

# The gut reaction

**Professor Jean-François Beaulieu** shares the details of some of his work in the field of gastrointestinal disease – and the challenges he and his team have faced along the way

**Could you outline the principal aims of your research?**

The overall goal of our research is to define the mechanisms that regulate epithelial functions in the human intestine under normal and pathological conditions. More specifically, we are investigating the influence of soluble mediators such as growth factors, cytokines and hormones as well as insoluble components such as the extracellular matrix macromolecules which can modulate intestinal epithelial cell functions including proliferation, migration, survival and differentiation via the activation of specific membrane receptors.

**What are the benefits of using the human intestinal mucosa and intestinal epithelial cell lines for investigating these questions?**

Working with human intestinal samples

## A lot to digest

Gastrointestinal diseases pose a tremendous problem to healthcare services worldwide. A **Université de Sherbrooke** team in Quebec has been tackling the problem for more than two decades and has developed some novel solutions

**IN CANADA, DISEASES** of the digestive system are responsible for 12 per cent of all hospitalisations and account for 15 per cent of the total economic burden of healthcare. Neoplasia – the abnormal growth of cells associated with tumours and cancer in the human body – is even more strongly represented; 20 per cent of all neoplasia is linked to diseases of the digestive system. Colorectal cancer and inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis are particularly prevalent in developed countries and are rising extensively in the developing world, indicating the growing and global nature of this health concern.

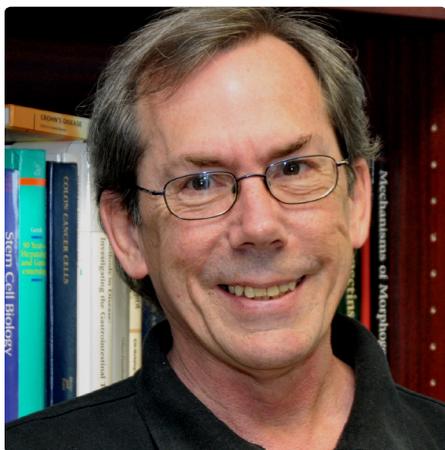
Treatment for diseases of the intestines is less effective than it could be because relatively little is known about the molecular basis of human intestinal development and disease. Further research into the epithelial function of the human intestine is thus a key research area, which could ultimately lead to novel diagnostic and therapeutic tools.

### UNDERSTANDING EPITHELIUM

Professor Jean-François Beaulieu's team in the Department of Anatomy and Cell Biology at the Université de Sherbrooke, Quebec, is working on understanding the renewal mechanisms of

cells that form the inner wall of the digestive system. A Canada Research Chair in Intestinal Physiopathology, Beaulieu has been increasing knowledge in this area for more than 25 years. His laboratory has developed some novel solutions to the challenges presented by this field of research and, with the help of these advances, the investigators have been able to cover a huge amount of ground in this field – and hope to translate their work into new treatments and diagnostics in the near future.

Their research focuses on better understanding the activities of the epithelial cell wall at a



presents obvious challenges over the use of experimental animal models. These challenges are numerous and include limited availability, ethical issues and inherent genetic variability. However, in light of accumulating evidence, data obtained from animal models, namely small laboratory animals, cannot always be transposed to the human situation; thus, the necessity of acquiring data using human tissue is becoming increasingly obvious. Our group has been particularly active in the establishment of human intestinal tissue banks for developing, normal and pathological adult intestines used for expression studies, immunolocalisation, laser capture microdissection and gene expression profiling experiments, as well as in the development of experimental models. This enables the study of the human intestinal mucosa in organ culture, in reconstituted 3D cell culture models and the use of normal intestinal epithelial cell cultures and cell lines.

### Could you explain the new approach your team developed for identifying primary pathways relevant to the initial disruption of epithelial barrier function in inflammatory bowel disease (IBD)?

The first line of defence of the intestinal mucosa is a single layer of epithelial cells. Damage resulting from disruption of this intestinal epithelial barrier is a key feature of inflammatory bowel diseases as it results in the translocation of commensal bacteria in the mucosa. The epithelial barrier is mainly regulated by environmental factors such as growth factors, immunoregulatory cytokines and the interacting microflora, but their role and interplay still remain incompletely understood, especially in the human.

