

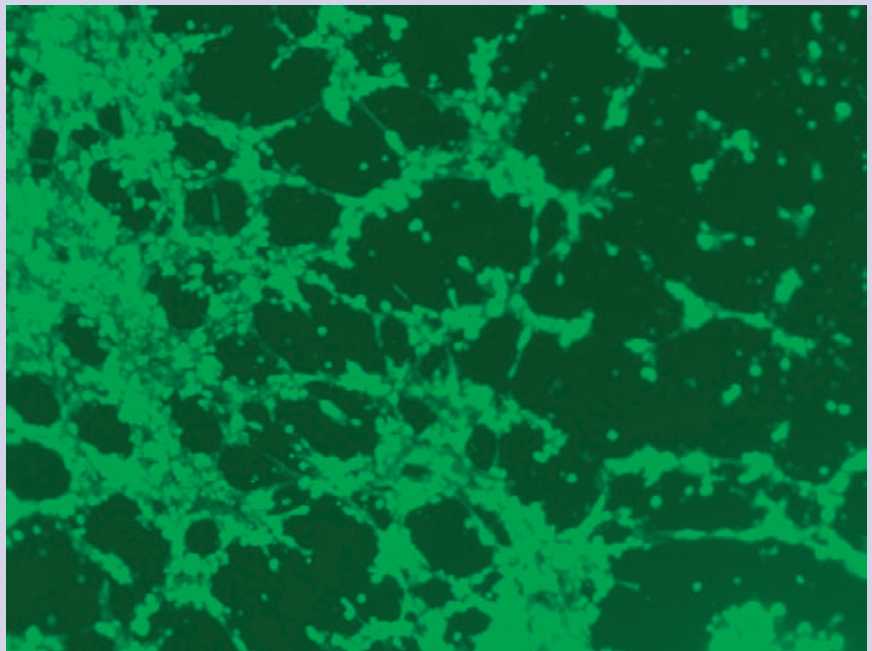
faculty



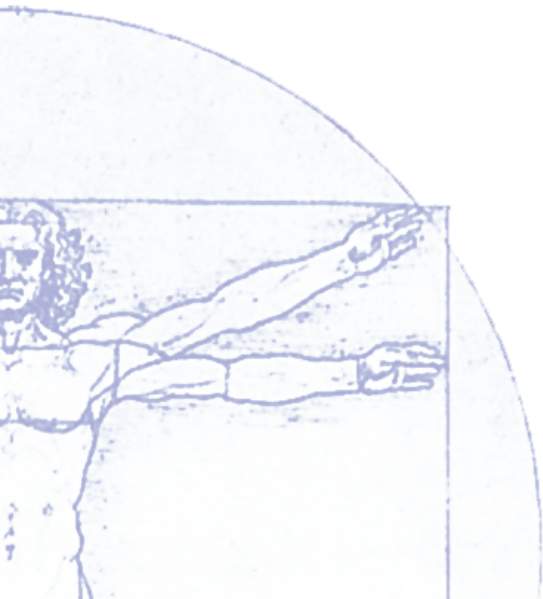
Jonathan Steven Alexander, PhD
Associate Professor
PhD, 1989
Boston University
email: jalex@lsuhsc.edu

Endothelial Cell Biology

The research in my laboratory deals mainly with endothelial cell biology, and how the junctional barrier maintained by different kinds of endothelial cells are altered in inflammation. The loss of the integrity of the endothelium and their junctions in particular, contributes to several important and familiar pathological conditions occurring acutely (respiratory distress, stroke, myocardial infarction) and chronically (diabetes, cancer and IBD). We are particularly interested in how certain receptors (glutamate receptors) on the brain vasculature respond during stroke to diminish the organization of junctions in the blood brain barrier. This defect is also apparently an important consequence in the injury and inflammation associated with multiple sclerosis. One new direction in the field of vascular biology we are pursuing is investigation of how lymphatic endothelial cells are molecularly distinct from blood vascular endothelium, and how they can be central targets in disease.



Lymphatic endothelial cells forming capillary tube structures on matrigel in response to VEGF-C



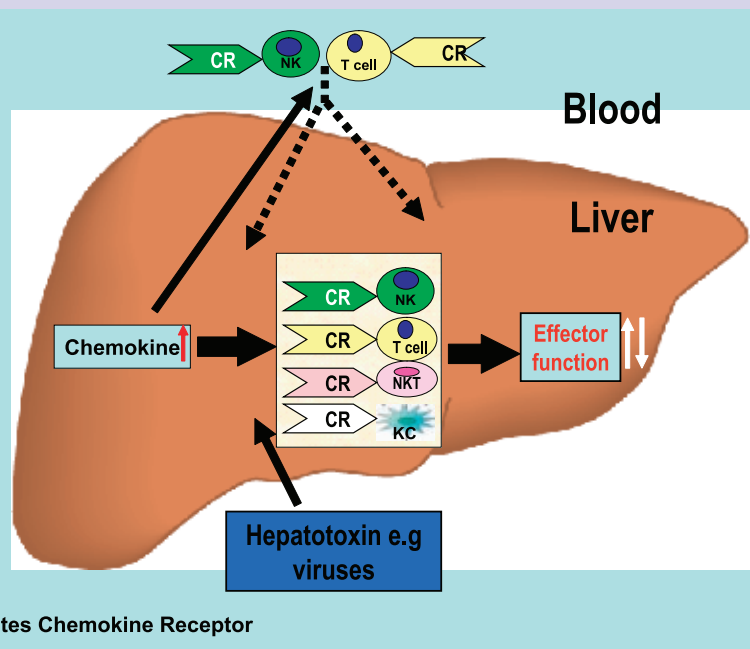
faculty



Maureen N. Ajuebor, PhD
Assistant Professor
PhD, 1998
The William Harvey
Research Institute
University of London
London, England
email: majuebor@lsuhsc.edu

Liver Immunopathology

Research in our laboratory is primarily focused on defining the role of innate immunity in the pathogenesis of acute viral hepatitis. The liver is home to an incredibly diverse population of immune cells including [(NK cells, NKT cells, macrophages) and conventional T cells [i.e. CD4(+) and CD8(+) cells] as well as non-immune cells (such as endothelial and stellate cells). This leads to a remarkable number of intercellular interactions in the liver. We are interested in defining how immune cell to immune cell interaction and immune cell to non-immune cell interaction can influence the development of liver diseases. In addition, we aim to investigate how chemokines (chemotactic cytokines) modulate immune cell recruitment into the inflamed liver and consequently alter effector function of leukocytes during viral liver diseases. It is envisaged that information obtained from these studies could help in the design of more effective therapeutic agents for viral liver diseases.



