Dalton Cardiovascular Research Center

Annual Report FY 07

"Committed to Interdiscplinary Collaboration in Research and Teaching"

Front cover: Hill, M.A., Sun, Z., Martinez-Lemus, L. and Meininger, G.A. Novel imaging approaches provide a driving force to advance the field of arteriolar and vascular cell mechanotransduction. Trends in Pharmacol. Sci. 28:308-315, 2007.

Understanding the mechanisms by which vascular cells respond to physical forces has remained an intriguiging puzzle for over a hundred years. Advanced imaging techniques including atomic force and confocal microscopy are providing novel approaches for both studying responses to nano- to pico-scale forces as well as applying such forces to cells. The Rubic's Cube depicts images of vascular cells obtained with these instruments at the DCRC

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FROM THE DIRECTOR

The Dalton Cardiovascular Research Center (DCRC) supports the objectives of the University of Missouri in its mission of teaching, research and service. Yet it is unique in its commitment to interdisciplinary collaborative research and teaching among various colleges, schools and departments across the Columbia campus. Under the auspices of DCRC, scientists from the fields of biochemistry, biological engineering, biological sciences, biomedical sciences, electrical engineering, medicine, pharmacology, physiology, physics, and veterinary medicine and surgery all come together and apply their particular expertise to research problems.

Our commitment to collaboration is grounded in the belief that interactions among scientists of diverse backgrounds will lead to multidisciplinary research producing meaningful, far-reaching results. Research programs at DCRC include investigations into cardiac functions, cystic fibrosis, exercise, kidney failure, membrane transport, muscular dystrophy, neurohumoral control of the circulation, shock, vascular wall biology, diabetes, hypertension, biomedical engineering, protein-protein interactions, and tumor angiogenesis. Because the mission of DCRC is to promote interaction and collaboration, no single group completely defines the research activity of its members.

The center is committed to excellence in cardiovascular research and in the education of students and fellows. Our investigators provide service to the University, the State of Missouri, and the nation through memberships on committees, peer review panels and editorial boards of scientific journals. During the period of this report, our investigators were awarded 4.8 million in research funding and published 70 manuscripts in nationally recognized journals and books and gave 83 invited presentations.

The Dalton Cardiovascular Research Center is accredited by both the American Association for the Advancement of Laboratory Animal Care and the American Association of Laboratory Animal Sciences.

DCRC Committees

The Internal Advisory Committee:

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Dr. Ronald L. Terjung
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Dr. Michael A. Hill

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Dr. Tzyh-Chang Hwang, Co-Chair
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Interdisciplinary Research Interests Groups

Biomedical Engineering
Investigators: M.J. Davis, Ding, Gillis, Gu, Hill, Huxley, Hwang, Jones, Meininger, Milanick, Polo-Parada, Rubin, Segal, Zou

Cystic Fibrosis
Investigators: Clarke, Hwang, Milanick, Price, Soma, Zou

Exercise/Inactivity Including Atherosclerosis, Muscle Biology, Obesity, Type II Diabetes, and Vascular Biology
Investigators: Booth, Bowles, Hamilton, Hasser, Hill, Huxley, Jones, Korthuis, Laughlin, Martinez-Lemus, Meininger, Mueller, Polo-Parada, Rubin, Segal, Soma, Terjung

Membrane Transport
Investigators: Clark, Gillis, Gu, Huxley, Hwang, Milanick, Polo-Parada, Price, Rovetto, Rubin, Zou

Microcirculation
Investigators: M.J. Davis, Ding, Hill, Huxley, Korthuis, Laughlin, Martinez-Lemus, Meininger, Segal,

Neurohumoral Control of the Circulation Including Ageing, Hypertension, Heart Failure, Respiration and Salt and Water Homeostasis
Investigators: Blaine, Ding, Fadel, Hasser, Heesch, Kline, Meininger, Milanick, Potts, Schadt, Segal,

Tumor Angiogenesis
Investigators: G.E. Davis, Hyder, Liang

SUMMARY OF ACCOMPLISHMENTS

Publications and Presentations

- Articles published: 70
- Invited Presentations: 83

Awards and Peer Review

- Thirty-five awards/contracts were active during FY07.
- Thirteen research awards/contract proposals were awarded totaling more than $4.8M during FY07 utilizing the Dalton Cardiovascular Research Center.
- Twenty-seven grant/contract proposals are currently pending totaling more than $15M.
- Seven graduate students were supported by R90/T90 training grants totaling $320,157.
- Five investigators served as editors or were on editorial boards of nine scientific journals.
- Ten investigators reviewed articles for twenty-nine scientific journals.
- Seven investigators reviewed grant applications for twelve granting agencies.
- Six investigators served on twelve national study sections.
- Three patents were filed (pending or issued).

Education and Training

- Resident Investigators: 25
- Non-resident Investigators: 15
- Research Staff: 30
- Non Tenure Track Faculty: 9
- Post Doctoral Fellows: 8
- Graduate Students: 17
- Undergraduate Students: 17
- Administrative Staff: 6
- Building Support Staff: 5
- High School Student: 1

Director

Gerald A. Meininger

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Education:
PhD University of Missouri-Columbia,
MS & BS Central Michigan University

Appointments: Director Dalton Cardiovascular Research Center
Professor, Department of Medical Pharmacology and Physiology
Adjunct Professor, Department of Biomedical Sciences

Research

Research interests in my laboratory have been focused on vascular physiology and cell biology, with an emphasis on the microvasculature. Currently active areas of research include: 1.) Cell adhesion, extracellular matrix and cell signaling in the vascular wall; 2.) Mechanotransduction in vascular cells; 3.) Regulation of vascular and cardiac responses to tissue injury by extracellular matrix derived signals; 4.) Cellular and molecular mechanisms responsible for mechanotransduction; 5.) Mechanisms of vascular remodeling; 6.) Mechanisms responsible for the myogenic properties of vascular smooth muscle; 7.) Application of fluorescence microscopy and 3D-image analysis for studies of microvascular cell biology and the cyto-architecture and function of the microvessel wall; and 8.) Mechanisms of blood flow autoregulation.

Laboratory models include studies of both the intact microcirculation and of isolated arterioles, freshly dispersed or cultured vascular smooth muscle cells, endothelial cells and cardiac muscle cells. Examples of technical approaches include pharmacology of the intact microvasculature and isolated microvessels; ability to manipulate pressure and flow in isolated microvessels; vessel culture and transfection; immuno-cytochemistry of the microvessel wall and isolated cells; three-dimensional fluorescence imaging using confocal, multiphoton or wide field microscopy in combination with deconvolution; atomic force microscopy combined with fluorescence microscopy (TIRF and FRET). Software development for high through-put analysis and display of atomic force microscopy force data.

An emphasis over the last several years has been to understand the role of the extracellular matrix, adhesion molecules and the cytoskeleton in regulation of vascular and cardiac cells; especially in the control of contractile function. A fundamental aim of this work has been to determine to what extent this matrix-adhesion-cytoskeletal axis may be involved in mechanotransduction phenomena that underlie the vascular myogenic response, flow-dependent responses of the endothelium and vascular remodeling. Advances in hybridizing atomic force microscopy with fluorescence microscopy are permitting higher throughput evaluation of cell surface receptors and their interactions with specific ligands.

Our future plans include continuing to study the role of the extracellular matrix and cell adhesion molecules in the regulation of vascular and cardiac cell function. We are extending our studies of mechanotransduction down to the level of single molecular interactions between integrins and extracellular matrix molecules, as well as to the mechanical dynamics of single focal contacts.

Associate Director

Michael A. Hill

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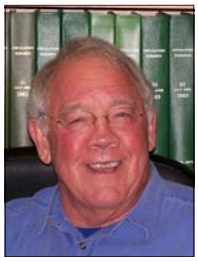
Education:
PhD & MS University of Melbourne

Appointment: Professor, Assistant Director, Department of Medical Pharmacology and Physiology

Research
Our laboratory has a principal interest in understanding the signaling mechanisms that underlie the vasoconstrictor response of an arteriole following an acute rise in intraluminal pressure (myogenic response). Our studies have examined the roles of a number of vascular smooth muscle signaling molecules including various kinases and intra cellular Ca^{2+}. More recently these studies have been extended to include approaches aimed at determining the relationships between pressure-induced changes in smooth muscle membrane potential and the resulting signaling events that ultimately lead to the contractile response.

In addition to basic studies on myogenic signaling, we are also studying how myogenic tone interacts with other vasoregulatory mechanisms (principally, endothelial-dependent dilation) and how myogenic response is altered in diabetes mellitus.

Principal Investigators



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Education:
PhD, MA & AB University of Missouri-Columbia

Appointment: Professor, Department of Medical Pharmacology and Physiology

Research
Currently, the primary focus of my laboratory is the underlying cause of hypertension that is associated with an adverse uterine environment. It is well documented that offspring of mothers who have undergone a variety of stressful circumstances during pregnancy may give birth to offspring who suffer from conditions such as hypertension, type II diabetes, and metabolic syndrome as adults. This phenomenon is known as fetal programming or the fetal origin of adult disease. One characteristic of these susceptible offspring is a reduced nephron number and several investigators have suggested that the lack of a full nephron complement is the underlying cause of the adult onset hypertension. How the reduction in nephron number causes or contributes to hypertension is not known. We are presently working on the hypothesis that there is a differential loss of nephrons. Based on inherent heterogeneity, loss of more “salt-losing” nephrons and retention of more “salt-saving nephrons” results in an overall tendency for the kidney of these offspring to retain sodium and, therefore, be more susceptible to hypertension as adults.

Our work involves whole animal studies which detail changes in the kidney's ability to excrete sodium and whether changes in ability to excrete a sodium load is a function of changes in glomerular filtration, sodium reabsorption, or both. These studies are conducted in conscious, freely moving animals to obtain data that is not compromised by anesthesia or restraint. We are also studying changes renal morphology, especially distribution of the loops of Henle, using immunohistochemistry techniques.

We continue our interest in neuroendocrine regulation of fluid balance and cardiovascular function, with emphasis on hypertension and heart failure. We are particularly interested in the actions of angiotensin II and vasopressin on brain cardiovascular centers. Our recent work has demonstrated two distinct actions of angiotensin on blood pressure regulation: acutely, angiotensin has its primary effect directly on vascular smooth muscle, while chronically, the hypertensive effects of angiotensin are mediated through activation of central nervous system pathways. Not only are the circumventricular organs important, but other brain areas are activated during acute and chronic angiotensin infusion. Our next step is to map the distribution of heightened nervous system activity in the peripheral vascular beds that is associated with chronic angiotensin hypertension. We are also investigating receptor regulation and post receptor signaling associated with angiotensin infusion.

We are also interested in the role of the renin-angiotensin system in diabetic nephropathy and the mechanism by which drugs that inhibit this system are effective in preventing renal damage.

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Education:
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Appointments: Professor, Department of Biomedical Sciences
Adjunct Professor, Department of Medical Pharmacology and Physiology

Research

Research interests in my laboratory currently focus on two areas.

