Le microbiome

Development of Next Generation Bacteria and Health, From the Bench to the Bedside

Patrice D. Cani, Louvain Drug Research Institute, UCLouvain, Brussels, Belgium

In 2007, we discovered that high-fat diet feeding was associated with a lower abundance of a newly identified bacteria, namely *Akkermansia muciniphila*. We then found that treating mice with this specific bacterium improved insulin sensitivity, metabolic endotoxemia, gut barrier and reduced fat mass. In 2019, we published the first randomized double-blind placebo controlled exploratory study during which we have administered daily live or pasteurized *Akkermansia* for 3 months, in subject with a metabolic syndrome and found that pasteurized *Akkermansia* was safe and induced beneficial effects on cardiometabolic risk factors (Depommier et al. *Nature Medicine July 2019*). The objectives of this presentation are to demonstrate how researches starting in rodent models may be extended to human beings and how the processes of development of fundamental research requires to overcome numerous problems before starting the first proof of concept studies in the targeted population.

Harnessing the Microbiome Through Prebiotics to Alleviate Metabolic Diseases

André Marette, Laval University, Quebec, Canada

Obesity and related metabolic diseases such as type 2 diabetes (T2D) are increasing at an alarming rate and calls for novel preventive and therapeutic measures. These diseases are linked to visceral obesity and ectopic fat accumulation in non-adipose tissues such as the liver leading to nonalcohol fatty liver disease (NAFLD). It is now well documented that perturbations in the gut microbiome contribute to diet-induced obesity, T2D and NAFLD. I will show that new prebiotic extracts enriched with polyphenols from various dietary sources protect against obesity-linked inflammation and alleviate T2D and NAFLD in high fat-fed animal models. This is associated with a reshaping of of the gut microbiome and with an increase in the abundance of selected bacterial species such as the mucin-degrading *Akkermansia muciniphila*. Increase in the *Akkermansia* population may therefore contribute to the anti-inflammatory and beneficial effects of dietary polyphenols in obese mice. I will also show that an extract from the amazonian fruit Camu Camu has a remarkable anti-obesity effect that is related to changes in the gut microbiome and in the profile of bile acids, leading to activation of brown fat thermogenesis through a gut-liver axis.

The Role of the Gut Microbiome in Cancer Therapy and Prevention

Scott Bultman, University of North Carolina, Chapel Hill, United States

The gut microbiome has a profound effect on our immune system and metabolism, which are recognized as hallmarks of cancer. Yet our knowledge of basic mechanisms is just beginning to be translated into cancer therapies. This talk will discuss: 1, The influence of the gut microbiome on the efficacy of checkpoint inhibitors for immunotherapy. 2, The prospect of developing drugs targeting microbial enzymes as chemotherapy adjuvants to mitigate inflammatory adverse events. 3, The role of diet and the microbiome in cancer prevention with an emphasis on dietary fiber being fermented by gut bacteria into butyrate, which is a tumor-suppressive metabolite with potent energetic and epigenetic properties.

The gut microbiome has a profound effect on our immune system and metabolism, which are recognized as hallmarks of cancer. Yet our knowledge of basic mechanisms is just beginning to be translated into cancer therapies. This talk will discuss:

- The influence of the gut microbiome on the efficacy of checkpoint inhibitors for immunotherapy.
- The prospect of developing drugs targeting microbial enzymes as chemotherapy adjuvants to mitigate inflammatory adverse events.
- The role of diet and the microbiome in cancer prevention.

Predicting and Improving Cancer Immunotherapy Using the Gut Microbiome

Bertand Routy, CRCHUM and Faculty of Medecine, Université de Montréal

The objective of this presentation is to understand the unforeseen role of the gut microbiome in the era of immuno-oncology. Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) and its ligand (PD-L1) have achieved unprecedented breakthroughs for the treatment of advanced cancers. ICI have rapidly become the standard of care for multiple tumor types; however, a significant proportion of patients do not respond, and a subset may progress faster than normally expected on ICI. Mouse models and observational studies in ICI recipients indicate that the gut microbiome is an important mediator of ICI efficacy, revealing interactions between specific bacteria and the host that influence ICI anti-tumor immunity and toxicity. Gut microbiome profiling in patients with metastatic melanoma, lung and genitourinary malignancies identified bacteria that are associated with responsiveness or toxicity in humans and can restore ICI responsiveness in mice. These initial studies have identified the importance of the gut microbiome as a novel diagnostic and therapeutic target in ICI recipients, yet critical questions remain about the generalizability, therapeutic viability and mechanistic significance of these findings.

