The Cardiovascular Center (CVC) at the Medical College of Wisconsin continues to play a vital role in the discovery of causes, novel diagnostic approaches, development of new treatments and cures, and the ways to prevent many cardiovascular diseases that continue to represent the leading causes of death in the US. The laboratories of more than 20 investigators reside within the CVC, and more than 100 clinicians and 50 basic scientists from various departments, carrying out cardiovascular related research, are affiliated with the Center and draw upon the core resources that it provides.

The CVC is flourishing and serving as it is intended as a vital campus incubator to stimulate the exchange of new ideas and nurture the development of research that will benefit those who are afflicted with cardiovascular diseases. The scientific seminar program is impressive and is taking full advantage of our newly created Conference Center within the CVC. In addition to speakers from within our own research programs, we have hosted many internationally recognized cardiovascular scientists over the past year (see Website).

Excellent progress continues to be made in coalescing scientific Affinity Groups among the members and affiliate members of the CVC, thereby fostering interdisciplinary collaborations in research areas of special interest that have emerged. These groups of scientists and brief descriptions of their research are represented in the following sections of this Annual Report.

Given the presence of a strong and well-funded group of basic scientists studying underlying mechanisms of cardiovascular function in normal and pathological states, it has been the major goal of the CVC to now recruit more clinically trained investigators who can collaborate and interact with the basic scientists in efforts to move new bench discoveries to the bedside and to the broader community served by our medical center. The recruitment of Dr. Roy Silverstein as the Chairman of the Department of Medicine at MCW is enabling this to happen. I have been working closely with him, and with a search committee appointed by Dean Joseph Kerschner, to bring a leading clinical scientist to our institution that could then lead and direct these translational research efforts. It is my hope that this search can be completed within the next fiscal year, after which I can give my full attention once again to my responsibilities as the Chairman of the Department of Physiology at MCW.

Despite the severe tightening of NIH research dollars to support cardiovascular research during 2012, funding of CVC associated investigators at MCW increased from $30.9 million in 2010 to $31.2 million in 2011. This is in the face of an overall decrease in the amount awarded by the National Heart Lung and Blood Institution (NHLBI) of the NIH from $467.5 million in 2010 to $445 million in 2011. It is also occurring at a time when success rates for funded NHLBI grant applications have fallen to 17.4% in 2011, down from 19.9% in 2010.

I am confident that cardiovascular research will continue to grow and flourish at MCW as we continue to develop strong interdisciplinary research and promote comparable excellence in our efforts to translate this knowledge into clinical and community settings.
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Administration and Core Support

CVC Administrative staff: Front row (left to right): Jane Brennan Nelson, Business Manager, Allen W. Cowley, Jr., PhD, Director, Diane Munzenmaier, PhD, Assistant Director; Back row (left to right): April Mays, Admin Asst, Tina Pearson, and Joanna McCormick

Machine and Electronics Core: Mike Kloehn and Dave Eick

CVC IT Core staff: Pedro Mendez, Andy Milbrath, and Greg McQuestion

CVC Microscopy Core: Glenn Slocum
Congenital Heart Disease

Summary of Affinity Group Progress

Congenital Heart Disease (CHD) is one of the leading causes of mortality in infants, however, the etiology of CHD in the majority of cases remains largely unknown. Children’s Hospital of Wisconsin Institutional Review Board has approved a repository of blood and surgical discards from subjects with congenital heart disease. This CHD tissue bank represents a unique opportunity to investigate molecular pathways and deficits in congenital heart disease. The goal of this endeavor is that researchers will be able to utilize this repository as a resource to uncover causal genetic, genomic, and molecular changes and improve the overall understanding of causes of congenital heart malformations.

One area of study for the CHD Tissue Bank goals is to assess genetic risk factors of CHD (i.e. sequence variants, single nucleotide polymorphisms SNPs, copy number variations), including inherited as well as somatic events. Our long-term goal is early detection of fetal and neonatal genetic abnormalities associated with CHD. An increasing number of medical conditions can be successfully managed during the neonatal period if an early diagnosis is made. With its partner hospitals, Children’s Hospital of Wisconsin and Froedtert Hospital, the Medical College of Wisconsin is among a handful of centers in the world that are uniquely positioned to deliver the care and aggressively treat conditions diagnosed at the prenatal stage effectively.

Key Group Members

- Aoy Tomita Mitchell, PhD, Cardiothoracic Surgery
- Michael Mitchell, MD, Cardiothoracic Surgery

Research Goals

To use genetic and genomic information coupled with clinical data to better understand the etiology of Congenital Heart Disease (CHD) and to develop reliable early detection strategies.