The first question being posed is: what are the aging mechanisms of decreased proliferation and differentiation of satellite cells, the adult stem cells in skeletal muscle? Experiments are concerned with regulation of $p21^{Cip1/WAF1}$, $p27^{Kip1}$, p53, FoxO3a, Sirt1 and other proteins as they regulate proliferation and differentiation.

The second question being posed is: by what mechanisms does physical inactivity trigger metabolic dysfunction? When rats that have voluntarily ran in wheels cease running, specific intra-peritoneal fat masses increase, insulin sensitivity in specific skeletal muscles falls, and enhanced vasodilatation of the aorta is lost. Research is under way to determine molecules responsible for these inactivity effects.

Doug Bowles

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PhD University of Texas-Austin

Appointments: Associate Director of the National Center for Gender Physiology
Associate Professor, Department of Biomedical Sciences
Adjunct Professor, Medical Pharmacology and Physiology

Research

The goal of our lab's research is to understand how ion channels affect the role of coronary smooth muscle (CSM) in vascular pathology, i.e. atherosclerosis and post-angioplasty restenosis. Our major research question is how physical activity/exercise and sex hormones alter ion channel function in coronary smooth muscle to affect the onset and progression of coronary vascular disease.

Currently, the major focus is on two distinct channels, the intermediate-conductance, calcium-activated K channel (IKCa1) and channels underlying store-operated calcium entry, most likely TRPC channels. We are interested on these as they are upregulated during CSM phenotype modulation that occurs during vascular injury. Our lab strives for a molecule to animal approach using cultured and native cells, intact vessels and in vivo models. The primary model is the swine, as its coronary physiology, antatomy and gene expression profile is most similar to human. Experimental techniques include whole-cell and patch clamp, fluorescent based calcium imaging, isometric vessel recordings, cannulated microvessels, immunoblot, real-time RT-PCR, laser capture microdissection and molecular biology (promoter/reporter constructs, etc) to examine gene regulation by ion channels.

Lastly, we have a state-of-the-art, fully digital cath lab exclusively for large animal (e.g. pig) research. With this we can do angiography, intravascular ultrasound, intracoronary flow and pressure. We can also induce coronary injury/ restenosis with balloons and stents. Our goal is to use this to provide direct, in vivo, "translational" endpoints to our cellular/genetic studies.

The results of these experiments will provide novel mechanisms by which a sedentary lifestyle and hormonal status impacts cardiovascular health and well being as well as define potential therapeutic targets for the treatment and prevention of cardiovascular diseases.

Lane Clarke

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Education:
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Appointments: Associate Professor, Department of Physical Medicine and Rehabilitation
Associate Professor, Department of Biomedical Sciences

Research

Our laboratory investigates electrolyte and nutrient transport across epithelial tissues (airway, reproductive and intestinal) during health and disease. The major focus is to understand the role of the cystic fibrosis transmembrane

conductance regulator protein (CFTR) in the regulation of acid-base and nutrient transport across alimentary epithelia. CFTR is the protein product of the gene that is mutated in cystic fibrosis (CF) and normally functions in epithelial cells as a cyclic AMP-regulated anion channel. Present studies investigate the role of anion exchange proteins that work with CFTR in promoting bicarbonate transport or that work with Na^+ transport proteins for NaCl absorption across intestinal epithelium. Most studies involve either measurements of acid-base or nutrient transporter activity using fluorescent dyes to monitor intracellular pH by microfluorimetry or electrophysiological recordings in Ussing chambers of native mucosa and cell lines derived from gene-targeted ("knockout") mice. In addition to the cystic fibrosis mice, the laboratory maintains colonies of mice with gene-targeted deletion of other acid-base transporting proteins, including Na^+/H^+ exchangers, Cl^-/HCO_3^- exchangers and $Na^+/K^+/2Cl^-$ cotransporters. Molecular studies in the laboratory involve the measurements of gene expression in the mice (quantitative real-time PCR, Northern blots and microarrays) and cloning of specific murine transporters for functional expression studies in heterologous cell systems. In addition to the above methods, other techniques employed in the laboratory include cell culture, retroviral and adenoviral gene transfer, pH stat/isotopic flux studies, laser capture microdissection and PCR-based genotyping.

George E. Davis

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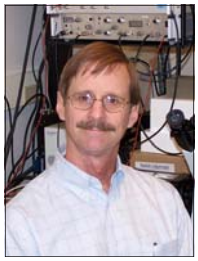
Education:
PhD, MD University of California-San Diego,
BS Arizona State University

Appointment: Professor, Department of Medical Pharmacology and Physiology

Research

My laboratory focuses on the following questions relevant to angiogenesis, wound repair and cancer research:

1. How do endothelial cells form cell-lined tube structures with lumens in three-dimensional (3D) extracellular matrices?
2. How do endothelial cells and other cell types such as tumor cells invade 3D matrices?
3. To what extent do endothelial cells directly or indirectly play a role in tumor invasion and metastasis?
4. What molecular events control the process of vascular regression?
5. How do vascular supporting cells, such as pericytes, stabilize vascular tubes?
6. How do distinct matrix metalloproteinases and their inhibitors control the processes of vascular morphogenesis versus regression in 3D matrices?
7. How do extracellular matrix fragments (matricryptins) regulate vascular morphogenesis versus regression in normal versus diseased states (such as diabetes)?



Michael J. Davis

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Education:
PhD University of Nebraska,
BS University of California, Davis

Appointments: Associate Department Head and Professor, Department of Medical Pharmacology and Physiology

Research

My general area of research is on the mechanisms of mechano-transduction by blood vessels: How does the smooth muscle layer of a blood vessel detect changes in pressure? What cellular proteins and signaling pathways are involved in this process? Currently, our focus is on a signaling axis linking the extracellular matrix with integrin receptors, the cytoskeleton, and ion channels. We focus on two ion channels: the L-type, voltage-gated calcium channel and the large-conductance, calcium-activated (BK) potassium channel that are acutely regulated by integrin signaling in vascular cells.
The experimental approaches used in my laboratory include isolated, perfused microvessel methods and single-cell electrophysiology. We combine these with variety of imaging methods, including confocal, atomic force, and TIRF microscopy. We also use molecular analyses, such as site-directed mutagenesis and co-immunoprecipitation, to identify and test which integrin-associated proteins are involved in modulation of ionic channels.

A related research interest is the role that collecting lymphatic vessels play in the regulation of extracellular fluid balance. These vessels exhibit spontaneous, phasic contractile behavior that propels lymph centrally. Lymphatic function is dramatically different than that of arterioles and venules and they express isoforms of contractile proteins that suggest lymphatic smooth muscle is a hybrid between cardiac muscle and vascular smooth muscle. We investigate their mechanical properties using servo-controlled systems to study isolated lymphatics from rats and mice under isobaric, isometric and isotonic conditions.

Shinghua Ding

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Education:
PhD & MS State University of New York,
BS Zhejiang University of Technology

Appointment: Assistant Professor, Department of Biological Engineering

Research

My current research focuses on glial cell function and neuron-glia interactions in the central nervous system using state -of-the-art *in vivo* two photon fluorescent imaging and electrophysiology. My research also involves stem cell differentiation and transplantation.

Paul J. Fadel

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Education:
PhD University of North Texas,
MS Northeastern University, Health Science Center,
BS Brooklyn College

Appointments: Assistant Professor, Department of Medical Pharmacology and Physiology

Research

Our laboratory's research focus entails the investigation of neural cardiovascular control at rest and during exercise in humans with a specific emphasis on the sympathetic branch of the autonomic nervous system. Ongoing studies involve assessing sympathetic responses during various physiological manipulations including isometric and aerobic forms of exercise, lower body negative pressure to simulate the effect of gravity when one stands up, and infusions of pharmacological agents. Studies are performed in normal healthy subjects as well as in patients with various pathophysiological conditions such as heart failure and hypertension. Our laboratory obtains direct measures of sympathetic neural firing using the technique of microneurography. This measurement allows for the assessment of moment-to-moment as well as long-term changes in sympathetic nerve activity. Also, with the application of partial autospectral and time series analyses to muscle sympathetic neurograms we are beginning to investigate the central origin(s) and pattern(s) of sympathetic discharge in humans. Our current research focus is on the neural mechanisms that contribute to exercise-induced sympathoexcitation as well as the peripheral modulators of sympathetically medicated vasoconstriction in contracting skeletal muscle with a particular emphasis on the potential roles of free radicals and changes in nitric oxide signaling in altering these responses. Considering the continually increasing population of elderly individuals, we are beginning to examine age-related alterations in neural cardiovascular control during exercise. Research in this area has been limited and is extremely important considering that an exaggerated blood pressure response to exercise increases the risk for mortality in otherwise healthy adults.

Kevin D. Gillis

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Education:
DSc, MSEE & BSEE Washington State University,
BA St. Louis University

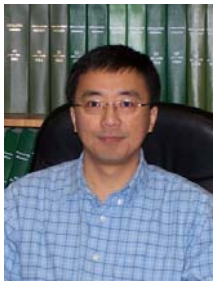
Appointments: Professor, Department of Biological Engineering Adjunct Professor, Department of Medical Pharmacology and Physiology

Research

My main area of interest is understanding the final steps of cell secretion and the modulation of these steps by protein kinases. We are presently using multiple biophysical approaches to assay dynamic aspects of secretion from individual adrenal chromaffin cells. We have found that activation of protein kinase C (PKC) enhances depolarization-induced exocytosis many fold while actually decreasing the calcium current which triggers release. Using several different protocols, we have shown that PKC enhances secretion by increasing the size of the "readily releasable pool" of

secretory granules. On the other hand, our experiments with caged Ca2+ show that PKC does not shift the Ca2+-sensitivity of the final step in secretion. Since protein kinases play a central role in regulating both secretion of hormones and release of neurotransmitter at synapses, the results of our research have an impact on understanding such diverse phenomena as the "fight or flight" response and the formation of short-term memory. In the future, we plan on further characterizing the kinetic steps modulated by protein kinases. For example, does PKC increase the size of the readily releasable pool by increasing the "filling" rate or does it stabilize vesicles in the "readily releasable" state? We also plan to examine the targets of kinase action at the molecular level.

Our research also has a strong engineering component with particular emphasis on developing or refining electrical and optical techniques for studying secretion. Techniques in use in the lab include patch-clamp electro-physiology with membrane capacitance measurements as an assay of involved with is investigating the effects of cardiovascular deconditioning which occurs after a period of bed rest or spaceflight. Deconditioning is associated with several changes in cardiovascular regulation including increased incidence of orthostatic hypotension, which is the inability to maintain blood pressure when a person stands up, and a reduced ability to maintain blood pressure during hemorrhagic events. Since females have higher incidence of problems following bed rest or spaceflight, we are evaluating gender differences in autonomic control of the circulation following cardiovascular deconditioning. Defining the central nervous system mechanisms that account for the changes in autonomic nervous system function during these states will increase our understanding and enhance our ability to treat problems associated with pregnancy and cardiovascular deconditioning.exocytosis/ endocytosis, amperometric detection of catecholamine secretion with carbon fiber electrodes, photometric measurement of membrane turnover and intracellular Ca2+ concentration with indicator dyes, and photo- release of intracellular Ca2+ from caged compounds.