This figure depicts that the administration of a hepatotoxin such as a virus into the liver can induce the production of chemokines from resident hepatic cells. Chemokine(s) in the liver via their cognate chemokine receptor(s) promote the recruitment of immune from the blood. Next, recruited cells can drive the development of pro- or anti-inflammatory responses in the liver.

faculty

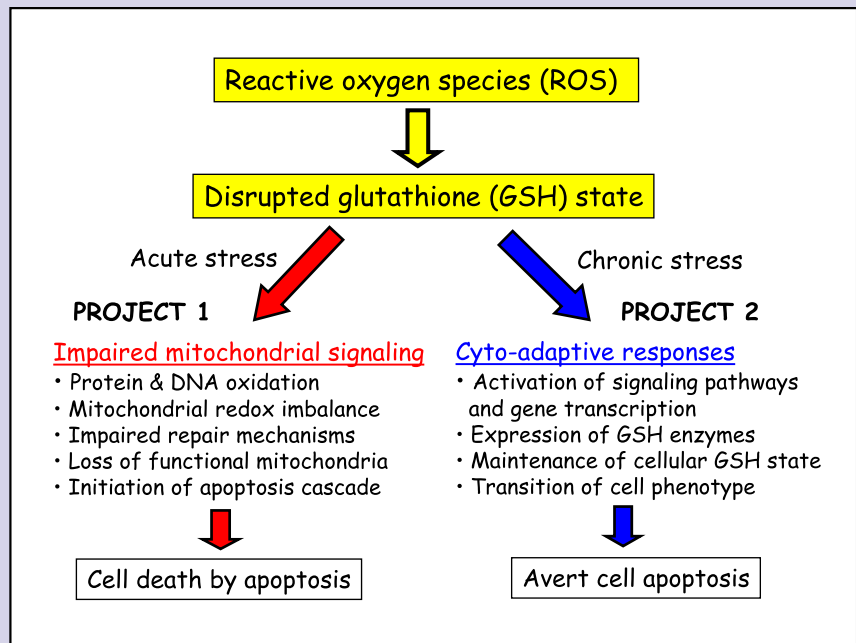


Tak Yee Aw, PhD
Professor
PhD, 1981
University of Otago
Dunedin, New Zealand
email: taw@lsuhsc.edu

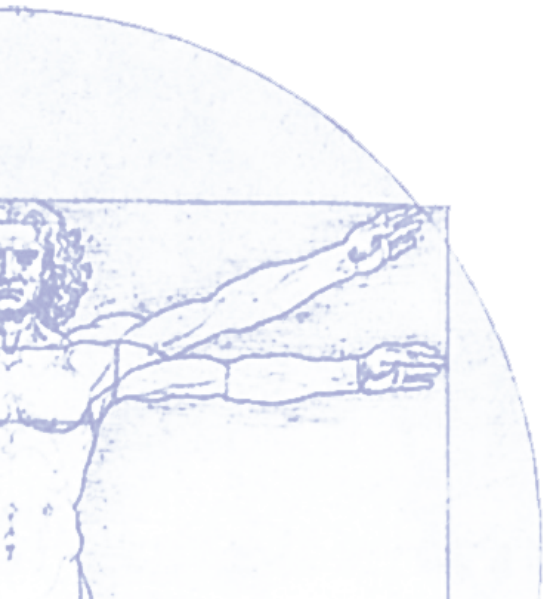
Oxidative Stress and Redox Mechanisms in Cell Signaling

My laboratory is focused on the study of oxidative stress and cell signaling that is relevant to the pathogenesis of cancer and degenerative diseases (e.g., diabetes, Alzheimer's). Oxidative stress is an important underlying cause in tissue malignant transformations and organ degeneration. Reactive oxygen species (ROS) derived from cell metabolism, inflammation and exogenous sources can disrupt cellular oxidation-reduction (redox) balance which governs metabolic fidelity and cell fate. Our laboratory examines the role of glutathione (GSH) redox in regulating cell death/survival and the mechanisms in cytoprotection against oxidative challenge. Ongoing research employs cell culture and animal models and various biochemical, analytical and molecular techniques. Our research addresses two major areas:

1. Oxidative stress and mitochondrial signaling. Mitochondria are sentinel in cell survival and are vulnerable to oxidative damage. This research investigates the relationship between oxidative stress and mitochondrial protein and DNA damage, the role of GSH redox in repair mechanisms, and how loss of mitochondrial function orchestrates and signals apoptotic death.
2. Chronic oxidative stress and tissue adaptation, transformation or death. This research investigates the role of GSH redox in controlling cell signaling and gene transcription and mechanisms in enzyme expression and function in maintaining GSH balance and cell survival, in phenotypic transitions, and in cellular adaptation and resistance to oxidative challenge.



