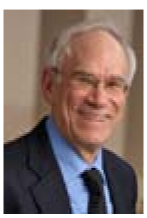
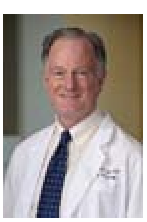
Scientific and Clinical Preceptors

Fiemu Nwariaku, MD, Associate Professor and Vice Chairman for Research of Surgery. The Nwariaku laboratory is interested in inflammatory endothelial dysfunction; specifically this laboratory examines the role of intracellular oxidants as mediators of cytokine signaling. Their work indicates that oxidants generated by endothelial NADPH oxidase leads to phosphorylation of junctional proteins and subsequent loss of endothelial barrier function. Their laboratory has expertise in molecular biology techniques including cloning, mutagenesis, construction of viral vectors and immunoblotting. Other techniques in the laboratory include the use of cDNA mini-arrays, confocal microscopy and transmonolayer electrical resistance.

Deborah L. Carlson, PhD, Assistant Professor of Pediatrics. Research in the Carlson laboratory is focused on examining the consequences of caspase activation in the heart foll9owing injury, independent of apoptosis. Our group is independently examining the roles of caspases-3, and -8 play in mediating cardiac dysfunction, inflammation, and in regulation of transcription factors such as NF-kB, using both transgenic and pharmacologic models. In addition, we are also beginning to assess the role that the inflammatory capsule, caspase-1 may play I both mediating the inflammatory and cardiac pathways. Our current results are very encouraging that caspase-1 plays a significant role in mediating the observed cardiac dysfunction, and in regulating expression of other caspases.



Frederick Grinnell, PhD, Professor of Cell Biology. Research in the Grinnell laboratory examines the regulation of cell migration and proliferation by the interaction of growth factors and extracellular matrix. Migration of fibroblasts in three dimensional collagen matrix cultures results in matrix remodeling and contraction, a process that is adaptive and progressive. Molecular signaling and mechanisms that regulate contraction vary according to local matrix organization, and cells switch between proliferative and quiescent states depending upon isometric tension. Tissues and organs are three dimensional structures, and extracellular matrix plays a key role in their organization in vivo. Grinnell and colleagues study this organizational function using three dimensional cultures because they introduce complex patterns of dynamic, cell-extracellular matrix interactions not observable in routine cell culture. Above all, this means on one hand that cells will be completely surrounded by extracellular matrix; and on the other hand, that cells will be able to remodel the matrix thereby changing matrix properties and, in reciprocal fashion, cell features will then change as well.



Joseph Hill, MD, PhD, Professor of Internal Medicine and Chief of Cardiology. Dr. Hill's research examines molecular mechanisms of structural and electrophysiological remodeling in cardiac hypertrophy and failure. Using molecular, physiological and electrophysiological approaches, they study mechanisms of structural, functional, and electrical remodeling in heart disease. These studies are based on genetic and surgical models of heart disease in animals, as well as patients with hypertrophic heart disease and cardiomyopathy. Specific questions being studies at present include: mechanisms governing the pathological growth response of the myocardium; autophagy as a novel mechanism of remodeling that contributes to the transition from stable hypertrophy to heart failure; mechanisms of Ca^2 metabolism in hypertrophied and failing ventricular myocytes with particular emphasis on transcriptional and post-translational regulation of the L-type, Ca^2 channel; phosphoinositide-dependent signaling pathways (and downstream targets) in cardiac hypertrophy and failure; and regulation of circadian gene expression by environmental stimuli.

Ahamed Idris, MD, Professor of Surgery, Director of Emergency Medicine Research and The Dallas Center for Resuscitation Research. Dr. Idris leads the Dallas Center for Resuscitation Research, one of 8 US and 2 Canadian centers funded by the NIH, Department of Defense, and the Canadian Health Service. This is the first time that resuscitation science has received major funding from national agencies. The purpose of these centers is to study novel interventions that may improve outcome from cardiac arrest and severe traumatic injury. The primary focus of the research centers is to study interventions that can be used by emergency personnel for immediate resuscitation before the patient arrives at a hospital. The Dallas Center alone annually cares for more than 2,000 cardiac arrest patients and 3,600 severe traumatic injuries. All 10 centers collectively have over 10,000 cardiac arrests, and 26,000 traumatic injuries per year. This group conducts controlled trials each year, including controlled ventilation for al intubated patients, hypertonic saline and antioxidants for trauma, recombinant factor VII for severe hemorrhage, and a number of different drugs, hypothermia, and the impedance threshold device for cardiac arrest.