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Education:
PhD Nankai University

Appointment: Assistant Professor, Department of Biological Engineering

Research

We are a newly established nano-biotech laboratory focusing on application of lab-in-hand nanotechnology to the exploration of life science problems and practical biomedical detection. Currently, we utilize various nanopores as receptive probes for single molecule detections. Nanopore refers to a pore structure adopting dimension from one to hundreds nanometer, which can either be formed by naturally-occurred self-assembled protein pore or fabricated by fashion nanotechnology on solid substrates. With the nanopore probe, any analyte, whether it is a single molecule, a molecular complex, or a single viral particle, can reversibly bind to a receptor which is pre-engineered in a properly sized nanopore, and be identified by recognizing the characteristic blocks to the nanopore conductance.

Our laboratory is initially supported by the University of Missouri Startup Fund, Research Board and Research Council. Recently, this laboratory successfully got a National Science Foundation (NSF) Career Award grant in support of a new direction focusing on single molecular protein-oligonucleotide interaction and molecular folding in a nanopore.

Specifically, we apply the nanopore technology to the single molecule investigation of dynamic aptamer-protein interactions and related folding processes involved in molecular recognition. Aptamers are engineered DNA/RNA that can specifically recognize broad species of proteins with high affinities, such as HIV-1 Integrase. Upon binding, these powerful molecules can form complex three-dimensional structures and possess sophisticated functions to inhibit pathogen protein, catalyze chemical reactions, control gene expression, and regulate cellular functions, therefore potentially be applied as tools for exploring biological systems. A complete understanding of dynamic processes in aptamer-target interactions and molecular folding is not only important to application-driven rational design, but also gives deep insight into the complexity of various nucleic acid-protein interactions in living cells.

Our research will be significant in the quantitative characterization and precise control of molecular scale components or nanomachinery of living cells by employing fashioning tools that allow us to manipulate complex biological processes in unique ways. Research using nanopore technology can be broadly applied to the study of diverse nucleic acid-protein and protein-protein interactions, which is essential for rational design of small organic molecules that block malfunctions of the cellular machinery, or act as new therapeutic reagents and products for biotechnology and bioengineering applications. This research will also greatly expand the capability of nanopore as the new generation of detection technology for analysis, high-throughput screening, bio-defense, and environmental engineering. In a broader impact, nanopore research will shed light on nanobiotechnology, an interdisciplinary and collaborative area related to biomolecular science, biotechnology, chemical engineering and nanotechnology.

Marc Hamilton

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Education:
PhD University of South Carolina,
MA University of Texas

Appointment: Assistant Professor, Department of Biomedical Sciences

Research

Dr. Hamilton studies the molecular and physiological mechanisms by which physical inactivity causes chronic metabolic diseases related to poor plasma lipid metabolism (coronary artery disease, Type II diabetes, obesity). A focus of the research in our laboratory is on translational research. In so doing, studies of humans, animal, and cell cultures are performed with the goal of integrating fundamental new insights regarding molecular processes while seeking solutions to practical clinical outcomes for metabolic diseases caused by physical inactivity. Multidisciplinary work exposes lab members to a diversity of modern research techniques. Studies have sought to discover the genes and signals linking physical inactivity to disease, especially those processes related to lipoprotein metabolism and skeletal muscle metabolism. A major question we are addressing is the underlying role of lipid metabolism in signaling for adaptations within vascular cells as one explanation for why exercise prevents atherosclerosis. This work largely involves pigs, isolated blood vessels in culture, and primary endothelial cell cultures. Rat and human work is also performed to understand regulation of processes controlling muscle metabolism and plasma lipids. Using microarray methodologies, our laboratory has been characterizing the response of a large percentage of the genome to exercise training, inactivity, and identifying both the transcriptional and post-transcriptional events influenced by lipids. In both human and animal studies, we have been testing the new paradigm of "inactivity physiology." Studies are partly focused on comparing and contrasting the underlying

metabolic responses to normal non-exercise physical activity to more intense and structured exercise. These studies are leading to the emerging school of thought that sitting too much (non-exercise activity deficiency) is a unique stimulus from exercising too little (exercise deficiency), while both types of physical activity can produce potent cellular signals important for combating the metabolic problems associated with metabolic syndrome, coronary artery disease, Type II diabetes, and obesity.

Eileen M. Hasser

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Education:
PhD University of Oklahoma, BA Gettysburg College

Appointments: Professor, Department of Biomedical Sciences
Adjunct Professor, Medical Pharmacology and Physiology

Research

The primary interest of the laboratory is in central nervous system control of the sympathetic nervous system and blood pressure, and how these reflex systems are modulated under physiological and pathophysiological conditions. Currently, the laboratory is involved in three primary projects.

The primary goal of the first project is to determine the neurotransmitter/receptor mechanisms involved in altered regulation of blood pressure in acute and chronic hypertension. The second project examines potential changes in both cardiovascular regulation and vascular function which may be responsible for cardiovascular deconditioning following prolonged exposure to spaceflight or bedrest. The focus here is on plasticity in specific brain regions that influence cardiovascular control. The third area of investigation focuses on the reflex effects of circulating humoral factors which act in the central nervous system to alter cardiovascular regulation. This project examines the central nervous system neurotransmitters and pathways involved in these effects. These questions are examined utilizing conscious animals which are chronically instrumented for recording of blood pressure, blood flow and sympathetic nerve activity. In addition, anesthetized preparations are utilized for experiments involving electrical and chemical stimulation of specific brain regions, microinjections of neurotransmitter agonists and antagonists, and central neurophysiological recording.

The overall goal of this work is to understand the central nervous system mechanisms underlying cardiovascular regulation in normal and disease states.

Cheryl M. Heesch

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Education:
PhD University of Texas Health Science Center,
BS New Mexico State University

Appointment: Professor, Department of Biomedical Sciences

Research

Our laboratory's major focus is to understand how the central nervous system controls arterial blood pressure and how blood pressure is modulated in physiological and pathophysiological states. We evaluate basic mechanisms involved in central nervous system control of autonomic outputs, particularly in brainstem regions which are critical for providing tonic drive to the sympathetic nervous system. We also study how ovarian hormones modulate these basic control mechanisms. Ongoing projects in the laboratory are focused on elucidating the role of central nervous system effects of ovarian hormones and progesterone metabolites in the alterations in control of sympathetic outflow associated with term pregnancy. Once we understand the mechanisms for attenuated sympathoexcitation in normal pregnancy, it may be possible to determine the mechanisms for elevations of arterial blood pressure in hypertensive disorders, where sympathoexcitatory responses are exaggerated. Also, women are generally protected from heart disease and hypertension until the onset of menopause. Understanding the mechanisms for the protective role of ovarian hormones could have important implications for treatment and prevention of cardiovascular disorders.

The possibility that a metabolite of progesterone, 3 -OH-dihydroprogesterone, may play a major role in suppression of sympathoexcitatory responses is especially intriguing. 3 -OH-dihydroprogesterone is the most potent endogenous positive modulator of central nervous system GABAA receptors and physiologically significant levels have been reported in the central nervous systems of both males and females. Experimental approaches include:
1.) measurement of sympathetic nerve activity; 2.) CNS microinjection of putative transmitters and modulators;
3.) extracellular single unit neuronal recording; and 4.) evaluation of neurotransmitter receptor expression in relevant brain regions.

Virginia Huxley

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Education:
PhD University of Virginia, BA Hollins University

Appointments: Director of the National Center for Gender Physiology
Professor, Department of Medical Pharmacology and Physiology
Adjunct Professor, Department of Biomedical Sciences

Research

Research Interests: Microvascular transport, *in vivo* imaging/microscopy, in vivo mass transfer, tissue engineering, mathematical modeling

We focus on the mechanisms controlling solute, water, and gas transfer between circulating blood and metabolizing tissue. Knowledge of the barriers to transport in living tissue is essential for elucidating the processes providing moment-to-moment regulation organ function and the etiology of dysfunctional states. These data facilitate design and implementation of rational strategies for treating diseases with the progressive goals of abating, arresting, and ultimately reversing disease processes.

Solute and water transfer results from "passive" and "cell mediated" mechanisms. Most have studied the passive mechanisms fewer study the cellular processes. From engaging in research in both arenas we find the exchange barrier to be a dynamic structure whose properties vary in time and space over time scales of seconds to days. Our global intent is to use this understanding of transport through pathways of microscopic geometry to investigate the relationship between blood supply and metabolic demand.

We are developing methods to extend these quantitative studies to mammalian microvessels in skeletal muscle, heart, gut, and brain in collaboration with colleagues in DCRC, MPP, Biomedical Sciences at MU and the University of Rochester. Knowing that microvascular exchange is subject to regulation under normal and pathological situations, we collaborate with clinical colleagues (Nephrology, Surgery, Anesthesia, Cardiology, Pulmonary Medicine, Infectious Disease, and Critical Care Medicine) to elucidate the cellular and molecular mechanisms involved in structuring and restructuring the barrier under conditions of peritoneal dialysis, following endurance exercise training, in coronary occlusive vessel disease, neurogenic edema, diabetes, cancer metastasis, and conditions of remote organ (brain) injury following burn. The combined clinical and basic science expertise provides the possibility of realizing our goal of designing and implementing treatments of permeability dysfunction. Consequent to the collaborative interactions at MU and in light of fundamental sex-related differences in physiological function and pathophysiology observed by us and others, we established the National Center for Gender Physiology. This virtual center is acting as a focus for research scientists at MU and collaborating institutions and augments the services provided by DCRC.

Tzyh-Chang Hwang

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Education:
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Appointment: Professor, Department of Medical Pharmacology and Physiology

Research
CFTR (Cystic Fibrosis Transmembrane conductance Regulator) is a chloride channel that plays a critical role in secretion and absorption of water and electrolytes across epithelia. Since CFTR channels are also expressed in cardiac myocytes and are found to shorten action potential duration and induce repetitive activity, they are implicated to be arrhythmogenic. One unique feature of the CFTR protein as an ion channel is that the free energy of ATP hydrolysis is harvested to drive the conformational changes that open and close the channel. Studies using mutant CFTR and various ATP or phosphate analogs have suggested a model that ATP hydrolysis at two nucleotide binding sites is tightly coupled to the opening and closing of the channel pore. Our understanding of the molecular basis of the coupling mechanism, however, remains primitive. Unresolved questions include: What is the

stoichiometry of ATP binding/hydrolysis to gating transitions? How are the biochemical states in ATP hydrolysis cycles translated to the open and closed states in the gating transitions? Which part of the protein forms the aqueous pore? What is the relationship between the gate and the pore? These are the fundamental questions that interest a broad spectrum of physiologists.