Representative Grants

- MCW Research Affairs: Mitchell “Developing a non-invasive method to monitor cardiac transplant rejection”
- NIH RO1: Mitchell “Systems Modeling of Highly Penetrant Genetic Alterations in Cardiogenesis” (pending)

A second area of study utilizing the CHD Tissue Bank is to assess the molecular changes in particular tissue and cell-types from CHD patients, including expression analysis and epigenetic modifications (i.e. methylation patterns and posttranslational modifications). We are ultimately interested in both identifying predictors of clinical outcomes in CHD, and understanding mechanisms of healing and plasticity following surgical repair.
Summary of Affinity Group in Progress

The inverse correlation between the risk for developing coronary artery disease and plasma concentrations of high density lipoprotein (HDL) has been attributed to the athero-protective effects of HDL that include inhibition of oxidative damage and platelet aggregation, as well as promotion of endothelial function and vascular reactivity. HDL also plays a key role in promoting the disposal of peripheral cholesterol at the liver via a process termed reverse cholesterol transport. The anti-atherogenic benefits of raising HDL levels have become controversial. Recent large-scale clinical studies revealed that patients who had normal levels of HDL-cholesterol still suffered cardiovascular events. Moreover, use of a drug that nearly doubled HDL levels in a phase III human clinical trial came to an abrupt end due to high patient mortality. For these reasons, there is now a greater emphasis on measuring “HDL function” as a better predictor of cardiovascular disease than low levels of HDL-cholesterol.

Over the past year and a half, our group has been developing novel in vitro assays of HDL function that have the potential to revolutionize the way physicians diagnose and treat patients with cardiovascular risk. Recent studies suggest that the oxidation status of HDL plays an important role in determining how this lipoprotein prevents or promotes atherosclerosis. As such, we hypothesize that oxidation impairs HDL

Key Group Members

Daisy Sahoo, PhD, Medicine and Endocrinology/Pharm & Tox
Kirkwood Pritchard, PhD, Surgery/Pharmacology & Toxicology
Hao Zhang, PhD, Pediatric Surgery
Hao Xu, PhD, Pediatric Surgery

Research Goals

There is a growing body of research that suggests that “HDL function” is a better indicator of cardiovascular risk than HDL-cholesterol levels. As such, the immediate goal of our two-lab group is to understand the factors that can alter HDL function during atherosclerosis and its related complications. Further, we wish to develop a clinical assay that can assess “HDL function” in a timely and cost-effective manner.

Representative Grants

NIH RO1: Pritchard/Sahoo “Biophysics of HDL Dysfunction” (pending 6th percentile)
NIH RO1: Pritchard/Sahoo “Biolayer Interferometry and In Vitro Measures of HDL Biophysics” (pending 12th percentile)
function by altering its ability to bind biomolecules that are involved in inflammation and HDL-dependent cholesterol metabolism, thus making it atherogenic and unable to efficiently participate in reverse cholesterol transport. Using Octet Red, a new biolayer interferometry (BLI) machine that employs a label-free technique for measuring biomolecular protein-protein interactions, we can now measure the rates at which functional and non-functional (i.e. oxidized) HDL bind key proteins that are critical for cholesterol removal from the body. BLI analyzes the interference pattern of light reflected from two surfaces. The first surface is the layer of immobilized protein that serves as an internal reference. As the number of biomolecules binding to the biosensor increases, the aqueous protein layer increases, causing a shift in interference that can be measured in real-time. The Octet Red requires extremely small sample sizes and is highly reproducible. This instrument can also measure protein concentration (via determining rates of antigen-antibody binding) in 96 samples at once, in less than 20 min and at a cost of ~30¢/sample. As such, HDL binding affinity for different proteins at the same time can be determined quickly and in real time.

Over the past year we have collected preliminary in vitro data that demonstrates that oxidized HDL directly impacts its ability to bind proteins associated with inflammation and cholesterol transfer as compared to HDL that was not oxidized. More importantly, we now have in vivo data showing that HDL isolated from hypercholesterolemic mice display increased binding affinities for pro-oxidant enzymes compared to HDL isolated from healthy mice. Moreover, HDL from humans with documented cardiovascular disease also binds pro-oxidant enzymes with a higher affinity than HDL from healthy patients. These exciting data provide strong support for the concept that BLI assays are able to distinguish between control HDL and HDL isolated from both rodents and humans with established atherosclerosis.