Michael Jessen, MD, Professor of Cardiovascular and Thoracic Surgery. The Research Laboratory of the Department of Cardiovascular and Thoracic Surgery has ongoing projects that investigate myocardial metabolism under conditions that are encountered during cardiac surgical procedures. A focus of these investigations has centered on increasing our understanding of changes in myocardial substrate oxidation rates and substrate selection by the heart, particularly under conditions of cardioplegic arrest and hypothermia. Investigators in the laboratory have made novel observations that these conditions, which mimic those created in cardiac surgical operations, lead to a suppression of fatty acid utilization by the heart. Additional studies have probed the metabolic mechanisms behind this process using conventional biochemical analyses and magnetic resonance spectroscopy. These studies will increase our understanding of myocardial biochemistry and metabolism and may enable us to devise new methods to protect the heart during open-heart surgery.

Investigators in the laboratory have also used these techniques to study metabolism of the lung under conditions that simulate storage for lung transplantation. Here, early studies made the observation that a considerable degree of oxidative metabolism continues within pulmonary tissue during hypothermic storage and is related to the available alveolar oxygen in the stored pulmonary allografts. Lung metabolism can be influenced by altering the composition of the storage solution and these alterations can lead to improvements in post-reperfusion lung function. These studies may lead to the development of superior strategies for lung preservation for transplantation.

Steven McKnight, PhD, Professor and Chairman, Department of Biochemistry, and holder of the Distinguished Chair in Basic Biomedical Research and the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry. Genes are switched on and off in eukaryotic cells via regulatory proteins commonly termed transcription factors. The research focus of the McKnight laboratory centers on a subset of transcription factors that are gene specific. In the simplest of terms, a gene may be subject to regulation by a given transcription factor if it contains high affinity binding sites for that factor in a functionally relevant region – promoter, enhancer or silencer. This simplistic dogma is complicated by a variety of complexities that have emerged from studies of eukaryotic gene regulation over the past decade. For example, individual transcription factors tend to exist as members of multiprotein families whose DNA binding activities can be indistinguishable when analyzed as isolated biochemical entities. It is therefore problematic to assess which member of a related family is responsible for a given regulatory event. It has also been recognized that gene specific transcription factors can obligatorily rely on heteromeric partners. A competent DNA binding version, that is, may rely on the formation of a protein complex consisting of two or more entirely distinct polypeptides. In certain cases, gene specific transcription factors retain the ability to bind DNA avidly, yet are unable to functionally regulate transcription at the level of activation or regression without the help of co-activator or co-repressor proteins. Biologic activities of transcription factors are universally regulated in cells by covalent post-translational modification, including phosphorylation and proteolysis, or by non-covalent interaction with small molecule metabolites or ligands.

Luis Parada, MD, Professor of Developmental Biology. Our long-standing interest lies in the elucidation of regulatory pathways that control the complex process of nervous system development and the consequences of inappropriate development which can include behavioral and mood disorders as well as cancer. We have focused on the functions of the trk gene family, which encodes transmembrane receptor tyrosine kinases (RTKs) that act as receptors for the nerve growth factor (NGF) family of neurotrophin ligands. Through the use of knockouts and conditional knockouts for the genes encoding the neurotrophins: brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), neurotrophin 4/5 (NT4/5), as well as for the TrkA, TrkB and TrkC receptors we study deficiencies in the formation of the nervous system. In addition to roles in sensory and sympathetic neuron survival, we have identified roles for the neurotrophins in CNS in stem cell development, nerve sprouting and synapse formation. Loss of function in discrete CNS regions can lead to complex behavioral disorders some of which may model neuropsychiatric disorders. A related line of study of the human disease Von Recklinghausen's Neurofibromatosis (NF1) which is a classic familial cancer disease. Study of the NF1 tumor suppressor have yielded unexpected findings in the regulation of neurotrophin signaling within the cell. We have developed mouse models of NF1 that replicate the tumor phenotypes in human including tumors of the peripheral nervous system and glioblastoma. A third area of research focuses on identifying molecules in myelin that inhibit nerve regeneration after injury. We have developed evidence the ephrins, molecules with nerve outgrowth inhibitory properties during embryonic development, have potent myelkin based inhibitory function in the mature spinal cord.