A combinational approach is being adopted to tackle the molecular physiology of CFTR chloride channels. Different configurations of the patch-clamp techniques will be used to record CFTR channel activity so that both the cytoplasmic and extracellular sides of the channel are accessible to channel blockers, modifiers, or channel openers. Structure-guided mutagenesis approaches will be employed to study the functional consequences of single amino acid substitutions on gating and permeation/blocking. State-dependent chemical modifications of engineered cysteines allow us to explore the dynamic protein conformational changes during gating transitions. The aims of our ongoing research are: 1. To understand the role of ATP binding and hydrolysis in controlling the opening and closing transitions of CFTR. 2. To probe the CFTR pore with permeant and impermeant anions. 3. To explore the structure/function relationship between the gate and the pore of CFTR. 4. To characterize how CFTR activators act to increase the activity of CFTR. 5. To apply structure-based drug design to identify chemicals that can correct trafficking defects in CF-associated mutations. A clear understanding of the molecular mechanism of CFTR function will aid in the design of pharmacological agents for therapeutic intervention in cystic fibrosis, secretory diarrhea and cardiac arrhythmia.

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Education:
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Appointment: Associate Professor, Department of Biomedical Sciences

Research

The main aim of our laboratory is to identify steroid hormone dependent molecular targets that can be utilized for anti-angiogenic therapy of endocrine dependent disease such as the breast, uterine, and prostate cancer. Formation of new blood vessels, or angiogenesis, is crucial for normal processes such as embryonic development, wound healing, and endometrial regeneration following menstruation. Angiogenesis is also essential for tumor growth, and metastasis. An emerging field in cancer therapeutics is the targeting of new blood vessels to curtail tumor growth. Our laboratory is currently focusing on the role of steroid hormones, clinically rele vant anti-hormones, and endocrine-disruptors to understand the basic mechanisms involved in hormone driven angiogenesis in breast, and uterine tissue. We are currently focusing on the role of estrogens, progestins, and their nuclear receptors in controlling the expression of potent angiogenic growth factors (e.g. VEGF and its receptors) at both molecular and cellular level. Another focus of the laboratory is to investigate the molecular mechanisms of steroid hormone action at the level of gene transcription. We are especially interested in the role of natural and synthetic ligands that have diverse biological effects in different target tissues (e.g. SERMS such as tamoxifen). Many synthetic ligands (agonists/antagonists) are consumed by millions of women all over the world for oral contraception, hormone replacement therapy, or treatment of breast cancer. Consumption of some of these ligands lead to increased risk of breast and/or uterine abnormalities, including cancer. We anticipate that understanding the molecular basis/ pharmacology of ligand-nuclear receptor interactions will allow development of better therapeutic modalities for treatment of hormone dependent tumors, as well as endometriosis, osteoporosis and infertility.

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Education:
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Appointment: Assistant Professor, Department of Biomedical Sciences

Research

Our laboratory focuses on the autonomic nervous system, in particular the cardiovascular and respiratory system. These vital systems operate to keep our bodies within "normal" physiological limits to preserve homeostasis. When challenged acutely or chronically with low environmental oxygen levels (hypoxia) respiration, blood pressure and heart rate compensate to maintain arterial blood gas levels. This can happen during high altitude assent or disease states such as sleep apnea by activation of the chemoreceptor reflex. Additionally, arterial blood pressure is maintained during swings in pressure by the baroreceptor reflex. Both reflex pathways result from activation of neurons in the peripheral and central nervous system. Determining the mechanism of action of these reflex pathways during health and disease is the focus of the laboratory.

Several techniques are used to elucidate these mechanisms. These include 1.) radiotelemetry in conscious animals to measure respiration, blood pressure or heart rate; 2.) immunohistochemical localization of ion channels and neurotransmitter receptors to specific regions of the nervous system and individual neurons; 3.) patch clamp techniques in isolated neurons for recording current flow through ion channels and 4.) electrical recording of synaptic transmission in brainstem slices. Using these techniques, we have recently discovered that chronic intermittent hypoxia, a model for obstructive sleep apnea, elicits a form of neural adaptation or plasticity in the brainstem. This includes changes in neurotransmitter release from presynaptic chemoreceptor afferent neurons as well as postsynaptic action potential firing. We are currently determining the mechanism of this altered neurotransmitter release.

Ronald J. Korthuis

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Education:
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Appointment: Chair Medical Pharmacology and Physiology
Professor, Department of Medical Pharmacology and Physiology

Research

Our research focuses on the mechanisms underlying the inflammatory responses to ischemia and reperfusion (I/R) and how blood vessels in the microcirculation (arterioles, capillaries and venules) can be preconditioned to resist the deleterious proinflammatory effects of I/R. When the blood supply is reduced (ischemia) and then subsequently reestablished (reperfusion), the ability of arterioles to regulate the distribution of blood flow is impaired, many capillaries fail to perfuse (capillary no-reflow), and white blood cells and platelets become adherent to and emigrate across the walls of postcapillary venules. Once in the tissues, these inflammatory phagocytes attack

parenchymal cells, thereby exacerbating injury induced by ischemia. In addition, the permeability of the cells lining capillaries and postcapillary venules is increased, leading to edema formation. We are studying how white blood cells which adhere to and emigrate across the walls of postcapillary venules, alter vasoregulatory function in arterioles, cause no-reflow in capillaries, and increase permeability in postcapillary venules.

Laboratory models include study of the intact microcirculation using intravital microscopy coupled with computerized image analysis, examination of vasomotor responses in isolated arterioles, assessment of cell adhesion and permeability in single postcapillary venules, and evaluation of cell signaling mechanisms in cultured endothelial cells. A wide variety of mutant mouse models (gene knockout and transgenic overexpression), coupled with pharmacologic approaches, immunocytochemistry of the microvessel wall and cultured cells, western blotting and RT-qPCR to measure protein and mRNA expression, quantitative assessment of adhesion molecule expression using a dual radiolabeled monoclonal antibody technique, and three-dimensional fluorescence imaging using confocal microscopy are used to explore signaling mechanisms cultured cells, isolated microvessels, and intact microcirculatory networks *in vivo*.

A major area of emphasis over the last several years has been to understand how exposing tissues to preconditioning stimuli such as nitric oxide donors, calcitonin gene-related peptide, or by ingestion of ethanol (at doses equivalent to drinking one to two alcoholic beverages) 24 hours prior to the onset of prolonged ischemia followed by reperfusion prevents postischemic microvascular and parenchymal cell dysfunction. A fundamental aim of this work is to determine the signaling mechanisms that are activated in response to these preconditioning stimuli to upregulate gene expression for proteins that mediate the development of the anti-inflammatory and anti-thrombogenic phenotype in postischemic tissues.

Our future plans include continuing the examination of the mechanisms whereby microvascular function is protected in preconditioned states by focusing on the role of the extracellular matrix and cell adhesion molecules, ion channel function and extravascular constituents such as mast cells in these responses. In addition, we are exploring how leukocytes, which adhere almost exclusively in postcapillary venules in our models, alter the function of upstream arterioles in tissues exposed to ischemia and reperfusion.

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Appointments: Chair of the Department of Biomedical Sciences
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Adjunct Professor, Department of Medical Pharmacology Physiology

Research

I focus my research on cardiorespiratory effects of exercise. The primary goal is understanding of the effects of exercise training on the coronary circulation and skeletal muscle vascular beds. Exercise training produces increases in the capacity of myocardial and skeletal muscle vascular beds to transport oxygen and other nutrients. The training induced changes in vascular transport capacity are associated with growth of new capillaries, enlargement of arteries and veins, and alterations in factors that control blood flow in the heart and skeletal muscle. The laboratory is

currently investigating the mechanisms responsible for these changes. Studies are conducted with: isolated hearts, isolated muscle tissue, single blood vessels and in conscious, chronically instrumented animals during exercise. To allow examination of the relationships among vascular adaptations and the response of the myocytes to training induced increases in the functional demands of the muscles, the effects of training on biochemical and histological characteristics of the muscles are also measured. The biochemical systems examined include: the metabolic pathways involved in supplying the myocytes with ATP, the contractile proteins, the systems responsible for controlling intracellular Ca^{++} levels and endothelin nitric oxide synthase. Most of our current experiments are focused on endothelial cell biology. We are determining the effects of physical activity on endothelial phenotype in normal animals and in models of vascular disease. We are also using genetically modified pigs to examine the role of endothelial nitric oxide synthase in the impact of endothelial cell phenotype on vascular health.

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Research
My research is focused on the mechanisms responsible for the architectural transformation of blood vessels also known as vascular remodeling. Vascular remodeling is a hallmark for numerous cardiovascular diseases, yet numerous questions remain to be answered regarding this process. What stimuli drive the remodeling process? How do blood vessels detect those stimuli? What are the mechanisms initiating the remodeling and under which conditions are they counterproductive participating in disease states?

Currently funded research in my laboratory is focused at determining the changes in the position and function of cells within the intact blood vessel wall that occur in response to common mechanical and vasoactive biochemical stimuli. Our studies indicate that cells within the vascular wall rapidly change their position in response to stimulation in as little as four hours. This adaptive cell behavior appears to allow the vessel to maintain a reduced diameter for extended periods of time with reduced levels of activation and energy expenditure. An additional goal is focused at determining the changes in the structure and compliance of the extracellular matrix that occur during the initial stages of the remodeling process.

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Appointment: Professor, Department of Medical Pharmacology and Physiology

Research
There are two major research efforts in our laboratory:
One effort is devoted to determining how proteins located in cell membranes move molecules across the membrane. This includes elucidating some of the mechanisms of transport, determining how changes of the

cytoplasmic mileau modulate transport, determining how changes in the rate of transport regulate cell function, and understanding the relationship between protein structure and transporter function. Our studies are currently focused on two transport systems: the plasma membrane calcium pump and the Na/K pump. Our recent work is devoted to examining the movement of the Na pump protein from plasma membrane to endosomes and back. We are determining the molecular basis for the integration of hormonal responses, e.g., what happens when one hormone signals increased endocytosis and another hormone signals exocytosis-who wins? We have also worked on zinc transporters, sodium/ calcium exchanges, and anion exchangers. We use biophysical, bioengineering, biochemical, and optical approaches to studying the relevant physiology and pharmacology of these transport systems, including the development of a molecular mechanistic view of their function and an integrated view of how regulation of cellular transport related to cell, tissue, organ and organism function and pathophysiology.

Another effort is the development of sensors for molecules of biological interest in collaboration with Sheila Grant in Bioengineering and Josh Millspaugh in Fisheries and Wildlife. We are designing sensors that can be used in vivo for continuous monitoring and also sensors that can be used in the field for monitoring wildlife or at home using saliva, urine, or sweat for measurement of pet or human samples. We are currently developing approaches for the measurement of glucose, cortisol, aldosterone and sex steroids. Our techniques include absorbance, fluorescence, FRET and lanthanide luminescence.