Oxidative stress in molecular signaling and cellular responses



faculty

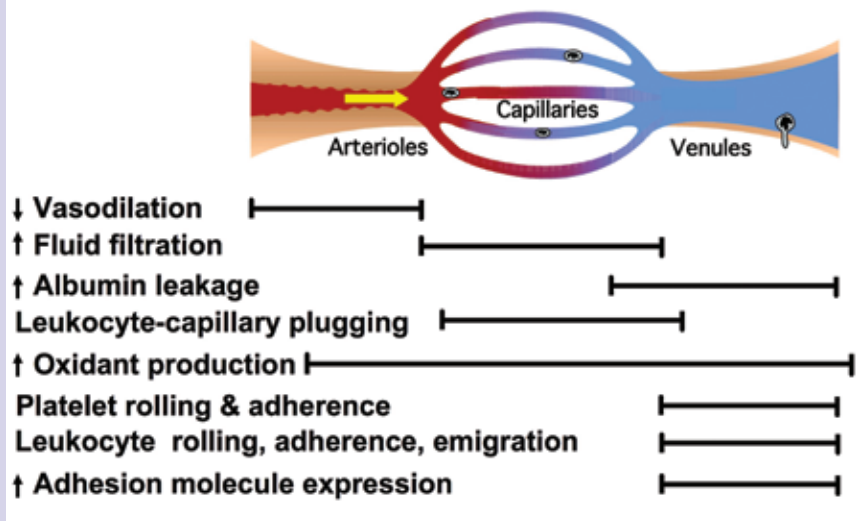


D. Neil Granger, PhD
Boyd Professor and Head
PhD, 1977
University of Mississippi
email: dgrang@lsuhsc.edu

Microcirculation

My research interests address the contribution of the microvascular dysfunction to cardiovascular diseases and has relevance to diseases such as stroke and myocardial ischemia (heart attack). There are several risk factors for the development of stroke, including hypertension (high blood pressure), hypercholesterolemia, diabetes, cigarette smoke, and obesity. We study the influence of these risk factors on the microcirculation in the presence and absence of an occluded blood vessel supplying the brain (to simulate stroke). The responses of all segments of the microcirculation (arterioles, capillaries, and venules) are evaluated using sophisticated imaging techniques that are applied directly to the brain. All of these components of the vascular tree show signs of dysfunction in the presence of one or more risk factors. Furthermore, the presence of these risk factors lead to more tissue damage in the brain following an ischemic stroke. We find that much of the microvascular dysfunction and exaggerated tissue damage associated with these risk factors is related to the accumulation of inflammatory cells and platelets on the inner surface of the microvessels. We are attempting to define the chemical and molecular basis for the negative influence of risk factors on the brain microcirculation in order to determine if and how the severity of brain damage following a stroke can be reduced.

Site-specificity of ischemia/reperfusion-induced microvascular dysfunction



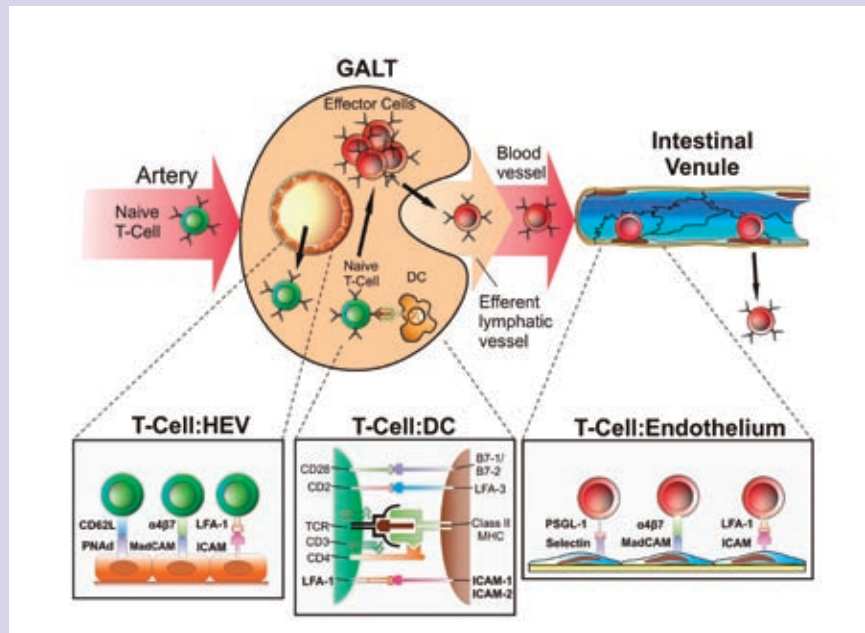
faculty



Matthew B. Grisham, PhD
Boyd Professor
PhD, 1982
Texas Tech University
Health Sciences Center
email: mgrish@lsuhsc.edu

Mucosal Immunology and Chronic Gut Inflammation

The intestinal mucosa encounters more antigens and potential pathogens than any other tissue in the body and consequently represents the largest and most complex component of the immune system. Fortunately, the gut-associated lymphoid tissue (GALT) has evolved efficient mechanisms to distinguish between potentially pathogenic bacteria, parasites, and viruses from harmless dietary proteins and commensal bacteria. The inability to properly regulate these different immune responses may ultimately lead to chronic inflammatory disorders such as the inflammatory bowel diseases (IBD; Crohn's disease; ulcerative colitis). Patients with IBD experience rectal bleeding, severe diarrhea, abdominal pain, fever and weight loss that appears to be associated with the infiltration of large numbers of inflammatory leukocytes into the intestinal interstitium. My laboratory is interested in defining the immunological mechanisms responsible for the induction and regulation of intestinal inflammation using different animal models of IBD. We are currently investigating three major areas of mucosal immunology related to the induction and perpetuation of chronic gut inflammation including T-cell trafficking to the GALT, activation and polarization of naïve T-cells to disease-producing effector cells and the homing mechanisms utilized by effector T-cells to migrate from the blood and into the small and large intestine where they promote intestinal inflammation.



faculty



Norman Harris, PhD
Associate Professor
PhD, 1991
Vanderbilt University
email: nharr6@lsuhsc.edu

Microvascular Physiology and Pathophysiology

Our laboratory investigates microcirculatory function and the changes that occur during inflammatory diseases such as diabetes, hypercholesterolemia, and inflammatory bowel disease. Exchange of molecules (such as water, nutrients, and metabolites) occurs between plasma and tissue at the level of the microcirculation. Blood flow through the microcirculation is regulated by the feeding arterioles, whose smooth muscle cells are able to constrict or dilate. The majority of plasma/tissue exchange occurs at the capillary level; the capillaries then join to form venules that drain the microvasculature. The microcirculation performs as a feedback loop, that is, venules can signal nearby parallel and countercurrent arterioles (see figure below) to modify the state of arteriolar dilation and enhance capillary flow when needed. However, in certain inflammatory conditions, venule-to-arteriole communication is altered significantly, which reduces capillary flow. This pathophysiological response may be due to white blood cell (leukocyte) or platelet adhesion in venules, which initiates the release of constricting mediators. Techniques used in our laboratory include intravital (brightfield and fluorescence) microscopy, measurement of microvascular flow and permeability, and computerized video analysis of microscope images.

