The Marquette Electronics Museum was dedicated at the Medical College in November, 2007. It is an archival collection of equipment that recognizes the historic contributions made by Marquette Electronics in the development of cardiovascular monitoring equipment. Milwaukee entrepreneur and philanthropist, Michael Cudaby, co-founder and former Chairman and CEO of Marquette Electronics and a founding member of the Cardiovascular Center Advisory Board, donated the equipment to establish the museum. The picture above shows several instruments including the first Central Electrocardiographic System built in 1965.
Specific ongoing CVC areas of research include atherosclerosis, cardiac regeneration, cardiac transplantation, heart attack, heart development, genetic risk factors of heart malformations, heart failure, vascular biology, development of new blood vessels (angiogenesis), chronic renal disease, genetics of hypertension, high blood pressure (hypertension), ischemic kidney disease, diabetes, pulmonary vascular diseases (pulmonary hypertension), intracellular signaling pathways, stem cells, and stroke (cerebral vascular disease).

To stimulate and foster greater interaction and collaborations between CVC investigators, working Affinity Groups have been initiated wherein new ideas are presented, research results are critiqued, and new strategic directions for research programs are developed. These groups usually include at least one clinician scientist and a senior, well-funded scientist to help mentor the others as needed. Their objectives and research represent the bulk of this Annual Report.

Current total research funding of faculty residing within the CVC amounts to $26.8 million (direct costs), with $6.9 million in annual direct costs.

In order to support this research effort, we are renovating and expanding the facilities of the CVC and the KDC, adding about 5000 square feet of new laboratory space and markedly increasing the space attributed to our center.
Mission Statement

The mission of the Cardiovascular Center is to further develop strong and nationally recognized interdisciplinary cardiovascular research programs at the Medical College of Wisconsin and to promote comparable excellence in clinical care and education while developing community outreach.

About the Cardiovascular Center

Created in 1992, the Cardiovascular Center (CVC) is focusing on the prevention, detection, treatment and cure of the large family of cardiovascular diseases. The newly created image representing the CVC seen above emphasizes the integrated importance of cardiovascular and kidney research with a symbolic representation of the heart with an overlying electrocardiogram and a nephron, the functional unit of the kidney.

The CVC Scientific Advisory Board will help us achieve our objectives. It is made up of the following MCW Faculty:

- 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 of the 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
- David Wartliet, MD, Chair of Anesthesiology
- Gilbert White, MD, Director of Research of Blood Research Center
- Michael Widlansky, MD, Assistant Professor Cardiovascular Medicine

A different and important component of the CVC is the Cardiovascular Center Advisory Board, which provides financial support for the research and clinical programs carried on by the CVC. It educates the community in cooperation with the Board of Trustees of the Medical College on the causes, prevention, diagnosis, and treatment of cardiovascular disease. Its members serve as advocates in the community in support of the Cardiovascular Center’s mission.

Further details about the CVC, including a description of the work conducted in each individual laboratory, are provided on the CVC website at http://www.mcw.edu/cvc.htm and on the Kidney Disease Center website at http://www.mcw.edu/kdc.
The Cardiovascular Center has initiated these groups to stimulate and foster greater interaction and collaborations between CVC investigators and other investigators from MCW departments and outside institutions, such as Marquette University, the University of Wisconsin Milwaukee and the University of Georgia.

Presented below are ten of the current Affinity Groups.

### Atherosclerosis

This group, comprised of Drs. Daisy Sahoo, Victor Drover, Kirkwood Pritchard, and Hiroto Miura, fosters collaborative work to improve the content of grants. The research conducted in the participating laboratories is summarized here.

Dr. Sahoo’s laboratory studies high density lipoproteins (HDL, also known as “good cholesterol”), which transport cholesterol from sites of accumulation (e.g. arteries) to the liver for excretion. Scavenger receptor BI (SR-BI) is a protein that binds HDL, and our research is designed to understand how SR-BI mediates the uptake of cholesterol from HDL into the liver for efficient breakdown of cholesterol and its subsequent removal from the body. Determining first how the structural organization of SR-BI can facilitate this movement of cholesterol and, second, the detailed mechanisms for the actual process of cholesterol breakdown may help us identify novel therapeutic strategies for treating conditions such as hypercholesterolemia (extremely high cholesterol levels) or atherosclerosis (massive cholesterol buildup within the arteries).