The current objectives of the Atherosclerosis Affinity Group are to use cell culture assays and BLI methodologies to: (1) determine how oxidized lipids and atherogenic proteins alter the overall rate of HDL interactions with biomolecules that mediate cholesterol metabolism and (2) develop and validate a new family of in vitro BLI assays that quantify differences in HDL binding affinity with biomolecules that mediate HDL-dependent cholesterol metabolism. We envision that these BLI assays will be used to analyze samples from healthy patients, as well as those with clinically-documented atherosclerosis, to determine if and the extent to which atherosclerosis impairs HDL interactions with biomolecules that mediate HDL metabolism. Successful completion of the above studies will lay the foundation for the development of new clinical assays for determining HDL “function” and identifying patients who are at increased risk of heart disease. In a separate project, we are studying the role of oxidatively modified extracellular matrix in the pathogenesis of atherosclerosis.

These studies investigate the mechanisms by which 4-hydroxynonenal (4-HNE) modification of fibronectin, an integral matrix protein, accelerates atherosclerosis, including its ability to increase lipid deposition, monocyte/macrophage adhesion and recruitment and to induce endothelial dysfunction.
Summary of Affinity Group Progress

This affinity group is a large and extremely productive one comprised of researchers involved in various collaborations to study both the etiology and the effects of chronic salt-sensitive hypertension. These successful collaborations have resulted in, and are supported by, several programmatic initiatives and a number of individual research grants.

An NIH Program Project Grant (PPG; Drs. Allen Cowley, Howard Jacob, Carol Moreno-Quinn, Mingyu Liang, Andrew Greene) utilizes genetically engineered rats that mimic many of the specific traits found in human salt-sensitive forms of hypertension to reveal the complex regulation and interplay of genes responsible for these traits. The uniqueness and strength of this program is that it is designed to explore the integrated genomic, cellular, tissue, organ and whole animal components of hypertension. This multi-scale approach brings together an interdisciplinary team of experts in genomics/genetics, proteomics, bioinformatics/computational biology and cell/organ/whole animal physiology required to study this complex disease at levels that no one has yet attempted.

A second NIH Program Project Grant (PPG; Drs. Cowley, L.ing, and David Mattson) is focused upon the role of the kidney in salt-sensitive hypertension. Experimental studies using salt-sensitive rat models examine mechanisms responsible for the production of reactive oxygen species in the outer medulla of the kidney which is known to occur in humans and animals that exhibit hypertension with high salt diets.

Key Group Members

Allen W. Cowley, Jr., PhD, Physiology
William Campbell, PhD, Pharmacology
Andrew S. Greene, PhD, Physiology
John Imig, PhD, Pharmacology
Julian Lombard, PhD, Physiology
Mingyu Liang, PhD, Physiology
David Mattson, PhD, Physiology
Carol Moreno-Quinn, MD, PhD, Physiology
Alexander Starushchenko, PhD, Physiology

Research Goals

Essential hypertension affects more than 50 million Americans and increased blood pressure salt-sensitivity is a prominent feature in certain populations of hypertensive patients, especially hypertensive African Americans who also exhibit significantly higher risk of end organ renal damage. Although it is evident that the common forms of hypertension are multifactorial (polygenic and environmental), little significant progress has been made in identifying the specific genetic basis of human hypertension and the biological pathways that are altered by the various combinations of genes that determine one’s blood pressure.

Representative Grants

NIH PO1: Cowley “Genetic and physiological basis of salt-sensitive hypertension”
NIH RO1: Lombard “Microvessel O2 responses in salt-sensitive hypertension”
NIH RO1: Imig “Exopxyeicosanoids and renal vascular function in obesity and hypertension”
Another project is directed toward the study of the inflammatory processes that develop within the kidney as initiated by infiltrating lymphocytes. A third project studies a novel mechanism and hypothesis based on evidence in this program that a genetic defect in the cellular pathways of metabolism play an important causal role in impaired pressure-natriuresis, sodium retention and the development of hypertension.

Other NIH grants support related research of Drs. Julian Lombard and A. Greene examining molecular mechanisms responsible for reduced vasodilatory capacity of blood vessels and for the reduced angio-
nesis capacity observed in salt-sensitive hypertension. Closely related research by Dr. Alexander Starushchenko is funded by the NIH to study the role of endothelial growth factor (EGF) upon sodium channels in the renal distal tubules upon salt-sensitive hypertension. These novel studies study the regulation of these important sodium channels by the small G protein Rac1 and signaling mechanisms which appear to serve as a coupling factor transducing EGF regulation to ENaC. In yet other novel studies, Dr. Mattson has found blood leukocytes to be important in salt sensitive hypertension whereby immune cell infiltration into the kidney provides an important functional link between kidney disease and hypertension.