Patrick Mueller

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Appointment: Adjunct Professor, Department of Biomedical Sciences

Research

The goal of my research is to learn more about how the brain controls the heart and blood vessels and therefore, its role in determining arterial blood pressure and organ blood flow. In particular, I am interested in how the brain adapts its control of the cardiovascular system to various physiological and pathophysiological states. Currently, research in the lab is focused on examining how levels of physical activity contribute to alterations in neurohumoral control of the circulation. A sedentary lifestyle is a major risk factor for cardiovascular disease, the leading cause of death in the United States. Nonetheless, rates of physical inactivity in the general population continue to increase and inactivity related diseases such as obesity, diabetes, and hypertension are burdening our health care system at an epidemic rate. Despite this important health care problem, the mechanisms by which a sedentary lifestyle contributes to cardiovascular disease are unknown. However, recent evidence suggests that overactivity the sympathetic nervous contributes to the development and maintenance of cardiovascular disease. Our hypothesis is that a sedentary lifestyle may result in overactivity of the sympathetic nervous system and contribute to the increased incidence of cardiovascular disease in inactive individuals. The goal of my current research is test the hypothesis that a sedentary lifestyle alters central nervous system mechanisms that result in overactivity of the sympathetic nervous system. Specifically, we will examine the structure and function of a specific population of neurons in the brain (i.e. spinally projecting rostral ventrolateral medulla neurons) that are critical for blood pressure regulation via generation of sympathetic nervous system activity. These neurons play important roles in physiological and pathophysiological disease processes and are likely to contribute to conditions involving overactivity of the sympathetic nervous system. The results of these experiments will provide novel mechanisms by which a sedentary lifestyle impacts cardiovascular health and well being as well as define potential therapeutic targets for the treatment and prevention of cardiovascular diseases.

Luis Polo-Parada

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Education:
PhD Case Western Reserve University, MS University of Connecticut,
BS School of Physics and Mathematics, National Polytechnic Institute

Appointment: Assistant Professor, Department of Medical Pharmacology and Physiology

Research

The heart is the first organ to form during embryogenesis, and its function is critical for the proper development and survival of the embryo. Although some information on ion-transport genes and their protein products in normal and diseased myocardial tissue is available, little is known about the role of cardiac extracellular matrix (ECM) proteins during cardiac development or in healthy and diseased adult hearts. My interest is to elucidate the role of the ECM in the ionic-transport proteins and molecular basis of cardiac regional electrical specialization during development and in the adult heart.

My recent studies of neural cell adhesion molecule (NCAM) null mice have indicated that NCAM plays a fundamental role in the transmitter release mechanism in neuroendocrine cells through mediation of granule recruitment. Other studies have shown that NCAM plays a functional role in the proper segregation of cell during development of islets of Langerhans in the pancreas. My interest is to elucidate whether NCAM or other cell adhesion molecules, are directly involved in the proper organization of the islets of Langerhans and in glucose-mediated insulin secretion. I also intend to investigate, whether the expression of any of these cell adhesion molecules is affected in diabetic type II patients and animal models of the disease.

Jeffrey T. Potts

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Education:
PhD University of North Texas Health Science Center,
MA Indiana State University,
BPE University of New Brunswick

Appointment: Associate Professor, Department of Biomedical Sciences

Research

Research in our laboratory examines how individual neurons and interconnected populations of neurons encode information in the central nervous system, particularly as it relates to reflex control of the cardiovascular and respiratory systems. The goal of this research is to identify causal relationships between cellular/molecular processes and systems level function. To bridge these levels of analyses, we use a variety of techniques including electrophysiological (extracellular, intracellular and patch-clamp recording), neuroanatomical tracing and neurochemical studies in conjunction with *in vivo*, *in situ* and *in vitro* preparations to examine the connectivity of neurons in the pontomedullary axis.

Currently, we are investigating the cellular mechanisms underlying short-term changes in synaptic strength (ie. synaptic plasticity) and the consequence of these changes on function of the arterial baroreflex system. We have found that peripheral neurogenic feedback alters the excitability of barosensitive medullary neurons via local GABAergic circuits. These findings suggest that activation of intrinsic GABA neurons modulate neurotransmission in central baroreceptor circuits. This mechanism, in addition to other cellular and molecular events, may contribute to the induction of short-term changes synaptic plasticity in central barorereflex circuits. These findings have direct relevance to the regulation of cardiovascular function during both physiological (wake, sleep, exercise) and pathological (hypertension, congestive heart failure, diabetes) states, which will be the focus of our future endeavors.

In addition, we are interested in examining the neural pathways and synaptic mechanisms responsible for establishing basal breathing rhythms. Breathing is an unconscious behavior that we all perform and it is tightly coordinated with other motor behaviors such as speaking, eating and exercising. Our research has identified the synaptic connections between skeletal muscle and respiratory neurons in the brainstem that are responsible for changing breathing patterns. In particular, we have found that respiratory neurons in the pontine region of the brain play an important role in shaping breathing rhythms during exercise. By identifying these pathways, we are striving to learn more about sleep disordered breathing, such as sleep apnea and Sudden Infant Death Syndrome (SIDS), which are characterized by alterations in the normal processing of sensory signals. In the future, we will also incorporate transgenic mice to investigate the cellular and molecular basis underlying the generation of breathing rhythms.

The overall goal of research in our laboratory is to better understand the role of sensory feedback in the induction of neuroplasticity in pontomedullary neural circuits in a physiologically relevant context and to determine whether short- and long-term changes in synaptic strength participate in cardiorespiratory homeostasis.

Michael Rovetto

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Education:
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Appointment: Professor, Department of Medical Pharmacology and Physiology

Research

Myocardial ischemia caused by inadequate blood flow to the heart muscle leads to purine loss from cells. The extent to which they are lost is directly related to recovery of mechanical function upon restoration of blood flow to the heart. Thus, decreased purine levels and decreased ability of the heart to perform useful work are coupled. I am interested in determining what controls rates of transport of purines into and out of cells and how this process can be altered to enhance the energy state of the heart.

Related to these studies are investigations of how the cardioprotective substance, fructose phosphate crosses heart cell membranes. These studies are done in collaboration with Dr. Christopher Hardin.

Membrane transport of glucose also is of interest and of naturally occurring and genetically-induced animal models that lead to diabetes and/or hypertension are used to understand the role of the renin-angiotensin system in the pathologic consequences of diabetes & hypertension. These studies are done in association with Drs. James Sowers and Craig Stump, Department of Medicine and the Truman V.A. Hospital.

A model of hypothyroidism is used to alter the contractile activity of myocardial muscle in order to determine how specific changes in the contractile protein myosin affect the rate of force development by isolated muscle cells and intact heart. This is a collaborative research project with Dr. Kerry McDonald.

A similar investigation to that in hypothyroidism, but in hearts from genetically altered mice that exhibit traits of an inherited form of muscular dystrophy, are being carried out in collaboration with Drs. Joe Kornegy and Casey Childers College Veterinary Medicine and Department of Physical and Rehabilitation Medicine.

Leona Rubin

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Education:
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Appointments: Associate Professor, Department of Biomedical Sciences
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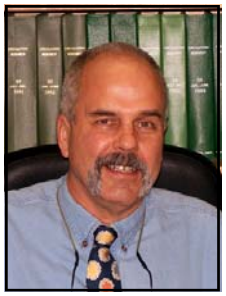
Research

Dr. Rubin's research is focused on understanding cellular pathways that regulate cardiovascular function during health and disease states. There are three major projects within the laboratory: 1.) How do immune mediators, released during inflammatory conditions (endotoxemia/sepsis, atherosclerosis) cause myocardial and/or vascular failure? Investigations focus on alterations in second messenger system(s) and cellular targets such as potassium and calcium channels. Therapeutic modalities also are probed as a means to identify affected pathways. 2.) What are the cellular pathways that mediate vascular hypoxic vasodilation? Matching of blood flow to meet tissue substrate needs is a fundamental property of the vasculature. However, the signals and vascular mechanisms responsible for dilation are unknown. We have targeted three sites for involvement in hypoxic vasodilation, AMP-activated kinase, Akt and voltage-dependent potassium channels. 3.) What is the role of sex hormones in modulating cardiovascular function? Specifically, do sex hormones alter expression of voltage-dependent potassium channels in either vascular smooth muscle or the myocardium? Myocardial studies examine both intrinsic (potassium currents of cardiac myocytes) and extrinsic (heart rate variability) control of heart rate. Methodologies include those needed to: 1.) measure contraction, Ca2+, and ionic currents of isolated ventricular myocytes; 2.) measure intracellular second messenger molecules, their substrates and products (gel electrophoresis ion chromatography, high performance liquid chromatography, gas chromatography and mass spectrometry), 3.) *in vitro* physiology of vascular function and 4.) *in vivo* assessment of heart rate variability. Our animal models include a swine model of sex hormone replacement (estrogen or testosterone), guinea pig and rat models of endotoxemia and genetically modified mouse models lacking components of signaling pathways that regulate cardiovascular function.



James C. Schadt

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Education:
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MS & BS Northern Illinois University

Appointment: Associate Professor, Department of Biomedical Sciences

Research

Traumatic injury is the leading cause of death for individuals under 40 years of age. While head trauma is the most common cause of death, blood loss is number two, and the effects of head injury are exacerbated by blood loss.

The goal of my research is to learn more about how the brain and endocrine systems control the heart and blood vessels during traumatic blood loss.

Steven S. Segal

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Appointment: Professor, Department of Medical Pharmacology and Physiology

Research

Our research is focused on understanding how oxygen delivery increases in response to metabolic demand. During exercise, the recruitment of skeletal muscle fibers (motor units) generates electrical and chemical signals in endothelial cells and smooth muscle cells of the microvessels that control the distribution and magnitude of muscle blood flow. Our experiments center on elucidating the cellular and molecular events which initiate these signals, how such signals are transmitted from cell to cell to orchestrate vasodilation and vasoconstriction in microvascular networks, and how these integrative processes are governed by the nervous system. Intravital video microscopy enables direct observations of blood flow control in the mammalian microcirculation. Histochemistry and vascular casting are used to quantify the architecture of neural and microvascular networks. Intracellular recording with dye labeling reveals cell-specific electrical signals which determine the contractile status of smooth muscle and its regulation by the endothelium. Calcium imaging provides unique insight into cellular responses which reflect the activity of ion channels and key regulatory enzymes. Complementary studies of isolated microvessels and their constitutive cells enable even greater resolution of specific regulatory processes. Pharmacology, immunolabeling, and Real-Time Polymerase Chain Reaction are used to resolve the functional expression of proteins which mediate cell-to-cell coupling through gap junctions and electrical signaling through ion channels.

Collaborative studies using transgenic mice afford unique insight into how particular signaling pathways affect control processes within the microcirculation. In turn, these basic relationships are athways affect control processes within the microcirculation. In turn, these basic relationships are being explored in light of how aging affects microvascular structure and function. Opportunities for graduate and postdoctoral training include: molecular physiology of vascular cells, electrical and optical monitoring of cell signaling, microsurgery and microdissection, intravital video microscopy, conventional and immunohistochemistry, evaluation of gene expression, and modeling the biophysical properties of cells and tissues.