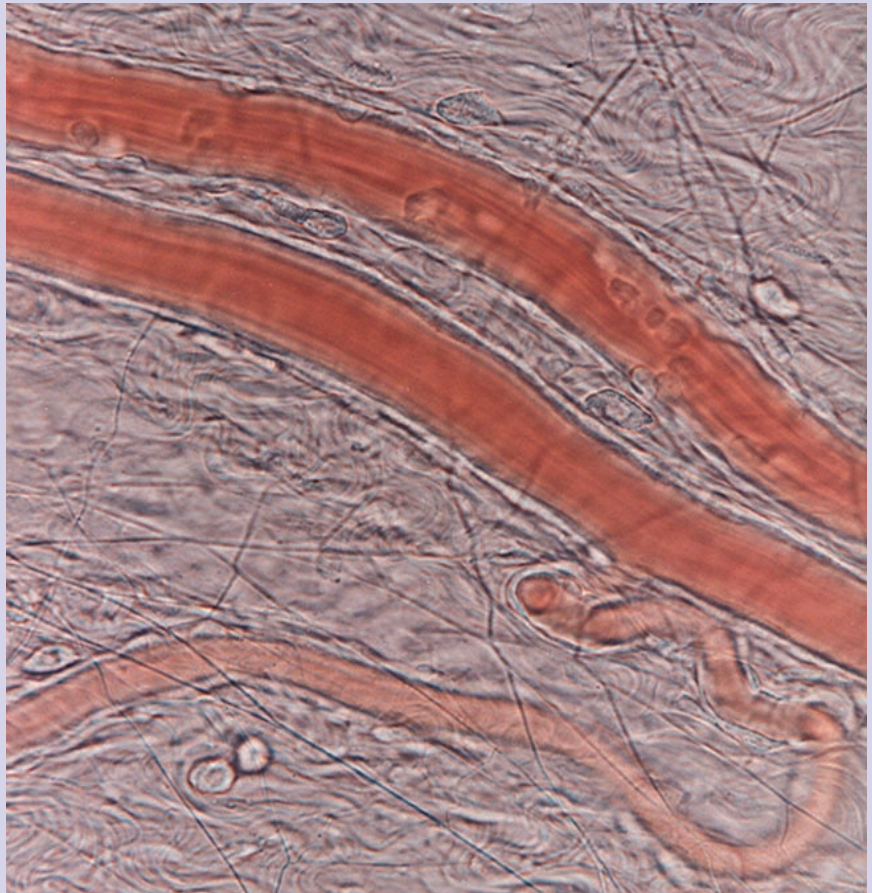
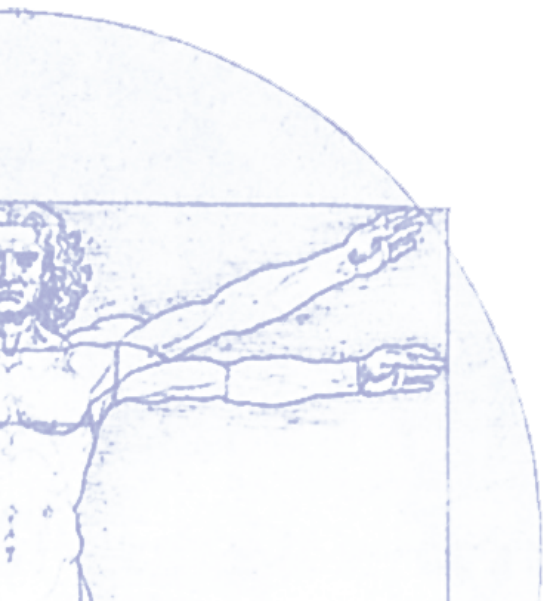
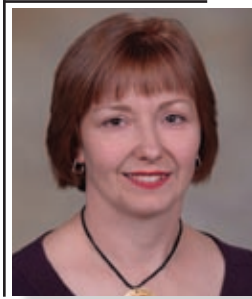


Figure Legend: Microscopic image of a countercurrent venule (vessel at top) and arteriole (middle), with a capillary branching from the arteriole



faculty



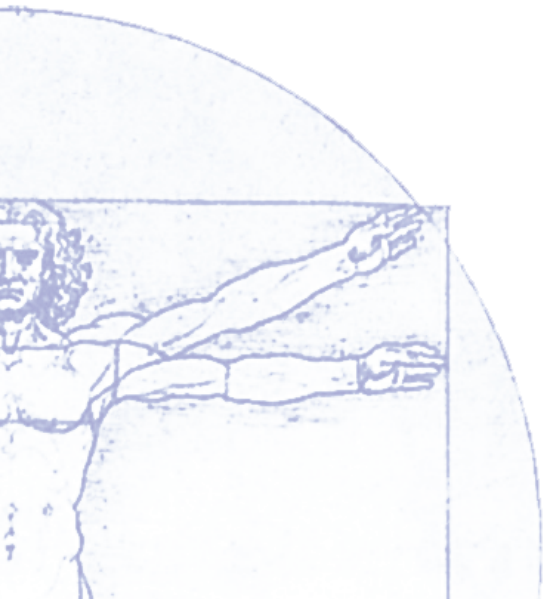
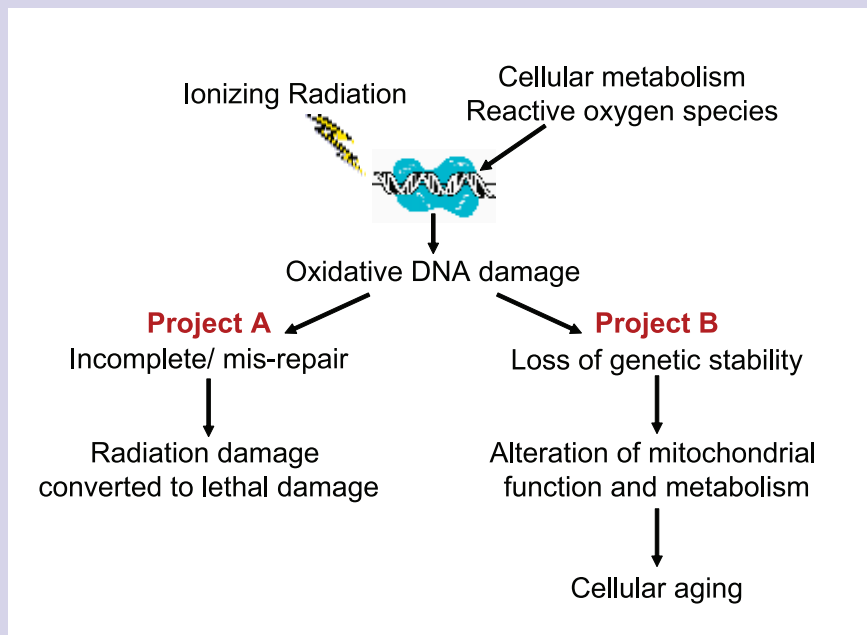
Lynn Harrison, PhD
Associate Professor
PhD, 1991
University of Manchester
England
email: lclary@lsuhsc.edu

DNA Repair of Oxidative DNA Damage

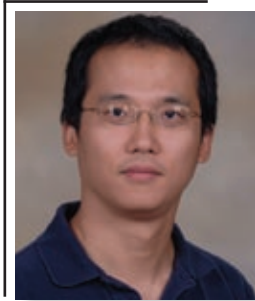
A wide variety of oxidative DNA damage is introduced into nuclear and mitochondrial DNA by reactive oxygen species (ROS). Sources of ROS include cellular metabolism, inflammation and exogenous agents used in the treatment of cancer. If DNA damage is not repaired or is mis-repaired, it can result in mutations, chromosomal aberrations or cell death. In fact DNA damage has been implicated in multistage carcinogenesis and aging. DNA repair is therefore important for the maintenance of genetic integrity and stability, and cell survival. This laboratory works on two projects:

Project A - Radiotherapy introduces clusters of DNA lesions, which can cause incomplete repair and the generation of lethal double-strand breaks. We want to identify repair enzymes that can generate lethal double-strand breaks from radiation DNA damage and determine whether it is possible to manipulate the DNA repair system in a tumor during radiotherapy to enhance tumor cell killing.

