Book of Abstracts

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Metagenomics and metabolomics in metabolic diseases

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Dr Sébastien BOURET, Ph.D.
Directeur de Recherche (DR1)
INSERM UMR-S 1172
Lille Neuroscience & Cognition
Development and Plasticity of the Neuroendocrine Brain
Lille, FRANCE

> The not so sweet effect of maternal diet on metabolic programming

The growing prevalence of obesity and associated diseases such as type II diabetes is an important health concern, including among children and pregnant women. Epidemiological and pre-clinical studies suggested that alterations of the metabolic and hormonal environments during critical periods of development are associated with increased risks for obesity and type 2 diabetes in later life. There is general recognition that the developing brain is more susceptible to environmental insults than the adult brain. In particular, there is growing appreciation that developmental programming of hypothalamic neuroendocrine systems by the perinatal environment represents a possible cause for these diseases. This lecture will summarize the major stages of hypothalamic development and discuss potential periods of vulnerability for the development of hypothalamic neurons involved in energy balance and glucose regulation. It will also provide an overview of evidence concerning the action of hormones (including leptin and ghrelin) and maternal obesity in programming the development and organization of hypothalamic melanocortin circuits. Recent data on the impact of maternal nutrition and low-calorie sweeteners consumption in the development and organization of hypothalamic circuits that regulate feeding and glucose homeostasis will also be presented.

Pr Rémy Burcelin, Ph.D.
Directeur de Recherche Inserm
I²MC, Institut des Maladies Métaboliques et Cardiovasculaires, Inserm U
Equipe « Dynamix»
Toulouse, FRANCE

> A Gut Immune to Brain axis for the control of diabetes

In the absorptive state the Gut Brain axis controls energy distribution ensuring its proper storage before being redistributed in fasting. An impairment of this axis leads to dysglycemia and impaired body weight management. The molecular mechanisms of this axis imply incretins receptors and glucose transporters to cite a few. However, the last decades has demonstrated the causal role of the gut microbiota on the control of metabolic diseases. Bacterial wall fragments such as LPS and peptidoglycans control the innate immune system to prevent from bacterial translocation leading to metabolic inflammation. We eventually shown through the humanization of germ free mice with human donor microbiota that a dysbiotic gut microbiota from type 2 diabetic patients impairs the GLP-1 dependent gut brain axis of the humanized mice. Transcriptomics analyses chow that changes in microbiota dependent bile acids hamper the activation of the innate to adaptive IL17released immune system. The causality of the gut microbiota is shown through microbiota transfer from diabetic donors to germ free mice. However, to identify the microbial components responsible for the causal role of the dysbiotic microbiota we have developed hybrid machine learning procedures to classify the bacterial taxa and their genomic functions according to the severity of the disease. Porphyromonadaceae and Lactobaciliaceae were shown to be inversely associated with the control of the Gut Brain axis.

Dr Grégoire Chevalier, Ph.D.
Scientific Program Leader, Enterome
Paris, FRANCE

> Looking for microbiome derived therapeutic compounds : the example of an anti inflammatory peptide and v GIP/GLP 1 secretagogues

The human gut microbiome represents a natural reservoir of millions of bacterial proteins that have specific roles in maintaining a symbiotic relationship with the human host. Enterome's unique ability to decode and interrogate the microbiome allows it to tap into the potential of this enormous bacterial protein reservoir to generate novel peptide drugs against a broad range of diseases. Enterome's Mimicry drug discovery platform has led to the development of first-in-class orally available bioactives drugs based on proteins secreted by the gut bacteria that act like human hormones or cytokines, called EndoMimics. Additionally, Enterome is developing a range of cancer treatments based on bacterial peptide mimics of tumor antigens, called OncoMimics.

With its EndoMimics platform, Enterome has already identified a bacterial peptide named EB1010 that modulates the immune system by inducing IL-10 secretion. Its novel mode of action allows for the development of an orally administered, GI-selective next generation IL-10 inducer for the treatment of Ulcerative Colitis. Enterome has also screened for potential GLP-1 secretagogues, leading to the identification of 3 potential hits.

Dr Marc DUMAS, Ph.D.

CNRS PI and Group Leader, U1283/UMR8199, EGID, University of Lille. Lille, FRANCE

> The Microbial Metabolome in Metabolic Diseases

The gut microbiome – the comprehensive set of bacterial genes in our guts – is now recognized as a key driver in the pathophysiology of obesity, type 2 diabetes and cardiometabolic diseases and their common low-grade inflammatory component. However, the signals sent by the gut microbes to the host remain elusive. Through machine learning and multivariate analysis of metabolomes and metagenomes our group identified clinically relevant and drug-deconfounded microbiome signatures for the progression along the cardiometabolic disease spectrum, paving the way for new hypotheses and elucidation of the mechanisms impacted by the gut microbiome.

Pr Amandine Everard, Ph.D.

