The mission of the Inflammatory Bowel Disease (IBD) Research Group at the Center for Perioperative Medicine at UTHealth aims to bring novel therapeutic treatments to the sufferers of inflammatory bowel disease (IBD). There are significant difficulties in finding a common treatment for sufferers of IBD as each person responds to therapy differently. IBD can come in cycles of remission and relapse which makes disease management more challenging.

Even with successful management therapies, many patients encounter a diminishing therapeutic response as their treatment continues, so it is critical to develop diverse therapeutic approaches that can be used sequentially and interchangeably to increase the quality of life for IBD sufferers.

New avenues of research offer a chance for innovative clinical therapies applicable across a range of IBD diseases and symptoms. With the help of translational medicine, we hope to take bench-top science to the bedside of patients and make new treatments available for IBD sufferers of all ages.
We would like to thank the Brad McWilliams IBD Research Gift for helping us to advance our studies toward finding new treatments for patients with inflammatory bowel diseases through the use of microRNAs and hypoxia research.

A very generous gift from Mr. McWilliams, combined with the vision and effort of physician-scientist Dr. Holger Eltzschig, has allowed us to establish an IBD research team to explore new avenues for the treatment of bowel inflammation through research on the hypoxia-inducible class of small RNAs.

Very low-oxygen conditions develop within an inflamed bowel leading to the activation of transcription factors called hypoxia-inducible-factors (HIFs), which in turn control a class of broad-acting microRNAs. These microRNAs are powerful regulators in a wide variety of diseases and their role in IBD has just begun to be appreciated. The small size and portability of miRNAs make them attractive candidates for therapeutic interventions in clinical settings. We anticipate that microRNA therapeutics have the potential to become a major new class of drugs in the treatment of bowel inflammation.

We are very thankful to Mr. McWilliams for supporting our efforts to identify, study, and evaluate the future of hypoxia-inducible miRNAs.

Ki67 marker labeling of proliferating cells in normal mucosa in the small intestine
Central Role of Hypoxia in IBD

Intestinal epithelial cells cover the inside of the small and large bowel in a single layer. The cells at the tips of intestinal projections called villi operate in conditions of low oxygen but the oxygen concentration is higher in the healthy intestinal crypts where intestinal stem cells live. State of inflammation in the cells covering the intestine leads to a decrease in the amount of available oxygen and leads to tissue hypoxia. Hypoxia is sensed and signaled through a family of highly-conserved transcription factors called HIFs (Hypoxia inducible factors), HIF-1a and HIF-2a are essential factors that maintain intestinal homeostasis and play a major role in intestinal responses during IBD.
Immunology of IBD and Immune Cell Function

The gut is an area of very high immunological challenge where tolerating what is inside the lumen of the intestine and delivering protection against intestinal pathogens must be maintained. The CD4+ T cells are key players in mediating both the protective and the tolerizing responses. We study the regulation of T-cell function by micro RNAs that show great promise to be employed as future therapeutic agents in human IBD patients.
Function of the intestinal epithelium: maintaining balance and integrity

The intestinal epithelial cells make up the mucosal barrier tissue of the gut and play an important function in the development of inflammatory diseases of the intestine. When this barrier is compromised and broken, bacteria present in the gut can move into the deeper tissue layers and promote inflammation by activating the immune cells normally present there. We are studying factors that enhance mucosal integrity and promote repair of the broken barrier function leading to resolution of gut inflammation.

Crosstalk of the immune and epithelial functions

The mucosal epithelial cells lining the gut have not only a barrier function that keeps the gut microflora at bay, but they are engaged in an active sampling of the gut contents. The information they gather is then relayed to the immune cells that adjust their behavior based on this information. In turn, the intestinal epithelial cells respond to the signals such as cytokines and peptides produced by the immune cells. Disruptions of this communication system are involved in many diseases such as chronic infections, inflammatory bowel disease and colon cancer.

Using cancer models in mice to halt progression of IBD to intestinal cancer

Colitis associated cancers develop in the setting of chronic inflammation that accompanies the ulcerative colitis and Crohn’s disease. The mechanisms that underly development of these malignancies are unclear and inadequately studied. The human cancers can be induced by many oncogenic pathways and are heterogenous so genetic mouse models of are used to study this disease. Growth of cancer cells induces hypoxic conditions inside many solid tumors and hypoxia-induced micro RNAs are emerging as regulators of cancer growth.
**CENTER**

**GOALS**

**Immediate:** We have set up colitis models in mice, developed new mouse mutant strains and designed assays to evaluate the role of hypoxia/adenosine pathway and microRNAs as regulators of intestinal homeostasis, the immune responses, and therapeutic agents in IBD. We are planning to submit a manuscript to Nature in which we describe a novel role for miR-29a, a hypoxia-regulated gene microRNA, in the development and activation of Th1 T cells which play a critical role in inflammatory bowel diseases in humans. The miR-29a shows promise as a therapeutic agent that could have clinical applications in alleviating disease progression IBD patients.