Project B - Is oxidative damage involved in cellular aging? We use a primary endothelial cell culture model of replicative senescence (or cellular aging) to understand the alterations that occur in cells as they progress towards the end of their replicative life.



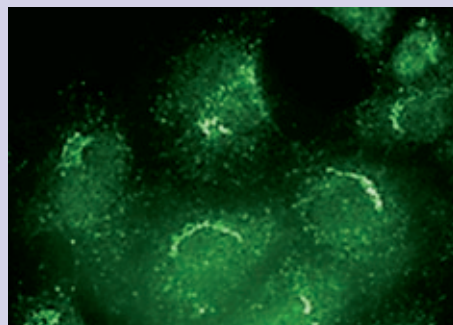
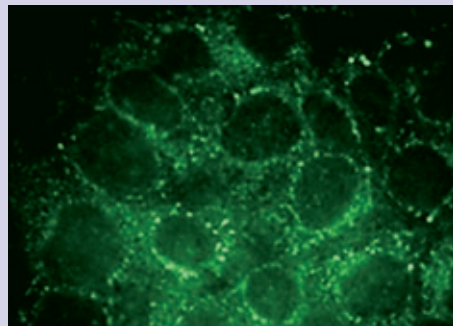
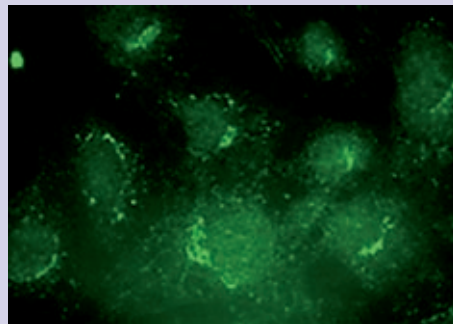
faculty



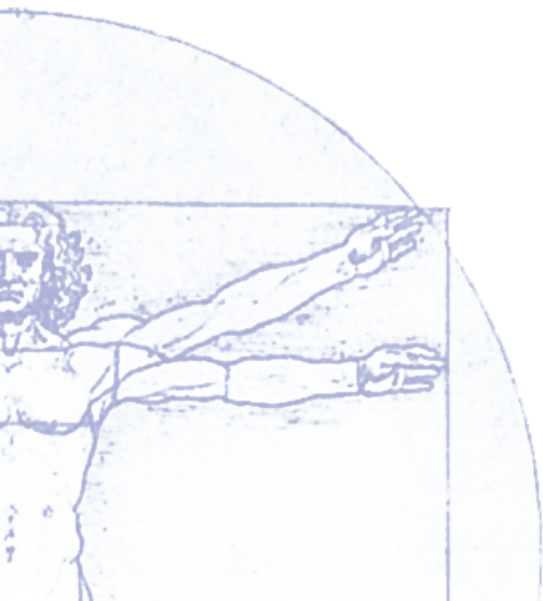
Yijun Jin, PhD
Assistant Professor
PhD, 2001
Indiana University
School of Medicine
Indianapolis
email: yjin@iuhsc.edu

Regulation of cellular signal transduction by receptor trafficking

Our research focuses on cellular signal transduction that leads to cardiomyocyte loss in diseases like heart disease and myocardial infarction. Tumor necrosis factor (TNF), upon binding its receptor on cell surface, leads to inflammation, proliferation and apoptosis. TNF signal transduction can be regulated by cytoskeleton dynamics. Movement of TNF receptor-1 between the plasma membrane and intracellular compartments such as Golgi apparatus is facilitated by myosin II, a motor protein that interacts with actin cytoskeleton. We are currently studying how cell surface TNF receptor dynamics impacts intracellular TNF signaling and the resulting cellular responses. We are also focusing on the molecular mechanisms underlying the association of myosin II motor and TNF receptor. Using genomic and proteomic approaches, more proteins are being identified as the cargoes moved by myosin II, expanding the important roles myosin II and the actin cytoskeleton play in regulating signal transduction and cellular functions.



The intracellular TNF receptor-1 (top) disperses to the plasma membrane (middle), the process of which is inhibited by ablation of myosin II motor activity (bottom).



faculty

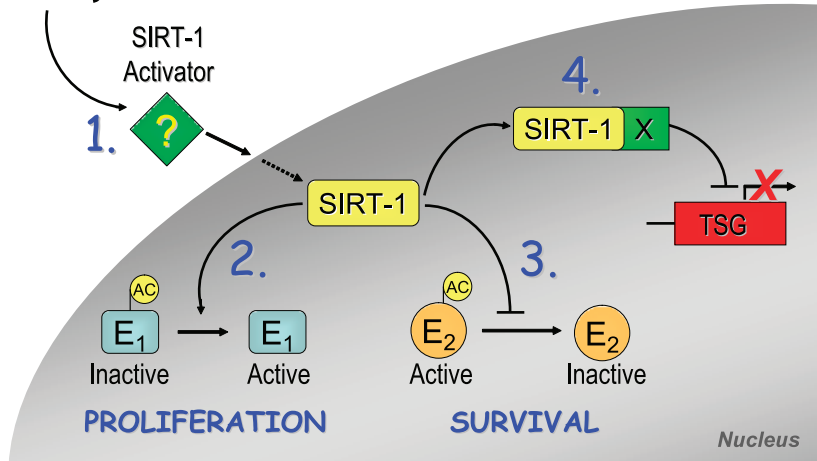


Kevin Pruitt, PhD
Assistant Professor
PhD, 2001
University of North
Carolina at Chapel Hill
email: kpruit@lsuhsc.edu

The Role of SIRT1 in Cancer Biology and Epigenetics

In recent years the widespread interest in epigenetics has revealed a fascinating and unique role that its deregulation plays in cancer biology and cellular transformation. One of the key players now under intense scrutiny is a member of a family of deacetylases (known as the sirtuins) that targets histone and non-histone proteins for deacetylation. The most prominent member of this family, SIRT1, has received considerable attention because of its link with human metabolism, diet and cancer. The long-term focus of our laboratory involves (1) defining the upstream regulators of SIRT1. Additionally, we are interested in defining the downstream effectors of SIRT1 that regulate (2) cellular metabolism, (3) longevity/lifespan, (4) apoptosis and (5) epigenetic silencing of tumor suppressor genes (TSG). Defining the contribution of SIRT1 within these contexts has major implications for identifying novel anti-cancer targets. Currently, there are several inhibitors of deacetylases advancing in various phases of clinical trials and we are excited about the potential that SIRT1 may be targeted as an anti-cancer therapy as well..