Over the last few years, our group has tested a new approach for identifying primary pathways relevant to the initial disruption of epithelial barrier in inflammatory bowel diseases based on organ culture of the human mid-gestation small intestine. This was developed by us three decades ago in combination with the detailed analysis of intestinal gene expression profiles. Previous studies from our group and others have clearly established that in the human, the mid-gestation small intestine is already morphologically and functionally similar to its adult counterpart. As proof of concept, we recently tested the effect of epidermal growth factor (EGF) and found that it exerts a net anti-inflammatory influence on the repertoire of genes expressed in the human intestinal mucosa. On the other hand, indomethacin was found to impair glucose metabolism and mitochondrial function and increase the production of reactive oxygen species leading to the disruption of intestinal barrier function.

### How might your findings lead to therapies for IBDs?

The aim of our current research is to discriminate between primary and secondary inflammatory-related events, an approach theoretically impossible to perform on intestinal specimens obtained from patients affected by IBDs. Using organ culture of the mid-gestation intestine under defined serum-free conditions, we are characterising the primary events involved in both the alteration and repair of human intestinal epithelial barrier function and investigating potential mediators such as EGF.

### What are your plans for the future direction of your research?

One aspect of our research that we expect to develop further is the characterisation of specific biomarkers for intestinal pathologies. Indeed, the identification of specific molecules and pathways that regulate human intestinal cell functions in both health and disease has been progressing over the last decade. Translation of this research to the clinic should contribute to better diagnoses and monitoring of the progression/resolution of intestinal pathologies such as IBDs, necrotising enterocolitis and colorectal cancer. Another aspect of our research pertains to the plasticity of normal intestinal epithelial crypt cells as demonstrated by the high interconversion potential of human intestinal epithelial cells (HIEC) toward either stemness or differentiation as a result of minimal gene manipulation. The outcome of these findings is likely to be significant in the field of human intestinal stem cells, considering the growing evidence in the literature for crypt stem cells as the cells of origin of intestinal cancer.

molecular level, and decoding how various genetic structures can come to be represented in certain phenotypic characteristics. These epithelial cells are responsible for protecting the inner surface of the intestine, constantly reproducing at a very high speed – but little is understood about how they go about this high-speed procreation, or the mechanisms that govern them as they do so. We do know, however, that deficiencies in this area lead to complex diseases such as colorectal cancer and IBD.

#### A DELICATE BALANCE

The health of the intestinal mucosa is maintained by a complex interaction between growth factors, immunoregulatory cytokines and microflora. When the epithelial function is disrupted, this leads to a chain of events resulting in inflammation – but, to have a better understanding of inflammation, we must first understand the other events in this chain, and whether they are primary or secondary to the final effect.

Over the last few years, Beaulieu's group has been testing a novel approach to the identification of primary events leading to the initial disruption of epithelial barrier function in IBD cases, based on organ culture of the human mid-gestation intestine in combination with the analysis of intestinal gene expression profiles.

### The group was among the first to highlight the need for human tissue samples as opposed to animal models

In addition, Beaulieu and his colleagues are currently working on the idea that epidermal growth factor (EGF), a kind of soluble mediator similar to a hormone, exerts anti-inflammatory effects on the human intestine that may be able

to counteract induced inflammation – this idea having been suggested by the team's previous work. If they can identify the cellular and molecular interactions involved in this process, which allows EGF to produce pro-healing and anti-inflammatory effects on the intestinal epithelium, they could advance our understanding of IBD and make available effective therapeutic tools.

#### LEADERS IN THE FIELD

The work has developed from a well-established body of research already accomplished by the investigators, and their discoveries have had wide-ranging applications. The group was the first to identify and establish the patterns of expression for a number of important macromolecules of the extracellular matrix in the intestine including type IV collagens, laminins, various proteoglycans, cellular fibronectins and tenascins, as well as their receptors in the integrin and non-integrin families. Performed across the board in normal and pathological tissue from adult and

## INTELLIGENCE

### CANADA RESEARCH CHAIR IN INTESTINAL PHYSIOPATHOLOGY

#### OBJECTIVES

To explain the mechanisms that regulate gene expression in cells which form the human intestinal system (both healthy and diseased). The group is analysing the main phases of intestinal cell renewal, which will potentially lead to the development of new treatments for numerous forms of gastro-intestinal ailments.