Yet another important area of research related to hypertension is being explored by Drs. William Campbell and John Imig. These studies focus upon elucidation of mechanisms whereby epoxyeicosatrienoic acids (EETs) and the epoxide hydrolase enzyme influence renal and cerebral vascular function in hypertension. Newly developed highly selective epoxide hydrolase inhibitors are being assessed to determine their ability to lower arterial blood pressure and improve renal vascular function and decrease stroke induced brain damage in hypertension.
Summary of Affinity Group Progress

This affinity group seeks to stimulate interactions between investigators around the common theme of understanding the machinery that regulates how the heart muscle responds to and protects itself from patho-physiologic stimuli. Included in this are the signaling mechanisms that regulate contraction, relaxation, remodeling of cellular and extracellular components, inflammation and mechanisms that instruct cells to form myocytes and build a heart. The group’s goal is to advance our knowledge and therapies directed at limiting damage to heart muscle, delay the progression of heart failure and enable tissue regeneration.

Many of the group’s investigators are studying mechanisms of cardiac function and dysfunction. Dr. Goldspink’s lab focuses on the role of insulin-like growth factor-1 isoforms and their function in the heart. They are focused on a particular isoform of IGF-1, called Mechano-Growth Factor (MGF), which improves cardiac contractility and prevents hypertrophy following myocardial infarction and are currently investigating the underlying mechanisms utilizing peptide analogs. This work is also directed at determining the influence of these IGF-1 isoform peptides on resident cardiac stem/progenitor cells, with a view of using them to enhance cardiac repair, by developing a technology that combines a microscopic physical

Key Group Members

Paul H. Goldspink, PhD, Physiology
John Auchampach, PhD, Pharmacology & Toxicology
John Lough, PhD, Cell Biology, Neurobiology & Anatomy
Jennifer Strande, MD, PhD, Cardiovascular Medicine
Scott Levick, PhD, Pharmacology & Toxicology
Dorothee Weihrauch, DVM, PhD, Anesthesiology
Alfred Nicolosi, MD, Cardiothoracic Surgery
Joshua Meskin, MD, Cardiovascular Medicine
Michael Cinquegrani, MD, Cardiovascular Medicine
Claudius Mahr, DO, Cardiovascular Medicine
Aoy Mitchell, PhD, Cardiothoracic Surgery

Research Goals

To foster collaborative research centered around the theme of cardiac function and remodeling in disease and injury. To develop interdisciplinary approaches to improving cardiac function and repair with the goal of enhancing funding opportunities.

Representative Grants

NIH RO1: Goldspink “Cardiac regeneration through growth factor eluting microrod scaffolds”
NIH ROO: Levick “Neuro-immune modulation of cardiac mast cell-mediated of cardiac remodeling”
scaffold with the capacity to deliver peptide therapeutics.

Dr. Strande’s laboratory is directed at unraveling the molecular dysfunction involved in the pathogenesis of cardiomyopathies. Her group studies heart disease at varying levels of biological complexity including patients, animal models and individual heart cells to obtain insights into disease mechanisms. They are currently investigating the cellular and molecular mechanisms that cause cardiomyopathy in patients with muscular dystrophy by using induced pluripotent stem cells (iPSCs) which are stem cells engineered from patient skin cells. These iPSCs retain the genetic background, including the specific dystrophin mutation of each patient. Dystrophin-mutation containing iPSCs can be directed into cardiomyocytes to allow the investigation of abnormal events that are normally required to maintain cardiomyocyte health.

Dr. Weihrauch’s lab focuses on how changes in the extracellular matrix influence vascular and myocardial function and intracellular signaling pathways. This is achieved by isolating the extracellular matrix by decellularizing hearts from Tsk+/− mice (a model of murine scleroderma) and using the decellularized myocardium as substrate.

The Auchampach laboratory is focused on the study of adenosine receptors – proteins on the surface of cells that recognize the purine nucleoside adenosine and related compounds. Adenosine production is increased during ischemic heart disease, where it functions to promote survival and repair of damaged muscle. They are testing the hypothesis that the A3 receptor mediates some of the protective actions of adenosine during acute myocardial infarction to promote cellular survival and suppress inflammatory responses, whereas the A2B receptor participates in mediating overactive healing responses during the process of post-infarction remodeling and heart failure progression. Other research within this affinity group is focused on cardiac remodeling and regeneration.

Dr. Levick’s lab focuses of two related mechanisms leading to adverse myocardial remodeling and heart failure. The first is the role of sensory nerves in mediating adverse myocardial remodeling and heart failure. They have determined that the neuropeptide substance P is important in this process and are currently investigating the mechanisms involved, including direct effects on cardiomyocytes and fibroblasts, as well as the possibility that substance P regulates known regulators of myocardial remodeling such as endothelin-1 and angiotensin II. A second area of interest is the mechanisms by which inflammatory cells interact with cardiac fibroblasts to regulate myocardial remodeling. They have previously demonstrated that mast cells regulate fibrosis in the hypertensive heart and are dissecting the mechanisms driving these effects by examining the role of tryptase and interferon-γ.