Michael G. Roth, PhD, Professor and Vice Chairman of Biochemistry. The basic unit of life is the single cell and understanding how living organisms function ultimately requires learning how the parts of a cell work together. The components of cells are made in a few locations and then transported to other places where they function and then to yet other locations for disposal. This requires a complex traffic of molecules within the cell, even in a simple cell such as a bacterium. Animal cells are far more complicated than bacteria and are compartmentalized into a number of distinct organelles; each separated from the others by a limiting membrane. The traffic of the lipids and proteins that make up these membranes is exceedingly complex and involves the exchange of small membrane vesicles between organelles. The focus of the Roth laboratory is to understand how these vesicles

and how they select the right cargo. They use recombinant DNA technology to make mutant proteins that they introduce into cells to see how they are recognized and transported within the cell. They rely upon a variety if biochemical techniques as well as light and electron microscopy to locate proteins within cells. They use genetics and biochemistry to identify cellular proteins required for the intracellular traffic of membrane proteins and lipids. Because intracellular membrane traffic is very fast, occurring on a time scale of seconds to minutes, they have started a new initiative to look for fast-acting small molecules that can diffuse into cells and inhibit or stimulate membrane traffic. Although the work is basic cell biology, defects in the processes cause human diseases such as cystic fibrosis, Alzheimer 's disease and lysosomal storage diseases.

Philip Shaul, MD, Professor of Pediatrics, and holder of the Lowe Foundation Professorship in Pediatric Critical Care Research. The signaling molecule nitric oxide (NO), produced by the enzyme NO synthase (NOS), plays a major role in vascular and airway homeostasis. Alterations in NOS function are critically involved in the pathogenesis of atherosclerosis and hypertension, and also many lung diseases. Studies in Shaul's laboratory have indicated that the endothelial isoform of NOS (eNOS) is expressed in a cell-specific manner in vascular endothelium and airway epithelium. We have demonstrated that eNOS is transcriptionally regulated by oxygen and estrogen, it is targeted to specialized plasma membrane domains called caveolae or lipid rafts, and its activity is acutely modulated by oxygen, estrogen and high density lipoprotein (HDL). The acute effects of estrogen on eNOS are mediated by a subpopulation of membrane-associated estrogen receptors acting in a novel, nongenomic manner. Regulation by HDL involves scavenger receptor BI, which we have discovered is localized in endothelial cell caveolae. HDL is the most robust agonist for eNOS that has been found to date, potentially explaining the dramatic antiatherogenic properties of the lipoprotein. Further, we have discovered that eNOS localization and function in caveolae are markedly attenuated by oxidized LDL through changes in membrane lipid composition. Cellular and molecular mechanisms underlying regulation of eNOS expression/function are currently under investigation in isolate caveolae membrane preparations, in native endothelial/epithelial cells, and in reconstitution paradigms using wild-type or mutant forms of the enzyme and interacting molecules.

James T. Stull, PhD, Chairman of Physiology and holder of the Fouad A. Bashour Chair in Physiology. The research in his laboratory addresses two general aspects of actin cytoskeleton regulation: acute and chronic adaptive. First, in acute studies they have concentrated on relating mechanical events manifested during the course of contraction and relaxation to the generation of biochemical intermediates that regulate contractility. Measurements of stress-strain relationships, shortening velocities, and stiffness are used to provide a primary description of physiological function whose molecular basis is explained with the assistance of structural and biochemical studies. Kinetic studies are used to relate rates and sites of phosphorylation of contractile proteins to mechanical activation. The importance of different components of the regulatory pathway (kinases, phosphatases, contractile proteins, etc.) is tested by antisense knockdowns, protein transduction domains, and by permeabilized muscle fibers.