Yoshiro Soma

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Education:
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Appointment: Visiting Professor, Department of Medical Pharmacology & Physiology

Research

I have a broad research interest that covers the molecular physiology and biophysics of ion channels and transporters, and their role in the physiological function of cells/tissue. I have studied the permeation and gating of a large-conductance, Ca^{2+}-activated, voltage-dependent potassium (BK_{Ca}) channel. BK_{Ca} channels are ubiquitously expressed in many different tissues and are known to be sensitive to membrane potential, intracellular calcium, magnesium, pH. These channels are also activated by CO and sensitive to O_2 associated with hemeoxygenase-2 and, moreover, some slice-variants respond to membrane stretch. Based on these findings, BK_{Ca} channels are suggested to play an important role in integrating cell signals, a recently proposed new function of an ion channel. I am also involved in a Japanese-based collaborative project undertaking a comprehensive study of the GABAergic system in peripheral tissues (not the central nervous system) and work on $GABA_A$ receptor channels and $GABA_B$-mediated modulation of K^+ and Ca^{2+} channels in peripheral tissues. In the Dalton Cardiovascular Research Center, I study the molecular mechanism of gating and permeation of the CFTR chloride channel, a member of the ATP-Binding Cassette (ABC) transporter superfamily, in collaboration with Dr. Tzyh-Chang Hwang. Our work has made a significant contribution to the recent advances in the biophysical understanding of the ATP-dependent gating mechanism in CFTR, and has provided great insight into a possible common functional mechanism that can be applied to the whole ABC transporter superfamily. The structure of the membrane spanning domain (MSD) in CFTR is known to be similar to that in the P-glycoprotein drug efflux pump. We therefore believe that understanding MSD structure/function in CFTR will lead to a better understanding of multi-drug resistance (MDR) proteins. In addition to investigating the biophysics of the CFTR molecule itself, I am also interested in studying the functional interactions of CFTR with other membrane proteins and lipids. This should help in our understanding of the complicated regulatory mechanisms that underlie physiological functions in cell membrane. I have also employed computer modeling to simulate ion transport processes in epithelial cells (e.g., bicarbonate transport in pancreatic duct cells). This approach is very useful to bridge information from molecular biophysics and cell/tissue physiology to the research field of epithelial transport. I believe that by taking such a general and comprehensive approach to the study of different channels/transporters and channel/transporter-mediated physiological systems, induces a 'positive cooperative effect' which accelerates each research project, and which also gives us a novel scientific standing point of view for the channel sciences.

Jim R. Sowers

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Education:
MD University of Missouri-Columbia,
BS Central Missouri State University

Appointment: Director of the MU Diabetes and Cardiovascular Center
Professor, Department of Medicine
Professor, Department of Medical Pharmacology and Physiology

Research
Fifty million people have high blood pressure and are prone to developing Type 2 diabetes. Dr. Sowers, directs the MU Diabetes and Cardiovascular Center and is associate dean for clinical research. His work addresses the link between high blood pressure and diabetes to better understand how to prevent and cure the diseases, which are growing problems in the United States.

Ronald Terjung

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Education:
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Appointment: Associate Dean of Research, Department of Biomedical Sciences
Professor, Department of Biomedical Sciences
Adjunct Professor, Department of Medical Pharmacology and Physiology

Research
Adenine nucleotide (And = ATP + ADP + AMP) metabolism occupies a pivotal role in cell regulation, particularly for skeletal muscle where contractile activity increases ATP hydrolysis rate manyfold. The control of [ATP] in contracting muscle depends upon: 1.) the control of energy supply pathways; 2.) And degradation reactions; 3.) And synthesis reactions from precursors; and 4.) contractile activity which determines the rate of ATP hydrolysis. He is evaluating differences in And metabol.ism among skeletal muscle fiber types, critical responses to exercise, and adaptations induced by chronic exercise. Enhanced physical activity represents an important treatment for persons with peripheral arterial insufficiency and leads to meaningful adaptations that increase exercise tolerance. These adaptations include neovascular development to improve a) blood/tissue exchange properties within muscle (enhanced capillarity) and b) flow capacity to active muscle (collateral vessel expansion). The exercise-induced increase in collateral blood flow likely involves the angiogenic growth factors (e.g. bFGF, VEGF). These potent cytokines stimulate neovascularization in experimental ischemia in vivo. His working hypothesis is that neovascularization occurs in response to tissue "need" established by flow deficits (ischemia) and/or by increased demands for vascular support (exercise). His research is evaluating: 1.) the interactions between ischemia, exercise and exogenously infused recombinant angiogenic growth factors; 2.) the functional significance of the vascular adaptations; and 3) the tissue events related to neovascularization.

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Education:
PhD University of California, San Diego,
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Appointment: Assistant Professor, Department of Biochemistry

Research

The molecular interactions that drive ligand-protein binding are a key to quantitatively understanding the basis of molecular recognition and to designing therapeutic interventions through rational drug design. Drug molecules usually act by binding to specific target proteins. Drug candidates that have high binding affinities can be identified by their geometric and chemical complementarity to the target in a process analogous to solving a "jigsaw puzzle," if the target structure is known. An energy model that can give rapid and accurate evaluation of the molecular interaction strength is thus essential for selecting plausible candidate compounds from a chemical database consisting of hundreds of thousands of molecules. We are developing novel and efficient algorithms to calculate binding free energies for ligand-receptor complexes. The derived energy models will be applied to protein-substrate interactions, protein-protein interactions, and structure-based drug design. We are also developing new docking algorithms to account for protein flexibility. Methods used in our laboratory include computer modeling, simulation and graphics display. A second line of research in the laboratory is quantitative studies on structure-function relationship of membrane proteins. Structures of membrane proteins will be predicted using homology modeling and structure alignment techniques. Structural information often suggests mechanisms of protein function, which will be experimentally tested in collaboration with other Dalton Investigators.

APPENDICES

PUBLICATIONS

PRESENTATIONS

INVITED SEMINAR SPEAKERS

ACTIVE GRANTS & CONTRACTS

PROFESSIONAL SERVICE ACTIVITIES

PUBLICATIONS

Arnett, K.
Reifenberger MS, Arnett KL, Gatto C, Milanick MA. Extra cellular terbium and divalent action effects on the red blood cell Na pump and chrysoidine effects on the renal Na pump.

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Ding, S.
Astrocytic responses to focal cerebral ischemia. Cardiovascular Day, University of Missouri-Columbia, Feb. 26, 2007 (New investigator speech).

Astrocytic Ca^{2+} signaling *in vivo*. Dept. of Biological Engineering, University of Missouri-Columbia, March 6, 2007.

Astrocytic Ca^{2+} signaling *in vivo* following photo thrombosis. Gordon Research Conference on Glial Biology. March 11-16, 2007, Ventura, CA.

Astrocytic Ca^{2+} signaling *in vivo* following photo thrombosis. Life Science Week. April 15-20, UMC.

Fadel, P.
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Mueller, P.J., S.A. Friskey, C.M. Heesch and E.M. Hasser. RVLM single unit and lumbar sympathetic nerve responses to blood pressure manipulations following hindlimb unloading. FASEB Journal, 21: A468, 2007.

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Mueller, J.T. Potts, and E.M. Hasser. Expression of group I metabotropic glutamate receptors on phenotypically different cells within the nucleus of the solitary tract (NTS). FASEB Journal, 21: A464, 2007.

Huxley, V.
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Hwang, T.C.
G551D, a mutation in the signature sequence of CFTR, abolishes ATP-dependent increase of the opening rate. Biophysical meeting, Baltimore.

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Hyder, S.
Hormonal regulation of angiogenic growth factors in breast cancer. 9th World Congress in Oncology, Crete, Greece (Oct 2006).

Carroll, C. E, Benakanakere, I., Ellerseick, M and Hyder, S. M. (2007) Curcumin inhibits progestin-induced vascular endothelial growth factor secretion in human breast cancer cells. AACR Annual Meeting, Abstract # 3337.

Speaker 14th Cardiovascular Day, University of Missouri, Feb 2007. Title: Sex-steroid regulation of VEGF in breast cancer: identification of novel molecular targets for anti-angiogenic therapy. Session: Integrins, Angiogenesis and Permeability.

Inhibition of MPA-Dependent VEGF Secretion from Human Breast Cancer Cells: A Spicy Approach. Presented by Ms. Candace Carroll at the Vet Med Seminar Series. Feb 2007.

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Carroll, C., Benakanakere, I. and Hyder, S. M. (2007). Curcumin: A Potential Chemo preventive Agent for Progestin-dependent Breast Tumors. Annual Endocrine Society Meeting, Toronto, Canada.

Carroll, C. E, Benakanakere, I., Ellerseick, M and Hyder, S. M. (2007) Curcumin inhibits progestin-induced vascular endothelial growth factor secretion in human breast cancer cells. Midwest Regional Molecular Endocrinology Conference, Bloomington, Indiana. Oral Presentation.

Benakanakere, I. and Hyder, S. M. (2007) Natural and synthetic progestins accelerate 7, 12-Dimethylbenz[a] anthracine (DMBA)-initiated mammary tumors and increase angiogenesis in Sprague-Dawley rats. Midwest Regional Molecular Endocrinology Conference, Bloomington, Indiana. Oral Presentation.

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Yusof M, K Kamada, FS Gaskin, RJ Korthuis. Angiotensin II promotes postischemic leukocyte/endothelial interactions in murine small intestine: role of chymase and ACE, AT1 and AT2 receptors, CGRP, and NADPH oxidase. FASEB J 21:A1236, 2007.

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Signaling mechanisms in ethanol-induced cardio protection, Truman State University, Kirksville, MO, September 2006.

Kvochina, L.
Pregnancy increases barareflex independent gabaergic inhibition of the rvlm in rats.
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Martinez-Lemus, Luis A.
Research Forum; Hypertension: Clinical Manifestations and Vascular Adaptations, College of Veterinary Medicine -University of Missouri-Columbia, Monday, February 19, 2007.

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"Matrix-Integrin interactions analyzed using Atomic Force Microscopy: Toward understanding mechanotransduction" at NAVBO sponsored meeting titled Vascular Matrix Biology and Bioengineering, Whistler Village, British Columbia, Canada March 2007.

"Assessment of cell mechanical function, properties and structural characteristics using Atomic Force Microscopy" to the Division of Nephrology, School of Medicine, University of Missouri-Columbia, 2007.

"Mechanical characteristics of extra cellular matrix integrin interactions in vascular smooth muscle studied using atomic force microscopy" to the College of Veterinary Medicine, University of Missouri, January 25, 2007.

"Extracellular matrix integrin interactions in the regulation of vascular function" to the Department of Physiology, School of Medicine, University of Toronto, February 2007.