SIRT-1 Signaling: Activators and Effectors



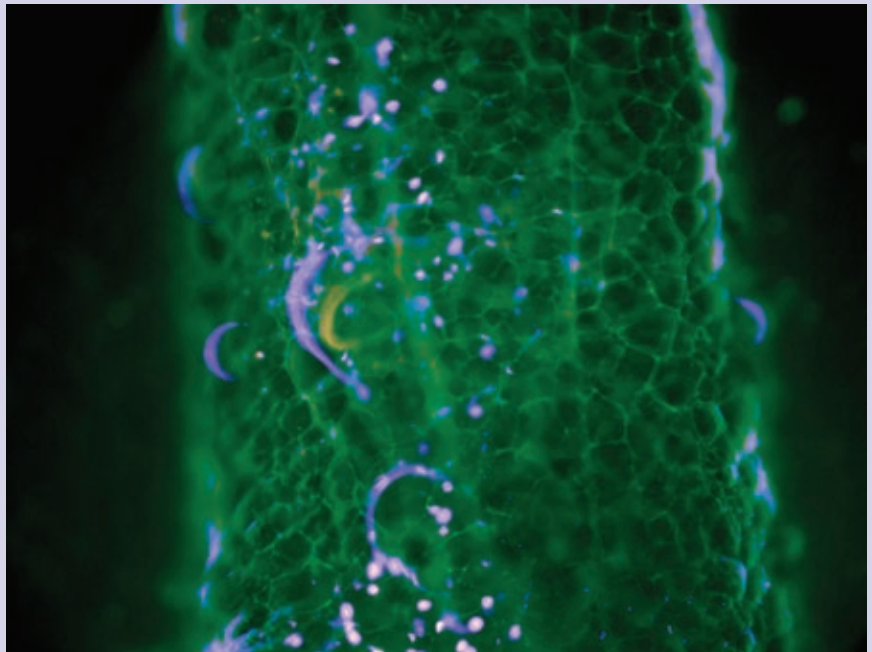
faculty



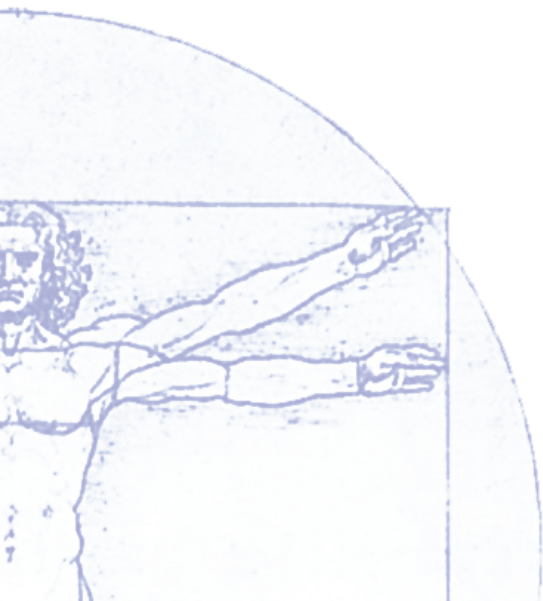
Chantal A. Rivera, PhD
Assistant Professor
PhD, 1998
University of North Carolina
at Chapel Hill
email: crive1@lsuhsc.edu

Unraveling Obesity-Associated Liver Disease

Research in my laboratory investigates mechanisms underlying non-alcoholic steatohepatitis (NASH). NASH is characterized by the accumulation of fat in hepatocytes, mixed cell type inflammation and necrosis; this disease is associated with chronic obesity in adults as well as children. The prevalence of overweight and obesity in this country is now estimated to be more than 60% of the population and is attributed primarily to inactivity and excessive caloric intake. Due to the prevalence of obesity in children, the typical adult onset complications of obesity are occurring earlier in life, which is likely to shorten life expectancy. Two of the major goals of my research are to 1) establish an adolescent model based on dietary manipulations to investigate the molecular mechanisms underlying the progression of NASH; and 2) use intravital microscopy to examine the obesity-associated inflammatory response in the mesentery, abdominal adipose tissue and liver. Clearly, research investigating mechanisms underlying obesity-associated inflammation has the potential to benefit a significant proportion of people in the United States and worldwide. Importantly, defining these mechanisms is a necessary first step toward the development of appropriate diagnostic and treatment strategies.



Intravital microscopic image of mesenteric adipose tissue (green) with several circulating leukocytes (blue).



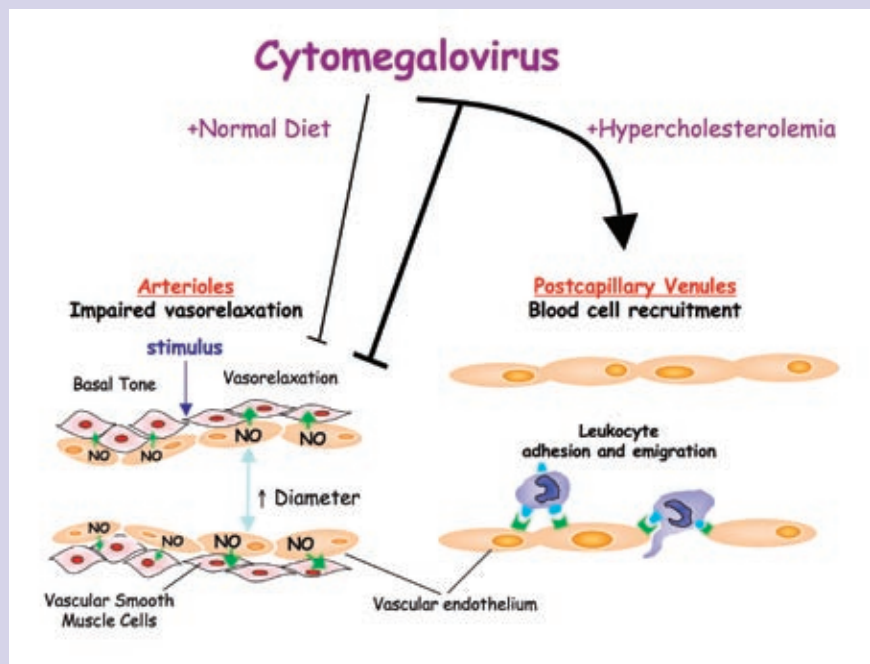
faculty



Karen Stokes, PhD
Instructor
PhD, 2004
Trinity College, Dublin, Ireland
email: kstoke@lsuhsc.edu