James Thomas, MD, Professor of Pediatrics. The innate immune response is an ancient form of host defense against infection, trauma, and other injury. Many elements of innate immunity are conserved in organisms, ranging from tomatoes to Drosophila melanogaster to human beings. We study the role of the Toll/IL-1 intracellular signaling pathway in both the afferent and effector arms of the innate immune response in humans and mice. The proteins MyD88, members of the interleukin-1 receptor associated kinase (IRAK) family, and TRAF6 make up this signaling cassette. They transduce signals from the Toll-like receptors in the afferent limb of the innate response (such as those triggered by Gram-negative and Gram-positive bacteria, LPS, peptidoglycan, lipotechoic acid, and heat shock proteins) and the IL-1 and IL-18 receptors in the efferent arm, and then distribute the signal to several downstream signaling cascades, including those activating NF-kB, the stress activated protein kinases, and p38a. Thus the Toll/IL-1 signaling module both senses injury and mounts the proinflammatory response to limit it.

We have genetically inactivated IRAK in mice and are characterizing the defects in host responses to numerous pathogens at the biochemical, cellular, and in vivo levels. We have found that IRAK-deficient mice and cell lines exhibit impaired intracellular signaling to LPS, IL-1, and IL-18. These derangements in signaling are tied to altered host defenses. We are currently examining the contributions of two additional IRAK family members, IRAK2 and IRAK-M, to signal transduction through this pathway. We have also uncovered a critical role for this pathway in a tissue not traditionally considered part of the immune system the myocardium. Results from these studies may lead to antiinflammatory therapy for children with severe infections, and may reverse or prevent the cardiovascular manifestations that characterize clinical septic shock.

Jane Wigginton, MD, Assistant Professor of Surgery. Dr. Wigginton's research has addressed controversial resuscitation/ethical issues such as the salvageability of patients with cardiac arrest presenting with pulseless electrical activity and asystole. Other studies have demonstrated counter-intuitive outcomes or unique findings regarding out-of-hospital resuscitation that have challenged conventional wisdom. One recent paper actually demonstrated better outcomes with manual compressions by EMS personnel versus mechanical (Thumper) compressions. Her highly notable study on gender-related differences in the presentation and outcomes of out-of-hospital cardiac arrests, found that, in contrast to women with myocardial infarction and other related coronary artery syndromes, women had a better outcome following out-of-hospital cardiac arrest.

Helen L. Yin, PhD, Professor of Physiology. The Yin lab has several major research interests: 1) PIP2 regulation of cellular functions. PIP2 is an important signaling and scaffolding lipid and this lab examines the role of PIP2 on regulation of the actin cytoskeleton, receptor-mediated endocytosis, and intracellular calcium signaling. 2) Phosphoinositide regulation of Golgi functions. The Golgi is the central sorting station for membrane trafficking. Phosphoinositides such as PIP2 and PI4P may be modulators of multiple Golgi functions. Yin identified a phosphatidylinositol 4 kinase (which synthesizes PI4P) as a Golgi resident protein, and it is the major source of the cell's PI4P. 3) The effect of burn trauma on phosphoinositide homeostatis and the rational design of therapeutic targets to decrease the morbidity and mortality associated with burn and burn/sepsis.

Clinical Preceptors

It is important to note that in addition to the assignment of a scientific mentor, each trainee in our program has a clinical preceptor assigned. The role of this clinical preceptor is to aid trainees in elating their basic science efforts to the clinical arena and to provide academic and career counseling. The recent addition of a clinical epidemiology program has been as significant benefit to our training program. Epidemiological and biostatistical resources available through this program are utilized by our trainees; injury surveillance and epidemiology efforts are directed at blunt and penetrating trauma in the Dallas metroplex are under the supervision of Dr. Paul Pepe, Director of Emergency Medical Services at UT Southwestern Medical Center and Parkland Hospital, Dallas.