Dr. Lough’s laboratory focuses on two separate goals, both of which may illuminate mechanisms by which the adult myocardium could be regenerated. The primary goal is to understand how pluripotent stem cells might be efficiently and reproducibly induced to become cardiac myocytes, for use in transplantations designed to repair injured or diseased heart tissue. The secondary goal is to follow-up indications that Tip60, an intriguing protein that remodels gene domains, serves as a natural endogenous inhibitor of cardiac myocyte renewal.
Summary of Affinity Group Progress

This affinity group is comprised of basic science and clinical researchers with a wide variety of interests in microvascular function and dysfunction. Several labs are interested in understanding the critical role of the endothelium in normal microvascular function and how it is altered in disease. Dr. Zhang’s current focus is to study the signaling mechanisms by which shear stress; a mechanical force generated by blood flow, stimulates endothelial relaxing factors and causes subsequent blood vessel dilation. Specifically, his lab examines the role of a calcium-permeable mechanosensitive ion channel (TRPV4) located on the cell surface membrane of vascular endothelial cells in shear-induced dilation in mice and humans. Dr. Widlansky’s lab is studying the influence of mitochondrial physiology on the endothelial dysfunction of patients with type 2 diabetes and other derangements of glucose control.

In addition, group members are interested in the mechanisms in the regulation of vascular tone and how it is modulated with stress, in disease, and by aging. Dr. Gutterman’s lab incorporates translational methods to study regulation of vascular tone in humans. In vitro studies examine the signaling mechanism surrounding mitochondrial ROS release in response to shear that leads to EDHF-mediated dilation.

Key Group Members

Andreas Beyer, PhD, Medicine
David D. Gutterman, MD, Medicine
David X. Zhang, Medicine, PhD
Michael Widlansky, MD, Medicine
Dorothee Weihrauh, DVM, PhD

Research Goals

To further the understanding and interactions of cardiovascular risk factors on the developmental and mechanism of microvascular changes eventually leading to cardiovascular disease such as coronary artery disease and atherosclerosis. The group focuses on the influence of reactive oxygen species and their cellular origin in several unique signaling pathways including potassium channel signaling, lipid signaling and mitochondrial function in health and disease.

Representative Grants

NIH RO1: Zhang “TRP channels in regulation of vascular tone”
NIH RO1: Weihrauh “Inflammation, fibrosis, and heart failure in murine scleroderma”
In vivo studies, complemented by in vitro examination of tissue biopsies, are used to determine the effect of different stressors on human microvessels. Preliminary studies indicate that conditioned weight lifters are protected from pressure-induced endothelial dysfunction compared to microvessels taken from sedentary subjects. The observed mechanism, which involves a switch from NO to H₂O₂ as the mediator of dilation, is observed in isolated microvessels. Interestingly the same mechanism is also observed in the presence of coronary artery disease (CAD). Ceramide, PGC1a, and telomerase are interconnected regulators of this dilator mechanism which are currently being studied in detail.

The Beyer laboratory is closely investigating the importance of telomerase in maintains of vascular tone. Telomerase, is negatively regulated by ceramide, is a prominent factor in the development of cellular senescence (cellular aging) and tissue aging. Decreased telomere length has been associated with a number of cardiovascular disease including hypertension and CAD. The effect of telomere independent effects of telomerase on the mechanism of vascular function is being assessed. Initial data suggest that inhibition of telomerase has similar effects as CAD on the mediator of vascular relaxation.
Summary of Affinity Group Progress

Several labs within this group are interested in the mechanisms of vascular development and remodeling.

The Ramchandran lab investigates the basic mechanisms of blood vessel formation in vertebrates and the contribution of the vasculature to disease states. Their focus is primarily on studying genes and pathways that are responsible for cardiovascular development. In addition, tools for performing drug screens using zebrafish developmental biology, cell culture models, and mouse genetics are utilized to unravel targets responsible for cardiovascular development.

The Miao lab studies Nogo-B and its cognate receptor (NgBR), neural guidance molecules in vascular remodeling and angiogenesis. Their focus is to translate the basic science knowledge gained from these studies into therapeutic applications targeting tumor angiogenesis and developmental disorders such as hemangiomas.