**Future:** An additional year of funding would help our group to accumulate data necessary to submit a competitive R01 grant application that will secure resources to expand our investigation into other microRNAs as therapeutics for inflammatory bowel disorders and intestinal cancers. We envision that taking novel microRNA mimic-based therapies from the bench to the bedside will open new avenues of treatment and are working to establish collaborations with the clinicians at the UTHHealth Gastroenterology.

**OUR**

**RESEARCHERS**

From L to R: Dr. Jennifer Bailey, Dr. Holger Eltzschig, Dr. Xiaoyi Yuan, Dr. Agnieszka Czopik, Mr. Trent Clark, and Dr. Yanyu Wang
JENNIFER BAILEY, MA, PHD

Dr. Bailey has been working in the field of inflammation and early cancer development with a focus on epithelial and stromal crosstalk in GI malignancies for over 15 years. She uses mouse models to study therapeutic targets for preclinical development. In addition, her lab uses techniques to indelibly label epithelial or inflammatory cells with fluorescent tags to allow for high resolution isolation and imaging.

AGNIESZKA CZOPIK, PHD

Dr. Czopik has trained as a basic immunologist at Yale University studying the signaling and activation of innate immune receptors. She subsequently worked as an American Cancer Society Postdoctoral Fellow at Massachusetts Institute of Technology studying immunity and metabolism with a focus on the inflammatory intestinal diseases and colon cancer. She has worked as a teaching faculty in Houston for 5 years and is now very excited to have returned to bench research in mucosal immunology of the gut.

FRANK CHEN

Mr. Chen supports the laboratories of Dr. Eltzschig, Dr. Bailey, and others within the Department of Anesthesiology. He manages the creation, breeding, and genotyping of the tissue specific to the Flox-Cre transgenic mouse models we use in our IBD research.
TRENT CLARK

Trent Clark graduated from Houston Baptist University magnum cum laude in 2019 with a Bachelor's in Biochemistry and Molecular Biology. He has always shown a passion for science and a strong desire to serve others. In July 2020, Trent joined the Eltzschig lab as a Research Assistant in the hopes of expanding our understanding of immune-related Gastrointestinal diseases to find better and unique approaches to treatment. Since his arrival, he has assisted in the creation of various murine models, performed a variety of assays, and quantified resulting data.

HOLGER ELTZSCHIG, MD, PHD

Dr. Eltzschig is a physician scientist with a strong record in mentoring the next generation of basic and translational scientists. His laboratory has studied inflammatory bowel disease for many years. The goal of these studies is to find new therapeutic targets to dampen intestinal inflammation that would be rapidly translated into novel treatment approaches for patients experiencing Crohn's disease or ulcerative colitis. The research of his team is focused on finding endogenous pathways that dampen inflammation, such as hypoxia-inducible factors (HIFs) or microRNAs that can be used to treat or prevent inflammation. In contrast to known anti-inflammatory medications (such as steroids), these endogenous anti-inflammatory mediators hopefully will have less detrimental side effects, since they are known to the human body. Thanks to the generous gift of Mr. Brad McWilliams and also the support of public funding agencies (e.g. the NIH), Dr. Eltzschig and his team are very close to taking some of their findings from the bench to bedside and are hoping to soon be able to find new therapies to help treat patients with inflammatory bowel disease.
COLLABORATORS

YANYU WANG, PHD

Dr. Wang is the lab manager of Dr. Eltzschig’s laboratory. She plans and coordinates laboratory activities for research projects, supervises lab members to execute projects with allotted budget and timelines, develops and maintains AWC protocols and work instructions, stays current with the lab research progress, and provides assistance and conducts training to lab members when needed. In addition, Dr. Wang has extensive training in mucosal inflammation and immunity from her postdoc study about functional roles of complement cascade during Clostridium difficile infection (CDI) and inflammatory bowel disease.

XIAOYI YUAN, PHD

Dr. Yuan research interests focus on studying mucosal immunology, specifically hypoxia signaling and microRNAs in the pathogenesis of acute and chronic mucosal inflammation. Her previous training at Baylor College of Medicine helped her obtain extensive knowledge in immunological and molecular aspects of mucosal inflammation, which is a key driver of IBD. She has further gained expertise in the past few years on the therapeutic targeting of novel pathways in preclinical models.

SEAN COLGAN, PHD

Dr. Colgan’s laboratory has a long-standing interest in defining novel mechanisms of mucosal inflammatory responses, specifically related to innate immunity, neutrophil function and tissue metabolism. For the past 20 years, his laboratory has identified a number of novel regulatory pathways related to role of neutrophils in molding tissue resolution responses and the generation of endogenous anti-inflammatory molecules. Ongoing work is directed at elucidating the contribution of innate immune cells in regulating antimicrobial defense, barrier function and mucosal tissue metabolism. This work has led to a better understanding of how and why inflammatory diseases develop, and in particular, how innate immune responses contribute to inflammatory resolution.