Microvascular Inflammation and Cardiovascular Risk Factors

My research interest focuses on microvascular responses to cardiovascular disease risk factors, in particular high cholesterol and cytomegalovirus (CMV). Inflammation is a key player in the pathogenesis of cardiovascular disease. In the case of several cardiovascular risk factors, including hypercholesterolemia, clinical signs of disease are preceded by the development of an inflammatory phenotype in the microvasculature, which may promote a low-grade systemic inflammation rendering tissues more susceptible to injurious stimuli or other risk factors. Recent epidemiological studies have revealed that infectious agents, for example CMV, may contribute to cardiovascular disease. CMV is a b-herpesvirus that has been identified in atherosclerotic lesions, and accelerates disease progression in hyperlipidemic animals. CMV induces an inflammatory phenotype in isolated cells. Our preliminary data suggests that CMV also induces endothelial dysfunction in vivo, and that it synergizes with hypercholesterolemia to promote an exaggerated inflammatory response. Therefore our focus is to investigate the underlying mechanisms involved in the microvascular responses to CMV, and its cooperation with hypercholesterolemia in the generation of a pro-inflammatory phenotype.



Microvascular responses to CMV infection in the absence or presence of elevated cholesterol levels

CMV infection impairs vasodilation responses in arterioles, but does not induce obvious venular inflammation. However, in combination with hypercholesterolemia, CMV-induced arteriolar function is impaired further, and leukocyte recruitment occurs in the venules

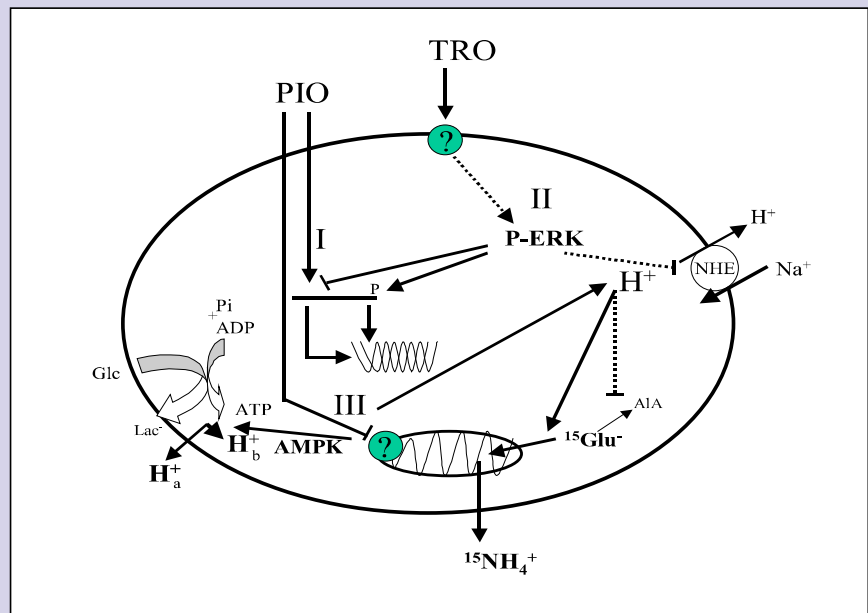
faculty



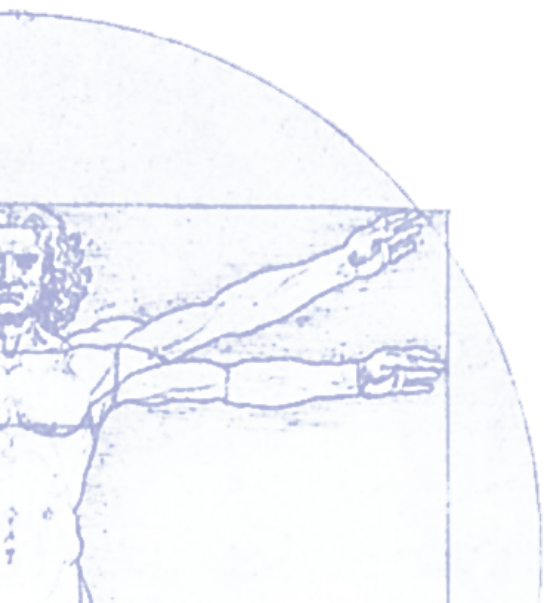
Tomas C. Welbourne, PhD
 Professor
 PhD, 1968
 University of Tennessee
 email: twelbo@lsuhsc.edu

Glutamine, NHE Activity, Acid-Based Metabolism

Dr. Welbourne's research interests focus on mechanisms involving interorgan and cellular signaling pathways effecting physiological responses to acid challenges. Longitudinal studies in humans have shown a spontaneous metabolic acidosis appears in the adult population over aged 50 contributing to a general catabolic state including muscle and bone wasting. Despite the intrinsic interest in this widespread homeostatic dysfunction little is known concerning the signal pathways involved and their regulation. Studies in Dr. Welbourne's lab have shown in humans that activating the growth hormone and renal acid extrusion axis through glutamine supplied glutamate stimulation of pituitary GH release and renal sodium hydrogen ion exchange acid extrusion, and , glutamine supplied ammonium stimulation of renal H⁺/K⁺ ATPase restores acid extrusion while generating new base for restoration of alkaline reserves. Impairing acid extrusion through the classical MAPK pathway along with acceleration of metabolic acid production via AMPK activation of glycolysis is currently studied as a paradigm for arresting tumor cell growth and activating apoptosis in cancers.



