produce drugs or be the drug.

Mechanistic insight in microbial contribution to health effects grows, via the identification of biomarkers, and draw rational design of live biotherapeutic products. There must be a cross-talk between:

- In vivo human intervention studies, providing clinical observational data, stratification of individuals, biological samples and model inoculation and validation
- In vitro enabling technologies: dynamics, multiparametric control, mode-of-action studies, to support and explain in vivo-observations
- In silico analysis and functional prediction, based on microbial genome databases, metabolic pathway prediction and metagenomics libraries.

ROUND TABLE

In silico / in vitro / in vivo: is the road safe for the microbiome?

During this second round table moderated by Thomas Carton (Scientific Operations Manager at Biofortis), experts and meeting attendees discussed about the assets, limits and complementarity of the three experimental approaches to unravel the mysteries of the microbiota, and to overcome the issues linked to this complex, multifactorial, intertwined ecosystem. The final goal is to achieve products or strategies to improve health and well-being adapted to everyone, with a high benefit/risk ratio, based on strong scientific evidence, as for more common medicinal products.

AWARD

Nantes research university / INRAE – Marie Bodinier

Over the past 2 decades, Biofortis has supported some of the most scientifically robust microbiome research projects. We would like during this special event to support a gut microbiome project by providing free shotgun sequencing services (~82.5Gb / up to 96 samples).

The awarded/winning project* will benefit from a comprehensive microbiome package, including shotgun metagenomics sequencing, bioinformatics analysis, as well as a dedicated access to our proprietary microbiome data visualisation platform, EasyBioM®.

Marie Bodinier
INRAE UR1268 BIA Nantes
Research director INRAE, team leader, BSc, BND, PhD
Modulation of MIcrobiota in early life by HMO to prevent allergy : MIHMO project

BiND 2022 OVERVIEW

During the Biofortis Innovation Day, the one main cross-cutting concept that emerged is that there is STILL A LOT TO DEFINE.

-> Define the microbiome (holobiont, ecosystem, metaorganism...), its normal composition (the famous "healthy" microbiome, that should be the main output of the MMHP/French gut project; and its opposite dysbiosis) and its normal localization (especially on the subject of tissue microbiomes: placenta, brain, etc.)

-> Define the place of the products that - act on/come from - microbiome (drug vs food supplement / intended use) and the rules of the game (regulation, health guidance)

-> Define the tools of analysis (when/which tool to use?), and their performance (standardization, inter-laboratory testing, reference material)

-> Define the relevant microbiome endpoints (consensus appears on diversity)

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This booklet is based on the notes taken by Biofortis staff during the BInD and aims to present as honestly as possible the discussed themes. However, as in any synthesis, this booklet cannot represent the precise and exhaustive thought of the conference speakers, nor in any way engage their responsibility.

Biofortis

20 years experience

EXPERT

DEDICATED

TRUSTWORTHY

SUPPORTIVE

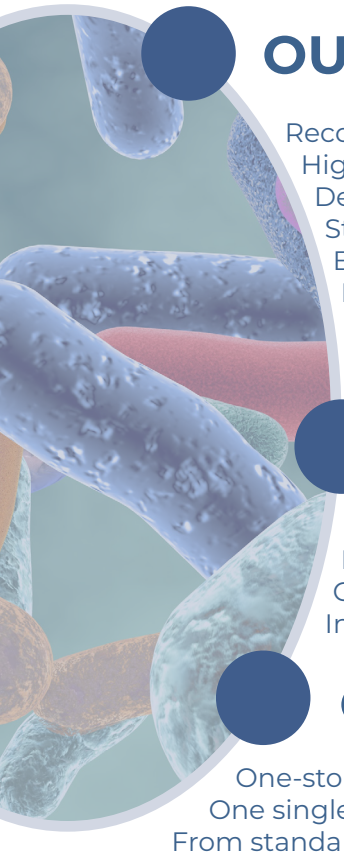
20 years

90+ collaborators

500+ projects

ABOUT BIOFORTIS

Biofortis is a unique full-service CRO providing Nutrition Clinical Trials, Microbiome Investigation and Data Science for Human and Animal Health.



OUR EXPERTISE

Recognized in nutrition clinical trials and microbiome investigations
Highly experienced multi-disciplinary team
Dedicated Biometrics & Data Science internal expertise
Strong network of scientists and medical experts
Biofortis' strategic and scientific advisory board
Partner in large Research Consortia Projects
Internal R&D developments
Contract Research in partnership with our customers

OUR CAPABILITIES

Two clinical investigations units
Internal Central Laboratory
Cutting-edge NGS platform
International network of partners (labs and investigational sites)

OUR ADDED VALUE

One-stop-shop solution
One single coordinator for all the steps of your project
From standard services to custom approaches

ICH harmonisation for better health

QUALITY SYSTEM CERTIFICATION DNV·GL ISO 9001

SILVER 2021 ecovadis Sustainability Rating

CRÉDIT D'IMPÔT AGRÉMENT CIR RECHERCHE

Accelerate Your Innovation With Your Clinical & Microbiome Partner

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