Dr. Drover’s laboratory studies protein CD36, which is attached to the arterial wall. CD36 binds the “bad cholesterol” circulating in the blood and deposits it in the artery. Left untreated, this buildup of cholesterol can cause heart attack and stroke. This lab is trying to understand the features of CD36 that make it such an efficient receptor for bad cholesterol. This type of research is critical to developing novel medicines that prevent cholesterol buildup in the arteries and heart disease.

Dr. Pritchard’s laboratory studies the mechanisms by which chronic inflammation and oxidative stress impair vascular function and induce disease. A major focus is on the mechanisms by which inflammation and oxidative stress increase pro-inflammatory HDL, which is dysfunctional, and the subsequent effects this dysfunctional HDL has on vascular endothelial cell function. This lab investigates how oxidative enzymes alter HDL and impair vascular endothelial cell nitric oxide and superoxide anion balance. To increase the

Drs. Pritchard, Sahoo, and Drover
translational aspect of its basic science studies, this lab routinely targets different pathways for new drug development. It has co-developed three peptide drugs that show promise for clinical studies for the treatment of vascular disease mediated by myeloperoxidase. The lab’s new drugs represent novel experimental approaches for specifically targeting different pathways of inflammation and oxidation that can be used to delineate novel mechanisms in vascular disease.

Dr. Miura’s laboratory studies the role of intermediate-conductance calcium-activated potassium channels KCa3.1 in vascular remodeling. Vascular and inflammatory cells express a variety of ion channels that regulate cellular homeostasis. The contribution of the activity of KCa3.1 to the pathogenesis of vascular remodeling, such as atherosclerosis, is being examined along with whether its blockade could be a novel therapeutic strategy for the prevention of vascular remodeling. The role of CD73 in vascular remodeling is also being studied. CD73, an enzyme normally expressed on vascular endothelial cells, produces adenosine, a potent vasodilator and anti-inflammatory molecule. The lab is examining if this enzyme expression and activity is modulated under diseased conditions, leading to dysregulation of blood perfusion and vascular homeostasis. The impairment will cause an increase in blood pressure and vascular inflammation, such as hypertension and atherosclerosis.

Genetic and Molecular Etiology of Congenital Heart Disease

This group includes Drs. Tomita-Mitchell and Michael E. Mitchell, who are interested in identifying genetic risk factors of heart malformations and in understanding how these genetic alterations impact pathways at the molecular level. The group hopes to be able to improve immediate and long-term outcomes for patients with congenital heart disease (CHD) by identifying patients at risk for CHD before their heart fails. Ultimately, the group hopes that by identifying the genes and the pathways that are altered in CHD, therapies that will repair these pathways can be targeted. To reach this goal, this laboratory is focused on the following:

1. patient recruitment to a CHD Tissue and DNA Bank, a repository of DNA and surgical discards from patients with congenital heart disease;
2. the development and utilization of high-throughput genetic technologies in order to reduce the high costs of performing large-scale genetic studies; and
3. the integration of genetic information with clinical variability and outcomes.
This group includes Drs. Michael Earing, David Gutterman, Anne Hoch, Srividya Kidambi, Margaret Samyn, David Saudek, J.C. Smith, Scott Strath, Denise Teves, and Michael Widlansky. The group centers its research efforts on applying tools to measure the health of blood vessels to determine novel influences on blood vessel health. These tools, including high-resolution ultrasound and pulse analysis, have been shown to be able to predict the risk for future heart attacks and strokes. Studies being performed by investigators in this group include:

1. determination of the effects of increasing physical activity on blood vessel function;
2. assessment of the effect of Vitamin D supplements on blood vessel function in patients with kidney disease;
3. determination of the importance of alterations in mitochondria (an important cell component) on blood vessel function in persons with diabetes;
4. measurement of the impact of increases in moderate physical activity on blood vessel function in healthy older adults; and
5. determination of the mechanisms of blood vessel dysfunction in humans with high blood pressure.

Many of these studies look to determine:

1. whether novel mechanisms of heart attacks and strokes discovered in animal models or isolated cell studies are relevant to human vascular physiology; and/or
2. whether novel associations between risk factors and heart disease from large population studies are linked through alterations in the health of blood vessels.