UCLouvain, Université catholique de Louvain, Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Walloon Excellence in Life Sciences and BIOtechnology (WELBIO)

Brussels, BELGIUM

> *Akkermansia muciniphila* in *metabolic* disorders, from mouse studies to clinical translation

The gut microbiota is a key player involved in health and diseases. Among the potential next-generation beneficial bacteria that are under investigation, *Akkermansia muciniphila* seems to be a promising candidate. *Akkermansia muciniphila* is inversely associated with obesity, diabetes, cardiometabolic diseases and low-grade inflammation. We initially highlight that *Akkermansia muciniphila* was the bacteria the most affected by a prebiotic treatment. Moreover, its abundance was positively correlated with the beneficial effects of prebiotic during obesity. Then, we demonstrated that this bacterium was able to counteract diet-induced obesity and metabolic disorders in mice. Nowadays, a large body of evidence also demonstrates the causal beneficial effects of *Akkermansia muciniphila* in several preclinical models. In order to translate these preclinical data into human applications, adaptations of the culture medium were required. Moreover, we highlighted that the pasteurization of *Akkermansia muciniphila* not only increases its stability but also its efficacy. We recently demonstrated that daily oral supplementation of *Akkermansia muciniphila* either live or pasteurized for three months was safe and well tolerated in volunteers suffering from overweight and metabolic syndrome. This first exploratory study also reveals that pasteurized *Akkermansia muciniphila* supplementation during 3 months improved insulin sensitivity and reduced insulinemia and plasma total cholesterol in comparison to placebo group. In conclusions, pasteurized *Akkermansia muciniphila* shows protectives effects on the deleterious progression of the metabolic syndrome over time in humans. These results support the interest of using *Akkermansia muciniphila* as a potential next-generation beneficial microbe.

Pr Bert A.K. Groen, Ph.D.
Professor of Systems Biology and Medicine
Experimental Vascular Medicine
Amsterdam University Medical Ceneters, Location AMC
Amsterdam, The Netherlands

> Microbiome-derived ethanol in non-alcoholic fatty liver disease

To test the hypothesis that the gut microbiota of individuals with non-alcoholic fatty liver disease (NAFLD) produce enough ethanol to be a driving force in the development and progression of this complex disease, we performed one prospective clinical study and one intervention study. Ethanol was measured in fasting and 120-minutes post mixed meal test (MMT) in 146 individuals. In a subset of 37 individuals' and in an external validation cohort, ethanol was measured in portal vein blood. In an intervention study, 10 individuals with NAFLD and 10 overweight but otherwise healthy controls were infused with the selective alcohol dehydrogenase inhibitor (ADH) before an MMT. Median portal vein ethanol concentrations increased with disease progression: 2.1mM; NAFL 8.0mM; NASH 21.0mM and were 187 (IQR:17-516) times higher compared to fasted peripheral blood. Inhibition of ADH induced a 15-fold (IQR:1.6-20) increase in peripheral blood ethanol concentration in individuals with NAFLD, though this effect was abolished after antibiotic treatment. Specifically, *Lactobacillaceae* correlated with post prandial peripheral ethanol concentrations (spearman rho:0.42; $p<10^{-5}$) in the prospective study. Our data shows that first pass effect obscures the levels of endogenous ethanol production and suggest that microbial ethanol could be considered in the pathogenesis of this highly prevalent liver disease.

Stoyan Ivanov, Ph.D.
Team Leader
Laboratoire PhysioMédecine Moléculaire, UMR 7370 CNRS, Université Côte d'Azur, Faculté de Médecine
Nice, FRANCE

> Brown adipose tissue myeloid cell diversity and functions

Glucose metabolism has been shown to control key macrophage functions including their ability to engulf and digest apoptotic cells. Importantly, genetic Glut1 ablation in myeloid cells triggered a slightly decreased blood monocyte number. How precisely intracellular glucose handling is involved in this process remains to be defined. Upon internalization, glucose could integrate two major metabolic pathways, namely glycolysis and the pentose phosphate pathway. The relative contribution of these pathways to monocyte and macrophage functions during atherosclerosis is yet to be fully defined. Of interest, Bay (a selective Glut1 pharmacological inhibitor) administration diminished monocyte blood numbers. However, and despite the strong decrease in blood monocyte numbers, Bay-treated mice had similar plaque area as vehicle-injected animals. In the present study we demonstrated that preventing Glut1-dependent glucose internalization reduced blood monocyte survival while facilitating their plaque recruitment.

Pr Gilles Mithieux, Ph.D.
Director of Research of the CNRS
Director of the Inserm laboratory 1213
Lyon, FRANCE

> The gut microbiota: a stable bioreactor of variable composition?