Summary of pathways responsive to Pio(I&III) or Tro(II) alone. Dotted arrows indicate connections through multiple steps not listed or resolved. In combination, interaction between pathways is depicted by /activating blocking arrows. Pathway I solid bar represents PPARγ phosphorylated by pathway II P-ERK to inhibit the ligand activated pathway I; double helix represents PPRE-containing DNA. Pathway II shows cell surface receptor and sodium hydrogen ion exchanger(NHE). Pathway III shows mitochondrial receptor and connection to glycolysis by broken arrow via P-AMPK(phosphorylated AMP kinase); Glc=glucose, Lac=lactate and H⁺ represents metabolic acid produced and either extruded(a) by NHE or retained in the cytosol(b) with pathway II activated.



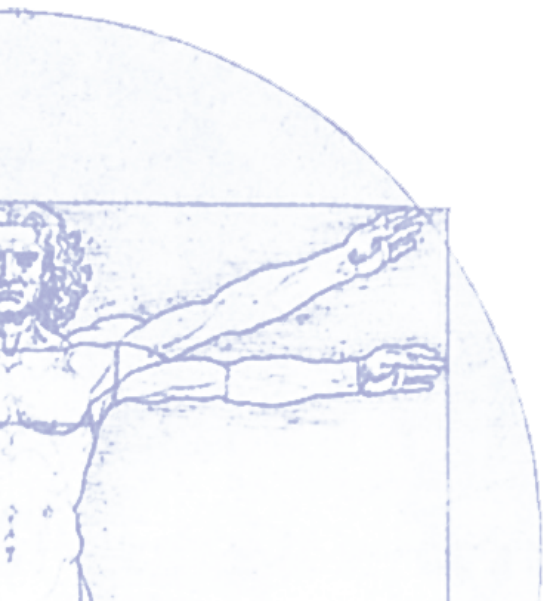
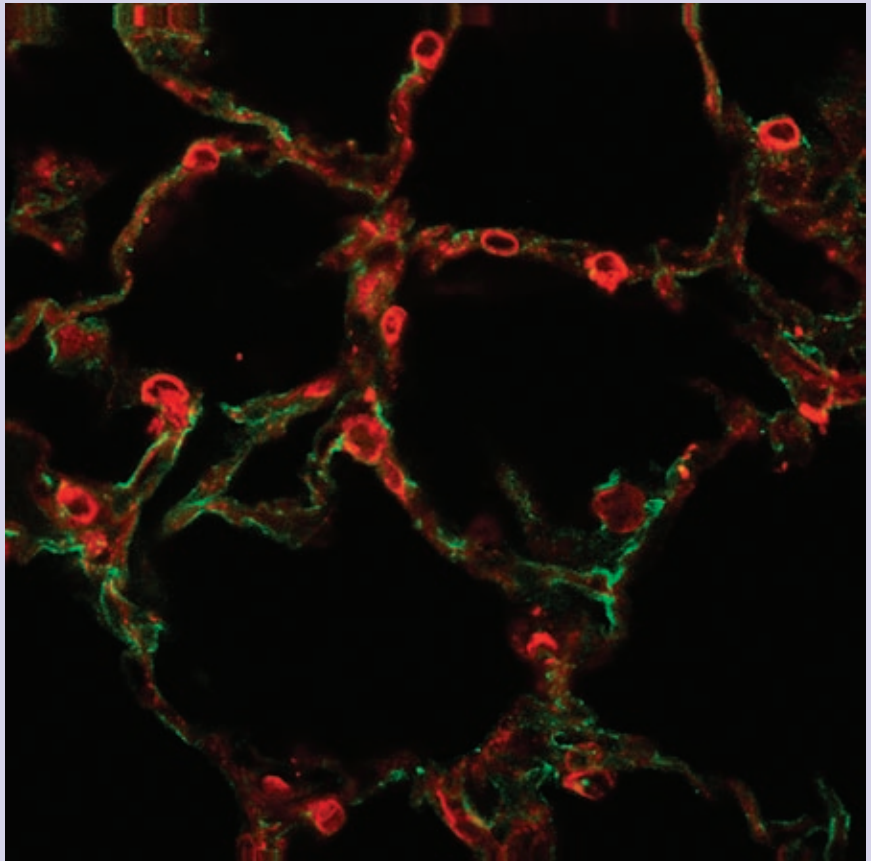
faculty



Robert Specian, PhD
Professor
PhD, 1980
Tulane University
email: rspeci@lsuhsc.edu

Repair of the Intestinal Mucosa

Injury to the gastrointestinal mucosa is a common feature of a number of diseases, including inflammatory bowel disease, ischemia-reperfusion injury and even in post-prandial (after eating) states. The ability of the intestinal mucosa to repair, controls the extent of the extra-intestinal injury and systemic dysfunction. The intestinal mucosa is responsible for nearly mutually exclusive functions: selectively allowing the uptake of critical nutrients and the exclusion of the resident intestinal flora. My laboratory has focused on the ability of the intestinal mucosa to accomplish these divergent goals. Critical to this process is the ability of the mucosa to secrete large molecular weight glycoproteins called mucins to help maintain mucosal integrity. Mucin secretion limits the extent of the injury and aids in the ability of the epithelium to repair. Our studies have demonstrated that when the mucosa is injured, the epithelium can very rapidly reconstitute and seal over the injured area. The approaches in my laboratory are varied, including immunologic and morphologic approaches using the latest in imaging techniques. The ability to understand how and when the mucosa is injured, and the mechanisms of repair, is essential to understanding many prevalent and destructive disease states.



faculty



V. Hugh Price, Jr., PhD
Associate Professor
DVM, 1980
Louisiana School of
Veterinary Medicine
email: hprice@lsuhsc.edu

Animal Resources

As a member of the department, I direct a genetically modified mouse breeding facility that provides the members of the department with mice to meet their research specifications. The breeding facility is located within the confines of the Animal Resource Facility and provides 1) consultations on the choice of mutant strains, 2) shipping and receiving of mutant strains from other institutions, both national and international, 3) breeding schemes to tailor production to research needs, and 4) production of adequate numbers and type of offspring to meet those needs. In addition, we continually review selections in the current literature to ascertain if newly developed mutant strains might be of use to the research ongoing in the department.

Also, I collaborate in the lab of Dr. Matthew Grisham which is studying the immunological mechanisms responsible for the induction and regulation of chronic intestinal inflammation, i.e., inflammatory bowel disease, Crohn's Disease, and ulcerative colitis. My primary interest has been in the area of the gut-associated lymphoid tissue (GALT) focusing on T-cell trafficking in the GALT and the identification of the different leukocyte and endothelial cell adhesion molecules that mediate this process.