These studies are performed by researchers from a large variety of disciplines, including adult and pediatric Cardiology, adult and pediatric Endocrinology, Orthopedic Surgery, Exercise Physiology, and Nephrology. The group includes investigators based both at the Medical College of Wisconsin and the University of Wisconsin—Milwaukee.

This group continues to grow its collaborative networks, leveraging the extensive assets of the Cardiovascular Center to translate novel findings into the realm of human subjects’ research.
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 a 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. Defining the physiological and genetic basis of common forms of human hypertension, however, remains a great challenge. There is a broad interest related to the field of hypertension at MCW that is supported by several programmatic initiatives and a number of individual research grants. One Program Project Grant, which includes Drs. Allen Cowley, Howard Jacob, Carol Moreno, Mingyu Liang, and Andrew Greene and is supported by the National Institutes of Health (NIH), is focused upon understanding the genetic regulation of the complex pathways regulating arterial pressure, the overriding challenge in the field of hypertension research. This program utilizes rat genetic model systems to advance our understanding of the complex regulation and interplay of a set of genes residing in two different regions of rat chromosome 13, which together are responsible in large measure for salt-induced hypertension, renal injury, and reduced blood vessel density of the microcirculation. This rat strain develops severe hypertension when placed on a high salt diet (Dahl salt-sensitive rat) and exhibits many of the same traits found in human forms of salt-sensitive hypertension. 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 Program Project Grant, comprised of Drs. Allen Cowley, Mingyu Liang, David Mattson, and Richard Roman, is focused upon the role of the kidney in hypertension and explores the physiological mechanisms responsible for the salt-induced renal dysfunction and hypertension found in the Dahl salt-sensitive rat model of hypertension. One of the projects hypothesizes that a high salt diet results in greater tubular sodium reabsorption in the outer medulla of the kidney in salt-sensitive rats and thereby stimulates excess production of reactive oxygen species (ROS) in the renal medullary thick ascending limb (mTAL). It is proposed that this will reduce medullary blood flow and drive the initial rise of arterial pressure during the first week.

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of hypertension. Another project hypothesizes that an inflammatory process develops within the renal inner cortex and outer medulla that is initiated by infiltrating macrophages that produce angiotensin II. This further stimulates ROS production and renal injury.

A third project focuses on defining a mutation in one of the cytochrome P4504A genes (CYP4A) responsible for renal 20-HETE production and proposes that this genetic defect plays an important causal role in impaired pressure natriuresis, sodium retention, and the development of hypertension.

In closely related NIH-supported studies, Drs. Julian Lombard and Andrew Greene carry out studies to determine why a high salt intake leads to a dramatic reduction in small vessel density in a number of organs, and why it leads to a reduced ability of larger blood vessels to relax, both of which result in reduced blood flow to critical organs even in the absence of hypertension. A number of studies are under way to determine the mechanisms responsible for these important observations and particularly for the role played by the renin-angiotensin system and vascular oxidative stress.

In another important area of research related to hypertension, Drs. William Campbell and John Imig focus on the 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.

Microvascular Function

The microvascular function affinity group is formed by the laboratories of Drs. David Gutterman, Michael Widlansky, and David Zhang. The research conducted in this affinity group focuses on the regulation of microvascular reactivity in health and disease states. In particular, the group is interested in understanding how vasodilation occurs in response to chemical and mechanical stimuli in isolated human microvessels, and how the dilatory response is altered by underlying vascular disorders such as atherosclerosis, hypertension, and diabetes. Following are the three main projects currently being carried out by this group.

Dr. Gutterman’s laboratory is studying the mechanism of hydrogen peroxide–induced dilation in human coronary arterioles. Dilation resulting from shear stress, a mechanical force generated by blood flow, is one of the most important physiological mechanisms of dilation, and it occurs in virtually every vascular bed. Although flow-induced dilation has been examined extensively in animals, few studies have been performed with human vessels. Dr. Gutterman’s lab has recently identified a novel mechanism whereby reactive oxygen species (ROS), specifically hydrogen peroxide (H$_2$O$_2$) from endothelial mitochondria, mediate flow–induced dilation in human coronary microvessels from patients with coronary artery disease. How H$_2$O$_2$ dilates coronary arterioles remains unclear. This project is designed to test the hypothesis that protein kinase G1 alpha (PKG1α) activation via protein dimerization is an important mechanism responsible for H$_2$O$_2$-induced dilation. These studies should provide novel insights into vascular redox signaling related to coronary blood flow regulation in health and disease.