Others are focused on the intracellular signaling involved in the vasculature and the changes that occur in disease. The Wodnicka lab is interested in the function of small G proteins in the cardiovascular system. They use transgenic mouse and zebrafish models for in vivo studies and a variety of biochemical, molecular, and genetic approaches to understand the function and regulation of these proteins.

Key Group Members

- Ramani Ramchandran, PhD, Pediatrics
- Kelly Duffy, PhD, Pediatrics
- Rashmi Sood, PhD, Pediatrics
- Ravi Misra, PhD, Biochemistry
- George Wilkinson, PhD, Pediatrics
- Robert Miao, PhD, Pediatrics
- Magdalena (Chrzanowska-)Wodnicka, PhD, Pharmacology & Toxicology, Blood Research Institute

Research Goals

The Vascular Biology Affinity Group in the Cardiovascular Center (CVC) at the Medical College of Wisconsin (MCW) consists of an eclectic group of seven basic science investigators with complementary expertise in basic developmental and cellular biology as it relates to vascular development. The common thread that connects these research groups is the ability to study vascular (endothelial and smooth muscle) cells in embryonic and adult development and disease. This area of research is directly related to the mission of CVC at MCW in that basic science discoveries at the bench are translated to outcomes that will benefit cardiovascular research areas of angiogenesis and vasculogenesis.

Representative Grants

- NIH RO1: Ramchandran “Targeting DUSP-5 to treat vascular anomalies”
- NIH RO1: Wodnicka “Rap1 in VEGF signaling in endothelial cells”
molecular and microscopy approaches to interrogate signaling by small GTPases in vascular cells \textit{ex vivo}. The Misra lab works to develop treatments for ischemic heart disease. They utilize cellular, molecular and genetic systems to define the mechanisms by which coronary vessels are generated, as well as to identify a population of progenitor cells that can be directly used to ameliorate ischemic heart disease.

The Chan lab explores the use of mouse models to study different malignant features of human cancer. Their research is focused on components of the phosphatidylinositol 3-kinase signaling cascade such as PTEN. In addition, the lab investigates the roles of Ras-related G-proteins in neurogenesis and tumor angiogenesis.

The Levy lab focuses on integrating genetic and genomics to advance the understanding of the contribution of environmental, genetic, and epigenetic factors influencing the progression of cystic fibrosis (CF) lung disease. Using patient sample data and microarray genomic approaches, the Levy lab has begun to harness the functional genomics infrastructure to longitudinally dissect molecular events in CF in response to infection status.

Other research being done within this group is geared toward understanding specialized vasculature. The Sood lab studies the vascular bed of the placenta and the mechanism of pregnancy-related cardiovascular disorders. They are developing rodent models of pregnancy disorder associated with vascular disease, such as thrombophilia and pre-eclampsia.
Integrative Cardiovascular Systems

This affinity group is focused on systems engineering approaches to understanding the operation of physiological systems in health and disease. Recent attention of both biomedical researchers and funding agencies has been directed to developing tools and techniques to simulate physiological processes that operate over wide ranging space and time scales. This is in part because chronic diseases are believed to arise from alternations to molecular and cellular processes that affect function at the level of whole organisms. Blood pressure, for example, is regulated through the interaction of multiple organs and organ systems (neural, cardiac, renal, and endocrine). Neural pathways modulate the operation of the heart on the time scale of the heart beat and the kidney on timescales minutes to days. Important mechanisms influencing whole-organ function in both the heart and the kidney operation on sub-cellular space scales.

The tremendous range of time and space scales makes research into causes and consequences of common complex diseases such as hypertension challenging. As the biomedical research community increasing adopts the view that computational modeling is an essential tool to probe the function of complex nonlinear phenomena, appropriate methods for multi-scale simulation will become increasingly important. Our group brings together leading researchers in multi-scale computational physiology, with an emphasis on cardiovascular function and hypertension and with a particular focus on scientific questions asked through multi-scale modeling and the development computational techniques to effectively ask such questions.

Summary of Affinity Group Progress

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Key Group Members

- Daniel Beard, PhD, Physiology
- Brian Carlson, PhD, Physiology
- Ranjan Dash, PhD, Physiology
- Kalyan Vinnakota, PhD, Physiology
- Aoy Tomita-Mitchell, PhD, Surgery
- Allen Cowley, PhD, Physiology
- Michael Widlansky, PhD, Medicine

Research Goals

Develop computational models of integrative cardiovascular physiology from the molecule to map the genotype to the phenotype.