Mueller, P.
"Physical Activity Dependent Plasticity in Neural Control of the Circulation: The Anti-Hypertensive Brain?", Wayne State University, 07/11/06.

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Polo-Parada, L.
The Role of the Extracellular Matrix in the Development of the Electrical Activity of the Heart. Cardiovascular Day. Feb-26.

Changes in Fibronectin and Laminin expression during chick heart development. Cardiovascular Day. Feb-263.
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Potts, J.
Clark CG and Potts JT (2007) Electrophysiological characterization of neurokinin-1 receptor expressing nucleus tractus solitarii neurons. Brain Awareness Week, Life Science Center, University of Missouri.

Gummadavalli, P, Kline, DD, Nair, S and Potts, JT (2007) Computational model of nucleus tractus solitarii (NTS) sensory circuits transmitting arterial baroreceptor signals. Brain Awareness Week, Life Science Center, University of Missouri.

Clark CG and Potts JT (2007) Electrophysiological characterization of neurokinin-1 receptor expressing nucleus tractus solitarii neurons. Cardiovascular Day, Dalton Cardiovascular Research Center, University of Missouri.

McGovern D and Potts JT (2007) Synaptic connectivity of barosensitive nucleus tractus solitarii (NTS) circuit neurons: A pseudo rabies virus study *FASEB J.* 21(5), abstract # 582.8.

Gummadavalli, P, Kline, DD, Nair, S and Potts, JT (2007) Computational model of nucleus tractus solitarii (NTS) sensory circuits transmitting arterial baroreceptor signals *FASEB J.* 21(5), abstract # 582.10.

Clark, CG, McGovern D, Fong AY and Potts JT (2007) Nucleus tractus solitarii (NTS) expression of GAD67 and neurokinin receptors (NK1-R) in transgenic GAD67-eGFP mice *FASEB J.* 21(5), abstract # 582.7.

Potts JT, Sun, Z, Pamidimukkala, J, Clark, C, and Meininger GA (2007) Atomic force microscopy (AFM) to characterize nicotinic receptor function on medullary respiratory neurons *FASEB J.* 21(5), abstract # 610.6.

2007 Experimental Biology, Washington, DC, New frontiers in functional imaging of autonomic circuits (Session Chair).

2007 ISAN 2007 Satellite Symposium, Central Control Mechanisms of the Circulation: New Insights and Strategies to Study Brain Function, Wakayama City, Japan (SPEAKER).

Segal, S.
Signaling Along Endothelium: Integration with smooth muscle relaxation. DCRC symposium on “Cellular Communication within the Vascular Wall, MU-Columbia (Acuff Aud.), 12/03/07.

Pamidimukkala, J.
Sex differences In the development of Cardiovascular Disease and the therapeutic implications, Nevada College of Osteopathic Medicine, Henderson, NV, September 29th, 2006.

Polo-Parada, L.
The Role of the extra cellular Matrix in the Development of the Electrical Activity of the Heart. Weinstein Cardiovascular Development Conference, May 10-12.

The Role of the Sodium Calcium Exchanger (NCX1) on the Electrical Activity of the Heart. Weinstein Cardiovascular Development Conference, May 10-12.

Changes in Fibronectin and Laminin Expression during Chick Heart Development. Weinstein Cardiovascular Development Conference, May 10-12.

Electrophysiological Characterization of Chicken Outflow Tract (OFT).Weinstein Cardiovascular Development Conference, May 10-12.

Price, E.
Development of Blood-Derived Adult Stem Cell Lines with Neurogenic Potential, Marshall University, 11/2/06.

Schadt, J.
War Related Injury and Illness Study Center, VA Medical Center, East Orange, New Jersey, The neurohumoral and hemodynamic response to blood loss: What's important and what's not? April 11, 2006. (Invited).

Departments of Pediatrics and Physiology, New York Medical College, Valhalla, New York, Neurohumoral, hemodynamic, and respiratory changes during hemorrhage: Changing priorities, April 10, 2006. (Invited).

Segal, S.
MU Cardiovascular Day seminar entitled: Endothelium-dependent Signaling Pathways Underlying Conducted Vasodilation. (MU-Columbia Alumni Center; 2/26/07).

Electrical Connectivity in Vascular Tissue, MU School of Veterinary Medicine, 12/11/06.

DCRC Special Symposium on Cell-Cell communication in the Vascular Wall (M. Hill). Presentation entitled: Signaling along Endothelium: Integration with Smooth Muscle Relaxation. (MU-Columbia, Acuff Auditorium; 3/12/07).

Zou, X.
Predicting protein-small molecule interactions for rational drug design. Department of Physics, University of Missouri-Columbia, Aug. 23.

Simultaneous docking and virtual screening against multiple targets: Application to protein kinase inhibitors. American Chemical Society National Meeting, Chicago, symposium talk, March 28, 2007.

An iterative knowledge-based scoring function to predict protein-ligand interactions. American Chemical Society National Meeting, Chicago, symposium talk, March 29, 2007.

Protein-ligand interactions and structure-based drug design, Department of Biochemistry, Univ. of Missouri-Columbia, Nov., 2006.

INVITED SEMINAR SPEAKERS

Jan. 29
"Microfabricated Biosensor Systems and Nanotechnology Research" Dr. Shubhra Gangopadhyay, Dept of Electrical and Computer Engineering, University of Missouri Dalton Cardiovascular Research Center Library

Feb. 26
"Cardiovascular Day at Reynolds Alumni Center"
Invited Speakers:
Dr. David Cheresh, University of CA-San Diego
Dr. Joseph Braydon, University of Vermont
Dr. Charlie Little, University of Kansas Medical Center
Plus University of Missouri Researchers

March 12
"Cellular Communications within the Vascular Wall"
Invited Speakers:
Dr. Chris Garland, Department of Pharmacy & Pharmacology
University of Bath, UK
Dr. Kim Dora, Department of Pharmacy & Pharmacology
University of Bath, UK
Dr. Steven Segal, Department of Medical Pharmacology & Physiology University of Missouri

April 23
Mini Symposium, Acuff Auditorium
"New Models of Human Breast Cancer. Role of Women's Hormones in Metastasis
Dr. Kate Horwitz, Department of Medicine
University of Colorado Health Sciences Center
Sinclair School of Nursing Auditorium S261

June 25
"Orthostatic Intolerance"
Dr. Julian Stewart, Professor of Pediatrics and Physiology and Director of The Center for Hypotension
New York Medical College

June 27
"Integrated computational and experimental approaches to quantify cell Matrix interactions"
Dr. Muhammad Zaman, Professor of Biomedical Engineering,
University of Texas at Austin

Blaine, Edward
Fetal Programming
Research Board
$30,800
09/05-09/07

Bompadre, Silvia
Physiology and pharmacology of G551D mutant CFTR
$88,531
Cystic Fibrosis Foundation
4/07-03/08

Clarke, Lane
Subcontract: Development of Tagged DF508 CFTR mutant mouse model
$38,421
Cystic Fibrosis Foundation Therapeutics
12/07-11/08

CFTR and Intestinal Acid-Base Transporters
$800,000
National Institute of Diabetes and Digestive Kidney Diseases
08/06-07/10

Structure-Guided Physiological Screening of Delta F508 CFTR Correctors
$1,349,781
Cystic Fibrosis Foundation Therapeutics
12/06–11/09

Ding, Shingua
American Heart Association-Delaware-Pennsylvania affiliate
$25,000 Beginning Grant-in-aid
01/07-06/07

Gu, Li-Qun
Single Molecule Study of Oligonucleotide-Protein Interaction and Folding in a Nanopore
$526,350
National Science Foundation Career Award
07/06-06/11

Heesch, Cheryl
Differential neurotransmitter modalities of CNS presympathetic neurons
$29,500
University of Missouri Research Board Grant
03/07–03/08

$142,227 direct costs
NIH, Neural Circulatory Control: Pregnancy & Ovarian Hormones (P.I.)
3/01/07 – 2/29/08.

Hwang, Tzyh-Chang
Gating of CFTR CL Channels by ATP Hydrolysis
$339,827
NIH R01HL53445
08/06 – 07/10

Structure-guided physiological screening of F508 CFTR correctors
$482,764
Cystic Fibrosis Foundation Therapeutics
12/01-11/07

Confocal equipment for biomedical and nanomedicine research
$402,030
NIH, S10
07/06-07/07

Molecular pathophysiology of cystic fibrosis
$640,000
NIH, National Institute of Diabetes and Digestive and Kidney Diseases
01/03-01/07

Gating of CFTR chloride channels by ATP hydrolysis
$933,056
NIH, National Heart, Lung, and Blood
01/06/01/10

Structure-guided physiological screening of □F508 CFTR corrector
$482,764
Cystic Fibrosis Foundation Therapeutics
07/06-07/07

Hyder, Salman
Development and characterization of a novel progestin-dependent human breast cancer model
$300,000
DOD Breast Cancer Program
01/08-12/10

Hyder, S. M. (mentor) Candace Carroll (Graduate Student, PI)
$750
Inhibition of progestin-induced VEGF secretion from human breast cancer cells by Cur cumin
10/06-09/07
Pi Chapter of Phi Zeta, MU

Therapeutic Potential of 2-Methoxyestradiol and Cur cumin for the Prevention and Treatment of Progestin-Accelerated Breast Cancers
$18,000
01/07-12/07
College of Veterinary Medicine, University of Missouri-Columbia

Korthius, Ronald
Ethanol prevents micro vascular dysfunction
$1,653,750
NIH
06/06-06/11

Anti-inflammatory mechanisms of ethanol preconditioning in Ischemia/reperfusion
$970,200 NIH
07/02-06/07

Venular leukocyte adhesion, impaired arteriolar vasoreactivity, and intestinal I/R
$1,490,000
NIH
12/06-11/10

Martinez-Lemus, L.
$53,000
A Confocal/ Multiphoton Microscopy System
01/07-01/08
University of Missouri-Columbia PRIME fund

Remodeling of the Resistance Vasculature: Early Mechanisms
$260,000
American Heart Association National Grant
07/05-07/06

A Confocal/ Multiphoton Microscopy System
$53,000
University of Missouri-Columbia PRIME fund
01/07-01/08

Meininger, Gerald
R21 combined FRET-Based Measurement of Membrane Potential
$395,723
NIH-National Heart, Lung and Blood
01/08-11/10

Meininger, Gerald (PI) with Sherman Fan (Co-PI) R21
Atomic force-FRET microscopy using quantum dots for cell mechanobiology
$375,000
NIH-National Institute of Biomedical Imaging and Bioengineering
09/07-08/10

Meininger, Gerald (Co-I) with James Lee (PI)
Effects of amyloid-b peptide on adhesion mechanics of cerebralendothelium
$90,090
Alzheimer's Association Research Grant
09/06-08/08

Potts, Jeff
Cardiovascular Regulation in Hind limb Unweighted Rats
$1,250,000
(Hasser) Co-I
01/07-01/12
NIH–R01

Price, Elmer M.
Adult Stem Cell Transplantation as a Therapy for Spinal Cord Injury
$ 50,000
Missouri Spinal Cord Injury Research Program
09/06-08/07

Price, Elmer M.
Peripheral Blood-Derived Multipotent Adult Stem Cells
$45,000
University of Missouri Research Board
09/06-08/07

Soma, Yoshiro
Mechanism of NBD gating engine in ABC transporters
$30,000
Japan Society for the Promotion of Science
04/07-03/10

Liang, Yayun
(Co-Investigator)
Development and Characterization of a progesterone-dependenthuman breast cancer mode
$300,000 01/08-01/09
Dept. of Defense

Zou, Xiaoqin
Molecular mechanisms and rational design of CFTR potentiators
$43,200
Cystic Fibrosis Foundation
07/07-06/08

Predicting Protein-Protein Interactions
$32,600
Research Board Grant
07/07-06/09

Structure-Guided Physiological Screening of ΔF508 CFTR Processing Correctors
$1,349, 781
Co-I, 10% effort (PI: Lane Clarke)
12/06-11/09
Cystic Fibrosis Foundation, Inc.