Dr. Zhang’s laboratory is studying endothelial TRPV4 channels in flow–mediated dilation. The lab’s current focus is to study the signaling mechanisms by
which shear stress activates endothelial cells, a thin layer of cells lining the lumen of all blood vessels, to induce the release of vasodilator factors leading to flow-induced dilation. Specifically, the study examines whether a calcium ion channel (TRPV4) located on the cell surface membrane of vascular endothelial cells serves an essential and conserved signaling component for shear-induced dilation in mice and humans. The findings of these studies will importantly contribute to our understanding of endothelial shear transduction and signaling, and may help identify new therapeutic targets for the treatment of vascular disorders.

Dr. Widlansky’s laboratory is looking at the role of disturbances in mitochondrial homeostasis in the development of endothelial dysfunction in humans with type 2 diabetes. Endothelial dysfunction has been shown to precede the development of atherosclerosis and portend cardiovascular events in both those with and without clinically evident cardiovascular disease. This project characterizes vasodilatory responses in human subcutaneous microvessels from subjects with or without type 2 diabetes, and examines whether and how disturbances in the function of endothelial mitochondria contribute to altered vascular responses in type 2 diabetes. This translational research will substantially increase our understanding with regard to pathophysiological mechanisms underlying the development of endothelial dysfunction in humans with a variety of disease states, including coronary artery disease and diabetes.

The members of the Pulmonary Focus Group are Drs. Said Audi, Dara Frank, Elizabeth Jacobs, Ganesh Konduri, Meetha Medhora, Marilyn Merker, Robert Molthen, Kirkwood Pritchard, and Yang (Scarlet) Shi. This group will examine overwhelming infections, called sepsis, that frequently lead to lung failure (called Respiratory Distress Syndrome, or RDS). These conditions consistently lead as causes of admission to Intensive Care Units.

Despite administration of antibiotics and the best therapy available, roughly 30% of patients with sepsis or RDS do not survive. Because low oxygen tensions in the blood (hypoxemia) is a hallmark of these disorders, patients with lung failure are necessarily treated with high fractions of inhaled oxygen.

Lung injury in patients with RDS is attributable in part to increased generation of unstable oxygen products (reactive oxygen species). Although high fractions of oxygen are required to sustain life in these conditions, treatment with high fractions of oxygen may increase lung injury above that expected by oxygen or sepsis alone.

Infants and adults both develop lung injury in response to sepsis, but the probability is that processes leading to lung injury are different because 1) infants have immature immune systems; and 2) before birth, infants’ lungs are optimized to function with very low oxygen levels compared to adults’ lungs.

It is the overarching goal of this project to learn more about the interaction of high fractions of oxygen or unstable oxygen products and sepsis in infants and adults. The benefit of treatment with two products that may protect lungs through novel means based upon our preliminary data will be explored.
Experimental models ranging from cells in culture derived from the lining of lung arteries in fetal lambs, to whole lungs and heart isolated and perfused in the lab, to images of cells of lung slices exposed to high fractions of oxygen in incubators will be used. This approach is called “vertically integrated” because a problem is studied from the perspective of whole lungs down to the level of parts of cells.

All labs will use a substance called “lipopolysaccharide,” or LPS, to mimic sepsis. LPS is a product of many bacteria, and is responsible for triggering much of the tissue injury.

Regenerative Medicine

This Program Project Grant (PPG) is led by the affinity group’s organizer, Dr. John W. Lough. Other principal investigators in the group include Drs. John Auchampach, Stephen Dalton, Stephen A. Duncan, Ravi Misra, Paula E. North, and Ming Zhao. With the exception of Dr. Dalton who is at the University of Georgia, all members are Medical College of Wisconsin faculty.

This affinity group is based on the recent receipt of a five-year, $8 million, multi-investigator PPG from the National Institutes of Health. The overall goal of this multi-laboratory investigation is to understand how human pluripotent stem cells, defined as cells that if left to their own designs can develop into any of the more than 200 cell types in the human body, can be channeled to exclusively become heart muscle cells. Fulfillment of this objective is of crucial importance, because the ability to replace the contractile component of the heart following injury or disease has not been achieved. If pluripotent cells can be used to produce the contractile cells of the heart (cardiac myocytes) these could potentially be transplanted into injured or diseased hearts to compensate for loss of this specialized muscle tissue.