Emerging Prevention Strategies for *Clostridioides Difficile* Infection (CDI): What Does the Future Hold?

Erik R. Dubberke, Washington University School of Medicine, United States

Current strategies to prevent *Clostridioides difficile* infection (CDI) are effective but have limitations. CDI is the prototypical example of how a healthy microbiome can protect against disease states. Potential future strategies to prevent CDI include preservation of the microbiome during antimicrobial exposures and harnessing microbial defense mechanisms. At the end of the session, the participant will be able to identify emerging next generation prevention strategies for *Clostridioides difficile*.

Prevention and Control of *C. Difficile* Infections – The Quebec Experience

Yves Longtin, Jewish General Hospital and Associate Professor, McGill University, Montreal, Canada

CDI is a major source of patient morbidity and mortality. The province of Quebec has been at the epicenter of the CDI pandemic that has spread throughout the world. This presentation will review the epidemiology and evolution of CDI in Quebec and Canada, present the current preventative strategies, and explore the role of various preventative strategies in its control including environmental control, antimicrobial stewardship and the detection and isolation of C. difficile asymptomatic carriers.

Insights Into the Gut-Brain Connection: Investigating the Intestinal Microbiota in Multiple Sclerosis and Alzheimer's Disease

Laura M. Cox, Brigham and Women's Hospital, Boston, United States

The objective of this presentation is to review the biologic pathways by which the microbiota can influence neurologic disease. The intestinal microbiota can influence the brain via bidirectional immunologic, neural, and endocrine signaling, which may play important roles in the initiation and progression of neurologic disease. Multiple sclerosis is an autoimmune mediated disease with strong environmental influence and an average age of onset of 20-40 years of age. We have now identified bacteria that are altered in MS and link these changes with disease progression, severity, brain volume, and quality of life. In the elderly, age-related changes in the gut microbiota contribute to immune dysfunction and have been hypothesized to play a role in Alzheimer's disease (AD). We found that mice that overexpress the amyloid-precursor protein have accelerated age-related changes in their gut microbiota, which can be rescued via a calorie-restriction diet. This dietary modification also prevented amyloid-beta plaque accumulation in female mice and enriched protective microbiota in a sex-dependent manner. All together, these studies identify disease-specific bacteria that may influence MS and AD, which may serve as novel therapeutic targets.

The Gut-Brain Axis in Parkinson's Disease: is PD an Autoimmune Disease?

Michel Desjardins, Department of Pathology and Cellular Biology, Faculty of Medecine, Université de Montréal

Parkinson's disease (PD) is a neurodegenerative disorder with motor symptoms linked to the loss of dopaminergic neurons (DNs) in the substantia nigra compacta. Although the mechanisms triggering the loss of DNs are unclear, mitochondrial dysfunction and inflammation are viewed as playing a key role. An early-onset form of PD is associated with mutations in the *PINK1* kinase and *PRKN* (*Parkin*) ubiquitin ligase genes. While PINK1 and Parkin have been shown to drive mitophagy and clearance of damaged mitochondria in cultured cells, recent evidence obtained using knock-out and knock-in mouse models have led to contradictory results regarding the contribution of PINK1/Parkin to mitophagy *in vivo*. We recently showed that PINK1 and Parkin play a role in adaptive immunity by repressing mitochondrial antigen presentation (MitAP) in inflammatory conditions induced by lipopolysaccharide (LPS) treatment, suggesting that autoimmune mechanisms participate in the aetiology of PD. Since LPS is the major component of the outer membrane of Gram-negative bacteria, the objective of this study was to determine whether infection with such bacteria would engage autoimmune mechanisms in PD-susceptible mice. We now have evidence that intestinal infection with Gram-negative bacteria in *Pink1*$^{-/-}$ mice engages MitAP and autoimmune mechanisms, eliciting the establishment of cytotoxic mitochondria-specific CD8+ T cells in the periphery and in the brain. Remarkably, infection in these mice leads to the emergence of motor impairment, reversed by L-DOPA treatment, accompanied by a sharp decrease in the density of dopaminergic axonal varicosities in the striatum. These data support a role for PINK1 as a repressor of the immune system and provide a new pathophysiological model where intestinal infection acts as a triggering event in PD, highlighting the relevance of the gut-brain axis in the disease. Further studies are currently investigating whether modification to the microbiome, induced by gut infection, might contribute to PD.