Metabolic diseases are associated with marked changes in the genetic composition of the gut microbiota, which has suggested that the gut microbiota itself might have a causal role in these diseases. However, animal and human studies have been published that run counter to this concept. An example relates to the metabolic benefits of dietary fibers that are mediated by short chain fatty acids deriving from the fermentation by the gut microbiota. These benefits are largely believed to be dependent on the fiber-associated change in the microbiota composition. Instead, they do not take in mice with deficient intestinal gluconeogenesis, despite the expected change in microbiota composition. This has strongly suggested that intestinal gluconeogenesis is essential in the benefits of fiber, whilst the fiber-induced change in the microbiota composition is not. In addition, the production of short-chain fatty acids is a redundant function, widely distributed among intestinal bacteria at all levels of classification.
It is proposed that the intestinal microbiota might be regarded as a stable metabolic bioreactor, where the microbes, independently of specific genetic composition, provide the specific enzymes absent from the body, but vital to carry out metabolic reactions permitting to supply from food metabolites that are essential to the host. Thus, the symbiosis between hosts and microbes allows any living organism to get the most out of the food eaten, irrespective of food content, in a given enzymatic equipment of the host for food digestion.

Pr Matej Oresic, Ph.D.
Professor of Medicine, with Specialization in Systems Medicine
School of Medical Sciences, Örebro University,
Örebro, SWEDEN

> Metabolome in non alcoholic fatty liver disease: pathways, metabolic models, and biomarkers

Nonalcoholic fatty liver disease (NAFLD) is a progressive liver disease that is strongly associated with type 2 diabetes. Accurate, non-invasive diagnostic tests to deliniate the different stages: degree of steatosis, grade of nonalcoholic steatohepatitis (NASH) and stage fibrosis represent an unmet medical need. In our previous studies, we successfully identified specific serum molecular lipid signatures which associate with the amount of liver fat as well as with NASH.

Here we report underlying associations between clinical data, lipidomic profiles, metabolic profiles and clinical outcomes, including downstream identification of potential biomarkers for various stages of the disease. We leverage several statistical and machine-learning approaches to analyze clinical, lipidomic and metabolomic profiles of individuals from the European NAFLD Registry. We interrogate data on patients representing the full spectrum of NAFLD (n = 627), across 3 clinical perspectives: steatosis, NASH, and fibrosis. We found that steatosis grade was strongly associated with (1) an increase of triglycerides with low carbon number and double bond count as well as (2) a decrease of specific phospholipids, including lysophosphatidylcholines. We identified that progression from F2 to F3 fibrosis coincides with a key pathophysiological transition point in disease natural history. In a related investigation, we also report that exposures to environmental chemicals impact hepatic metabolic pathways in sexually dimorphic manner.

Taken together, analysis of circulating metabolites and environmental chemicals provides important insights into the metabolic changes during NAFLD progression, revealing metabolic signatures across the NAFLD spectrum and features that are specific to NAFL, NASH, and fibrosis.

Pr Oluf Pedersen, Ph.D.

MD, DMSCi, Professor of Human Metabolism, Chief Research Physician, Specialist of Endocrinology, Center for Clinical Metabolic Research, Gentofte University Hospital and Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen
Copenhagen, DENMARK

> On the move from observation to causality in microbiome research

Skepticism about any impact of the commensal gut microbiome on human health is receding, while the research field is rapidly moving from descriptive microbiota census analyses to cause-and-effect documentary studies. In my talk I discuss our findings on how 1) a disrupted gut bacteriome and virome contribute to the pathogenesis of anorexia nervosa; 2) low microbiome gene richness predicts the conversion from prediabetes to incident type 2 diabetes over a period of four years; and 3) discovery and characterization of two bacterial polypeptides produced by prevalent bacterial strains in the gut microbiota from healthy individuals impacting energy metabolism, bone formation and muscle differentiation.

Dr Valentina Tremaroli, Ph.D.

Team Leader for gut microbiota metagenomics at the Wallenberg Laboratory, Department of Molecular and Clinical Medicine, University of Gothenburg, SWEDEN

> Gut microbiota and type 2 diabetes

Trillions of bacteria populate the human body, and particularly the gut. The interactions of these bacteria with the host form a symbiosis that contributes to homeostasis and is affected in the transition between health and disease[1]. Cross-sectional studies show that the gut microbiota is altered in cardiometabolic diseases, including type 2 diabetes (T2D). We show that the alterations occur before the development of T2D, in individuals with prediabetes and particularly in those with impaired glucose tolerance, possibly reflecting the status of insulin resistance[2,3]. The most consistent alterations associated with prediabetes and T2D are a decrease in the abundance of commensals, such as butyrate producers, and a decrease of microbial gene richness. These results stress the importance of the functional alterations of the gut microbiota, and suggest that the loss of gene richness and butyrate producers might represent a degraded state of the gut microbiota with altered metabolism, broken homeostasis, and decreased colonization resistance. Microbiota-based approaches might need to further investigate and consider the drivers of gut microbiota assembly and stability[4,5], which might be required to promote transitions from degraded states back to homeostasis.

References

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