PROFESSIONAL SERVICE ACTIVITIES

Blaine, E.
- Development
- Gilead collaboration
- Dalton Advisory Committee
- Campus Planning Committee
- Graduate Education Committee
- Campus Grievance Committee chairman
- University of Missouri Research Board; grant review and awards
- Reviewer, various journals
- External tenure review (Tahir Hussain, University of Houston)

Bompadre, S.
- Reviewer for the Cystic Fibrosis Foundation
- Reviewer for the Journal of General Physiology

Bowles, D.
- Member, NIH Special Emphasis Panel/Scientific Review ZRG1 MDCN-G
- Reviewer; Microcirculation, Am. J. Physiol. Heart, J. Appl. Physiol.

Clarke, L.
- Reviewer, Regional Develop Program Review Committee, Cystic Fibrosis Foundation, May 15, 2007
- Moderator, Topic Forum: Duodenal BicarbonateTransport, Am. Gastroenterological Assoc., May 20, 2007
- Moderator, Liver Disease in Cystic Fibrosis, Williamsburg Cystic Fibrosis Conference, June 2, 2007
- Organizer and moderator, Workshop: Model Systems, North American Cystic Fibrosis Conference, Denver, CO Nov. 3, 2006
- Grant Reviewer
- Cystic Fibrosis Foundation Research and Research Training Committee, Bethesda, MD Dec 6-7, 2006
- Abstract Reviewer – Intestinal Disorders section, Am. Gastroenterological Assoc., Dec. 29, 2006

Davis, M.
- Appointed to editorial board of Am J Physiology: Heart & Circulatory Physiology

Fadel, P.
- Reviewed for Journal of Applied Physiology; Experimental Physiology; and Experimental Biology and Medicine
- Reviewed grant for Alberta Heritage Foundation for Medical Research

Gu, Li-Qun
- MU Committee of Undergraduate Education
- Serving on the committee entitled “MU Partnership” in Dean's Engineering Advisory Council (DEAC) Meeting

PROFESSIONAL SERVICE ACTIVITIES

Heesch, Cheryl
- Chair, Research Committee; American Heart Association, Heartland Affiliate
- Reviewer, Research Board Grants, University of Missouri
- Manuscript reviews July – September: *Amer J Physiol. Reg. & Integrative* - 2 manuscripts; *Brain Research* - 1 manuscript
- Grant reviews April 1- June 31, 2007: May '07, Univ. of MO Research Board Grants – 2 reviews
- University of Missouri, Interdisciplinary Neuroscience Program, Executive Committee
- University of Missouri, Dept. Biomed. Sci., Chair Promotion & Tenure Committee

Hill, Michael
- Reviewer: Amer. J. Physiol.; J. Vasc. Res.; Clin. Exp. Physiol. Pharmacol.
- Organized imaging mini-symposium at the University of Missouri-Columbia

Huxley, V.
- Rippel Foundation grant reviewer; U Missouri Research Board Member & reviewer
- Associate Editor, Am J Physiol Heart & Circ (continues); Editorial Board J Vasc. Res (continues)
- AHA Missouri Affiliate awards panelist

Hwang, Tzyh-Chang
- Editorial Board, Biophysical Journal
- AHA Study Section

Hyder, S.
- Ad hoc Manuscript Reviewer: J Endocrinology
- Ad hoc Manuscript Reviewer: Cancer Research
- Ad hoc Manuscript Reviewer: Molecular Endocrinology
- Grant Review: Invited Reviewer Philip Morris External Research Program
- Teaching: ECE 8001 Bioelectrics in Electrical Engineering; I hour lecture on "Steroid Hormones, Angiogenesis and Breast Cancer: is this really an unusual topic for electrical engineers? (April 2007
- Reviewer – *European J Cancer*
- Reviewer – *Endocrinology*
- Grant Reviewer: American Medical Association
- Grant Reviewer: Univ. of Missouri-Columbia Committee College Vet. Med. Research Funding (COR)
- Co-Chair, 9th World Congress in Oncology, Crete, Greece (2006)

Kline, D.
- Reviewer, J Neurophysiol
- Co-Chair. Neural Plasticity of the hypoxic reflex: carotid bodies, NTS and pons
- Reviewer: J Physiology (London), J Neurophysiology, J Applied Physiology
- Instructor: Bio8187; Neurobiology Journal Club

PROFESSIONAL SERVICE ACTIVITIES

Korthius, R.

- American Physiological Society, Joint Programming Committee
- Editorial Board: American Journal of Physiology: Heart and Circulatory Physiology
- Editorial Board: Microcirculation
- American Heart Association, National Center: Peer Review Steering Committee
- American Physiological Society, Finance Committee
- American Physiological Society, Cardiovascular Section Steering Committee
- National Institutes of Health, Pathophysiology of the Organ Systems Study Section
- National Center for Complementary and Alternative Medicine, NIH, Basic Science Study Section
- American Institute of Biological Science, Cardiovascular Study Section
- Editorial Board, Pathophysiology
- Liason Committee, Microcirculatory Society
- Peer Review Steering Committee, American Heart Assocation, National Center
- Grant Peer Review Team, Welcome Trust, Great Britain
- Manuscript reviewer for Journal of Vascular Research, Cardiovascular Research, Critical Care Medicine, Pathophysiology, American Journal of Physiology, Microcirculation

Martinez-Lemus, L.

- Associate Editor for the Physiology and Reproduction section of Poultry Science
- Reviewer for the Journal of Vascular Research
- Member, Committee for appointment and Promotion of Non-Tenure Research Track Faculty. Dalton Cardiovascular Research Center, University of Missouri-Columbia
- American Heart Association – National. Member, Vascular Biology and Blood Pressure / Regulation, April 18, 2007
- Appointed to serve on the Program Committee for the Microcirculatory Society on 6/11/07

Meininger, G.

- Chair of Cardiovascular Section American Physiological Society
- US Co-Editor for Journal of Vascular Research
- Associate Editor for American Journal of Physiology: Heart and Circulatory Physiology
- Chair, Vascular Wall Biology 2 Review Committee, American Heart Association - National, 2006-2008
- Appointed Member, National Committee to the International Union of Physiological Sciences, 2006
- Appointed Liaison Committee: Member, 2006-2009, Microcirculatory Society
- Completed University of Missouri Leadership Development Program, Sept. 2006
- Member of Section Advisory Committee, American Physiological Society
- Member of Nominating Committee, American Physiological Society

Milanick, M.

- American Heart Association Study Section

- NIH T90/R90 Directors and RoadMap Meeting

Mueller, P.

- APS Research Career Enhancement Award
- Host Laboratory: Patrice Guyenet, Ph.D., University of Virginia
- Faculty Grant Writing Institute
- Office of Research, University of Missouri-Columbia Reviewer
- Journal of Applied Physiology Hypertension

Price, E.

- Course Director, Veterinary Cellular Biology (VBMS 5506), 37 lectures/contact hours during this timeframe

Polo-Parada, L.

- Moderator and co-chair session entitled "Cardiac Conduction System Development," Weinstein Cardiovascular Development Conference

Schadt, J.

- Dalton Science Teacher's Symposium
- Ad hoc, Am. J. Physiol. Reg – Two manuscripts reviewed
- Editorial Board, *Am. J. Physiol. Heart* – One manuscript reviewed
- Ad hoc, *Brain Research* – One manuscript reviewed
- College of Veterinary Medicine, University of Missouri, Committee on Research, Grant Review, 2 grants, December 2006

Segal, S.

- Associate Editor for *Microcirculation*
- Reviewer for: *Am. J. Physiol. Heart Circ. Physiol.* and for *J. Physiol.*
- Planning Committee Member, Specialty Meeting of the American Physiological Society: "Integrative Biology of Exercise" (to be held 09/08)
- Manuscript referee: American Journal of Physiology (3), Journal of Physiology (1), Microcirculation (5)
- Chairman, Nominations Committee of the Microcirculatory Society, Inc.
- Chairman, Awards Committee of the Cardiovascular Section of the American Physiological Society
- Ad-hoc member of Special Emphasis Panel for NIH Study Section: Hypertension and Microcirculation

Soma, Y.

- Member, Editorial/Publicity Committee, Physiological Society of Japan

Zou, X.

- Editorial Advisory Board Member for Current Computer-Aided Drug Design
- Reviewed manuscript for Proteins: Structure, Function, and Bioinformatics
- Judge for MU Undergraduate Research & Creative Achievements Forum
- Peer review for *Journal of Medicinal Chemistry*
- Peer review for Journal of Chemical Information and Modeling
- Peer Review for Indian Journal of Medical Research
- Thesis Committee for Dr. Zhaofeng Ding, Biochemistry PhD student
- Graduate Committee for Ms. Xiaohui Wang, MPP PhD student

Explanation of Figures

Top
Xioquin Zou
Comparison between the observed and predicted orientations of the ligand that bind to the protein. The ligand orientations are displayed in the stick representation. The surface of the protein is colored by atom type (red: oxygen; blue: nitrogen; grey: carbon). The ligand orientation identified by the X-ray study is colored by atom type. The predicted ligand orientation is colored in magenta. (Figure prepared by Sheng-You Huang and Xiaoqin Zou)

Middle
Xioquin Zou
Comparison of the crystal structures and computationally predicted structures for a flexible loop in a protein-ligand complex, in order to account for induced-fit (i.e., protein flexibility) in ligand binding. The bound protein (catalytic subunit of cAMP-dependent protein kinase) is colored in cyan, and the ligand (adenosine) is colored by atom type. The free protein structure is superimposed and colored in gold. The proteins are represented in ribbon diagram, and the ligand is represented in stick diagram. The large loop movement upon ligand binding is highlighted in the box. (Figure prepared by Sheng-You Huang and Xiaoqin Zou)

Bottom
Luis Polo-Parada
Imunnostaining of Fibronectin in a chick embryo Stage 20. The picture shows high levels of Fibronectin distribution mainly in the spinal cord and in the different regions of the heart.