George Buchanan, MD, Professor, Department of Pediatrics. Dr. Buchanan's research interests include the development of improved means of diagnosing and treating patients with hereditary blood coagulation disorders; the epidemiology and pathophysiology of childhood anemias, including iron deficiency, hereditary spherocytosi and Diamond-Blackfan anemia; the management of immune thrombocytopenia (ITP) during childhood, emphasizing outcome measures other than platelet count (e.g., bleeding signs and symptoms, cost of therapy, and quality of life); the prevention and treatment of complications of sickle cell disease; and vascular complications following splenectomy.

Michael DiMaio, MD, Associate Professor of Cardiovascular and Thoracic Surgery. Dr. DiMaio's research interests include cardiac regeneration, lung cancer, and the reduction of death and disability from arteriosclerotic heart disease.

Edward Livingston, MD, Professor of Surgery. Dr. Livingston's research interests include appendicitis, bariatrics, imaging and surgical outcomes.

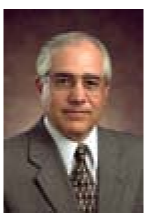
Christopher Yu-Hua Lu, MD, Professor of Medicine. Ischemic acute kidney injury (AKI - previously called "acute renal failure" or "acute tubular necrosis") confronts the physician with major clinical problems, and the scientist with fundamental unsolved questions. The physician is confronted a disease with no accepted treatment other than supportive care. Although there is often some renal recovery, the acute mortality and morbidity remains high, and the longterm problems include progressive chronic kidney disease and longterm mortality. The scientist is confronted by a disease where the underlying pathophysiology is not understood. Although it is now recognized that the initial insult to the kidney is exacerbated by a maladaptive inflammatory response, how injury is translated into inflammation remains a fundament unsolved problem.

The overall goal of our laboratory is elucidating this unsolved problem in the hope this will led to more effective therapies. To this end, we use in vivo models of ischemic AKI in mice, and in vitro model systems to perform detailed studies of proinflammatory genes activated by renal ischemia/ reperfusion. We have found that molecules, normally residing within healthy cells, are released into the extracellular space when renal cells are injured by ischemia in vivo and in vitro. These molecules elicit activate proinflammatory genes (see recent references). We are also translating this bench research into the clinic by studying clinically indicated pre-transplant renal biopsies; these biopsy studies will determine if the genes associated with the inflammatory response to ischemia in mice also are activated in man. In addition to addressing fundamental questions, these clinical studies may predict the course and guide therapy of renal transplant recipients.

Ischemic AKI inevitably occurs during the process of renal transplantation - the donor hypotension, cold storage, and the transplant surgery. The inflammatory response to this allograft ischemia will include recipient leukocytes that should exacerbate allograft rejection Thus, our studies will also help us understand allograft rejection.

Joseph Minei, MD, Professor of Surgery. Dr. Minei's research interests include the development of trauma systems and the use of evidence-based medicine to develop clinical practice guidelines.

Paul E. Pepe, MD, Professor, Department of Surgery. Renown for a grass-roots, street-wise style in planning, implementing and overseeing a systems approach to saving lives, both operationally and through clinical trials, his programs have resulted in some of the highest cardiac arrest and trauma survival rates worldwide. In addition to the Chain of Survival publication, he is known for his original measurements of physiological mechanisms (eg, Auto-PEEP), intrepid clinical concepts (eg, deferred rescue breaths in CPR), and ground-breaking clinical trials (eg, deferred IV fluids for trauma). Published years ago by Dr. Pepe & colleagues, these studies are now part of mainstream medical practice and research. Many of his numerous studies, injury prevention programs and media interactions have consistently affected public policy and legislation. Helping to set national priorities for cardiac and trauma resuscitation research, the NIH now has formally designated his EM program as a federally-funded resuscitation research center set to conduct 10 clinical trials over the next 5-10 years.



Robert Rege, MD, Professor and Chairman of Surgery. In recent years, Dr. Rege has been a leader in development of advanced laparoscopic surgery, including laparoscopic hernia repair, Nissen fundoplication, esophagomyotomy, colectomy and splenectomy. Dr. Rege maintained an active basic research program to study the pathogenesis of gallstones, which has been continuously funded via external sources since its inception in 1983.

Pablo Sanchez, MD, Professor, Department of Pediatrics. Dr. Sanchez' research interests include Congenital Cytomegalovirus Infection, Congenital syphilis and other Neonatal and congenital infections.