Representative Grants

- NIH RO1: Beard “Integrated modeling of cardiac metabolism and transport”
- NIH RO1: Beard “Mechanisms of metabolic dysfunction in heart disease”
A recent major effort in our group has been on theoretical and experimental characterization of the thermodynamics, kinetics, and electrophysiology of cardiac mitochondria. We use computational simulation to translate our findings on the function at the organelle level to analyze and interpret in vivo data on cardiac energetics obtained, for example, from 31P-magnetic resonance spectroscopy.

Similarly, the development of a mechanistic understanding of the long-term and short-term responses of the myocardium to ischemia and hypoxia requires the development of a model that can predict the effects of modulating expression and activity of mitochondrial and sarcolemmal ion channels on whole-heart mechanical function. This work involves building integrated models of cardiac mechanics, energetics, mitochondrial ion handling, and microvascular oxygen transport. Additional research interests include non-equilibrium thermodynamics in biochemical networks, mass transport and microvascular exchange in physiological systems, and drug metabolism and physiologically-based pharmacokinetics. All of these efforts involve a multi-disciplinary team of mathematicians, engineers, and biologists at the Medical College of Wisconsin.
Kidney Disease

Summary of Affinity Group Progress

Twenty million Americans have chronic renal disease and another 20 million are at risk but do not know it. For many, this condition will develop into end-stage kidney disease requiring dialysis or a kidney transplant. Currently, there are approximately 400,000 Americans on dialysis. The cost of this treatment to the federal government is staggering; 20 billion a year and the number of patients and costs are projected to increase exponentially over the next ten years.

Using a multidisciplinary approach fostered by having investigators contribute their varied expertise in a shared facility, this affinity group focuses on finding the cause and new treatments for the development of hypertension and diabetes induced renal disease as well as the development of polycystic kidney disease and the of renal injury following organ transplant. Assembling these top researchers together in one facility nurtures collaborative effort for cross disciplinary discoveries that will collectively lead to new therapeutic pathways.

Key Group Members

- Frank Park, PhD, Medicine-Nephrology
- Ellis D. Avner, MD, Pediatrics-Nephrology
- Mingyu Liang, PhD, Physiology
- Ashraf El-Meanawy, MD, Medicine-Nephrology
- John Raymond, MD, MCW President and CEO
- Kevin R. Regner, MD, Medicine-Nephrology
- Andrey Sorokin, PhD, Medicine-Nephrology
- Alexander Starushchenko, PhD, Physiology
- William E. Sweeney, Jr., PhD, Pediatrics-Nephrology
- Niloofar Tabatabai, PhD, Medicine-Endocrinology
- Xiaogang Li, PhD, Pediatrics-Nephrology

Research Goals

The mission of this group is to identify the genetic basis of major kidney diseases and to create better treatment options.

Representative Grants

- NIH RO1: Park “AGS3 in ischemic renal injury”
- NIH RO1: Tabatabai “Role of SGLY3 in diabetes-mediated increased renal sodium reabsorption”
Summary of Affinity Group Progress

This group is made up of a multi-disciplinary team of clinical and basic science researchers from three Milwaukee-area institutions. Members of the group studying vascular injury in the lungs include Dr. Jacobs, who is interested lung vasculature biology and injury, Dr. Pritchard, who studies factors modifying endothelial cell products that predispose to injury or protection in conditions including hypercholesterolemia, sepsis, enterocolitis and others, and Dr. Densmore, who has an interest in pulmonary endothelial injury associated with sepsis. Dr. Medhora investigates mechanisms underlying radiation-induced lung injury and mitigators of this injury. In addition, Dr. Konduri studies cellular signaling systems which define the success or failure of the transition of the pulmonary circulation from fetal to neonatal physiology. Several members of the groups are interested in computational lung research such as Dr. Clough, who investigates quantitative functional and structural parameters obtained from lung imaging, and Dr. Audi, who employs computational modeling to probe signaling in complex systems such as an intact lung. Other group members include Dr. Ranji who explores the redox status of the microcirculation using optical spectroscopy to define the state of the mitochondria. Dr. Camara studies the role of mitochondria in cardiac preservation during ischemia and reperfusion in isolated hearts or cardiomyocytes. Dr. Merker studies the mechanisms underlying the interactions of the pulmonary endothelium with redox active pro- and antioxidant physiological, pharmacological and xenobiotic compounds.

Key Group Members

Elizabeth Jacobs, Medicine and Research
Ganesh Konduri, Pediatrics
Kirkwood Pritchard, Pediatric Surgery
Meetha Medhora, Radiation Oncology
John Densmore, Pediatric Surgery
Anne Clough, Mathematics, Marquette
Said Audi, Biomedical Engineering, Marquette
Mahsa Ranji, Engineering, UWM
Amadou Camara, Anesthesiology
Marilyn Merker, Anesthesiology

Research Goals

This group has benefitted greatly from the diverse expertise of our investigators which permits application of novel methodologies including optical and SPECT imaging to clinically relevant questions. Because the group includes 3 clinician investigators, translational arms to the work are possible which are highly attractive to external funding agencies. Finally all grant applications have undergone rigorous internal review by affinity group members prior to submission. In a difficult funding environment, these critiques are invaluable in producing the highest quality of proposals possible.