#### KEY COLLABORATORS

**Professor Emile Levy**, Department of Nutrition, Université de Montréal and CHU Sainte-Justine, Canada

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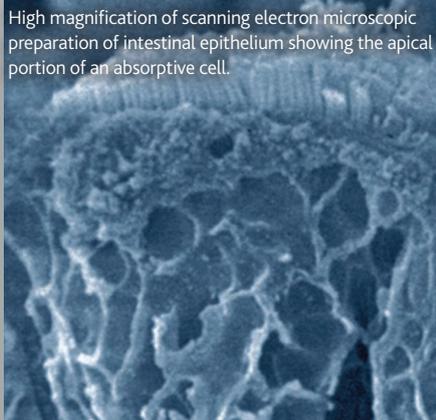
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**JEAN-FRANÇOIS BEAULIEU** is a professor at, and a member of, the Mother and Child Research Axis of the Centre de recherche clinique Étienne-Le Bel, CHUS. He received the Étienne-Le Bel Senior Investigator Award for excellence in research from his institution in 2010. He holds the Canada Research Chair in Intestinal Physiopathology and is the co-leader of the Research Consortium on Child Intestinal Inflammation which regroups several investigators of the Eastern Canada in this field. He is also Associate Editor for *BMC Molecular Biology* and Strategy Associate Editor for *World Journal of Gastrointestinal Pathophysiology*, and serves on several editorial boards of peer-reviewed scientific journals.

High magnification of scanning electron microscopic preparation of intestinal epithelium showing the apical portion of an absorptive cell.



developing subjects, these studies have led to the identification of potential therapeutic targets and diagnostic markers for a number of pathological conditions. These studies have been cited in numerous research papers and reviews.

The team has also been influential in tackling a number of obstacles. For example, they were among the first to highlight the need for human tissue samples as opposed to animal models. The standard method of examining IBD and colorectal cancer is to develop animal models for laboratory use – usually small mammals such as rodents. But as knowledge in the area has progressed, the usefulness of animal models has been questioned; we have reached a tipping point whereby the science needs to be advanced through observation of the diseases in human tissue.

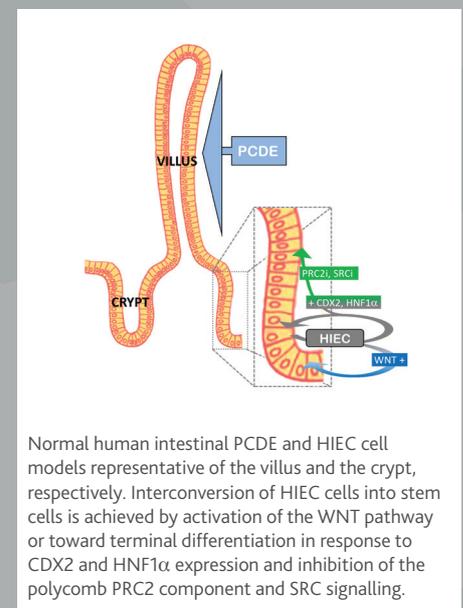
#### THE HUMAN DIMENSION

For Beaulieu's group, this step from animal model to human tissue was prompted by the evident difference in the expression and distribution patterns between human and animal tissues, which made it prohibitively hard for the researchers to further their studies into the role of cell matrices in normal and diseased intestine. In response, they developed their own models of normal human intestinal cells that enable study of intestinal cells that are not only human, but also unaffected by other

diseases such as colorectal cancer. Using these, they have been able to better study the growth, differentiation, migration and survival abilities of the cells under conditions that recapitulate the main events observed in the intact intestine. These new models have proven incredibly useful for other researchers, and have been frequently referenced in various studies and publications. Indeed, in the last 10 years, the models have been the subject of more than 50 publications.

#### GLOBAL RESEARCH

In the words of Canada Research Chairs, a leadership programme that is at the heart of Canadian national research strategy, the group's studies 'promise to be significant'. As the second highest cause of hospitalisation in Canada and the fourth highest cause of temporary disability, gastro-intestinal diseases cost the country an estimated \$100 billion annually. However, the scope of this research is not merely national; millions worldwide could benefit from the diagnostic tools and therapeutics that are on the cusp of being developed thanks to this knowledge.



Normal human intestinal PCDE and HIEC cell models representative of the villus and the crypt, respectively. Interconversion of HIEC cells into stem cells is achieved by activation of the WNT pathway or toward terminal differentiation in response to CDX2 and HNF1 $\alpha$  expression and inhibition of the polycomb PRC2 component and SRC signalling.

#### A PREVALENT PROBLEM

According to the Crohn's and Colitis Foundation of Canada, there are approximately 233,000 Canadians living with IBD. Moreover the Crohn's & Colitis Foundation of America states that as many as 1.4 million Americans are affected by the disease. In terms of colorectal cancer, Canadian Statistics 2012 found that nearly 40 per cent of all cancer deaths in Canada are due to lung and colorectal cancers, and the American Cancer Society estimates that there will be 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer in the US in 2013.

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