Representative Grants

NIH RO1: Jacobs “Lipid modulators of pulmonary vascular tone”
NIH RO3: Teng/ Konduri “BH4 in hyperoxic lung injury in the newborn” ( pending 1st percentile)
Financials

Cardiovascular Center—FY 2012

Annual Revenue Sources

<table>
<thead>
<tr>
<th>Revenue Source</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCW Central Grants</td>
<td>$479,014</td>
</tr>
<tr>
<td>Dean Program Development</td>
<td>$100,000</td>
</tr>
<tr>
<td>Philanthropy</td>
<td>$1,669,055</td>
</tr>
<tr>
<td><strong>Total Revenues</strong></td>
<td><strong>$2,248,069</strong></td>
</tr>
</tbody>
</table>

Fiscal Year 2012 in the Cardiovascular Center was highlighted by the search for the new CVC Director. A number of internationally renowned experts in cardiovascular medicine visited MCW over the past several months and gave research presentations in the recently remodeled CVC conference room. Each of the candidates is an outstanding clinician and researcher making the job of the search committee a difficult one. The decision will be made shortly and the new director is expected to join the CVC by Fall 2012.

The CVC Scientific Advisory Committee was again of great help to us in achieving our objectives and will continue to provide guidance. This Committee is made of the following MCW Faculty:

- Tom P. Aufderheide, MD, FACEP, Professor of Emergency Medicine
- Ellis Avner, MD, Associate Dean of Research, Children’s Research Institute, Professor, Pediatrics
- Joseph Besharse, PhD, Chair of Cell Biology, Neurosciences and Anatomy
- William Campbell, PhD, Chair of Pharmacology
- Michael Cinquegrani, MD, Chief of Cardiovascular Medicine
- Stephen Duncan, PhD, Professor of Cell Biology
- Andrew Greene, PhD, Director, Bioengineering and Biotechnology Center
- David Gutterman, MD, Professor in Cardiology, Senior Associate Dean for Research
- David Harder, PhD, Professor of Physiology, Associate Dean for Research Mentoring
- Howard Jacob, PhD, Director of the Human and Molecular Genetics Center
- Elizabeth Jacobs, MD, Chief of Pulmonary and Critical Care Medicine
- Michael E. Mitchell, MD, Associate Professor Surgery, Division of Cardiothoracic Surgery
- Ramani Ramchandran, PhD, Investigator Children’s Research Institute, Associate Professor, Pediatrics
- David Warltier, MD, Chair of Anesthesiology
- Gilbert White, MD, Director of Research of Blood Research Center
- Michael Widlansky, MD, Assistant Professor, Cardiovascular Medicine

Further details about the CVC are provided on the CVC website at [http://www.mcw.edu/cvc.htm](http://www.mcw.edu/cvc.htm) and on the Kidney Disease Center website at [http://www.mcw.edu/kdc](http://www.mcw.edu/kdc).
Fundraising Events

Cardiovascular Center Golf Challenge

The 13th annual CVC golf event was held on July 25th, 2011 at scenic Chenequa Country Club. Twenty-five foursomes golfed during the day while many more joined them for the banquet and the silent and oral auctions that followed. The Golf Challenge remains the premier fundraising activity for the CVC. The 2012 event is slated for July 23rd.
“Have a Heart” Motorcycle Ride

This year’s ride took place on June 9th, 2012 on a beautiful spring day over a scenic 70-mile course through the countryside of Southeastern Wisconsin. A record number of almost 137 riders participated in the 4th annual event sponsored by Suburban Motors Harley-Davidson of Thiensville. The day included a pre-ride breakfast and post-ride lunch with live music by Press Play and Boogie Chillen’.
The CVC event with the longest history and highest level of participation is the Cullen Run/Walk that winds along the Underwood Parkway in Wauwatosa adjacent to the MCW campus each winter. The 16th annual event took place on February 11th, 2012 which was by far the coldest day in the history of the event. Despite single-digit temperatures and below-zero wind chills, hundreds of “hearty” souls, young and old, showed up that morning to battle the elements. A total of 920 runners and walkers registered for the event, which was only 27 less than the all-time record. Participants were rewarded for their extraordinary efforts with live music, homemade hot chili and other refreshments.