The integrative theme of this group’s research regards the role of “definitive endoderm,” a group of cells in the embryo that direct and induce the development of the heart in the embryo. During the past 15–20 years, acquiring an understanding of these cells has been the independent focus of four of the team’s members, who are now pooling their expertise to assess whether endoderm-generated signals can efficiently and reproducibly induce pluripotent stem cells into the cardiomyogenic (i.e., heart muscle) lineage. Theoretically, this should result in the generation of a pure cardiac myocyte population, in sufficient numbers (tens of millions) for remedial transplantation, the efficacy of which will be evaluated using animal models of heart disease.

Success achieving these tasks is promoted by synergy with MCW’s shared core facilities, especially researchers in the MCW Cardiovascular and Human and Molecular Genetics Centers.
The members of this group are Drs. Dave Mattson, Vani Nilakantan, Frank Park, Kevin Regner, Rajasree Sreedaran, and Scott Van Why.

The common themes explored by work in the laboratories of members of this group are centered upon the physiological and pathophysiological consequences of renal ischemia/reperfusion (I/R) injury. Renal I/R injury is a commonly employed model of acute kidney injury (AKI), also known as acute renal failure. AKI is a serious disease with grave consequences; the mortality rate of patients with AKI is approximately 50%. AKI is characterized by a rapid decline in the filtration function of the kidney that is accompanied by the retention of waste products. The impairment in function in AKI can be caused by a number of different factors and occurs in a significant fraction of patients in the Intensive Care Unit. In addition to the clinical relevance of studies that examine renal I/R injury to acute kidney injury, experimental renal I/R injury is also an important model that is used to assess the conditions that occur in patients receiving a kidney transplant. Depending upon the donor, transplanted kidneys are not perfused with blood for a variable amount of time prior to transplantation. Because AKI has such serious effects in patients, and all transplanted kidneys experience renal I/R injury to some extent, the clinical relevance and translational importance of this type of research to human health is extremely high.

Members of the Renal Ischemia/Reperfusion group are examining a multitude of mechanisms that mediate injury in the short-term and in the long-term. A number of members of the group are focusing their scientific efforts upon the acute changes in different factors that lead to cell death or alterations in cellular function in the first minutes to hours after injury. The major focus of this work is to understand what biochemical or cellular signals are activated in the kidney following injury that leads to alterations in blood flow and the development of tissue damage. The ultimate goal of this type of research is to develop strategies that can be used to decrease the impairment in renal function and reduce the mortality associated with AKI.

Other work by members of this affinity group is focused upon the long-term (days to months to years) consequences of AKI due to I/R injury. It has been and is still largely believed that individuals who survive AKI spontaneously recover full kidney function. Studies by members of this group, and by colleagues throughout the world, have demonstrated that there are long-term deleterious effects in individuals who have recovered from AKI. The more extreme, long-term consequences include chronic kidney disease and hypertension. The goal of research into the long-term effects of renal I/R injury is to develop methodologies to prevent these chronic diseases that significantly reduce life expectancy and the quality of life.
This affinity group brings together investigators from two basic research departments and four interdisciplinary research centers. The common theme connecting these investigators is an interest in cutting-edge technologies for answering fundamental questions about mammalian biology and disease. Dr. Aron Geurts organizes the group and focuses on generating genetically engineered rat models of human disease by altering genes in the rat genome. One technology, zinc-finger nuclease genome editing, was used to produce the world’s first “knockout rats” where specific genes are mutated to disrupt their function in order to understand their role in disease. Another approach uses jumping genes, called “transposons,” to add new genes to the rat genome to see how they impact disease processes.

Combined efforts in several labs also have goals of developing stem cell technology for engineering genetic changes in laboratory model organisms, developing tissues that can be manipulated and studied in vitro, and understanding organ development. A continuing collaboration between Dr. Geurts’s lab and researchers in the lab of Dr. Howard Jacob is aimed at developing stem cells from rats. Embryonic stem cells (ESCs) derived from rat embryos will be a useful tool for altering the genome sequence of the rat and generating new disease models. Members of these two groups also work closely with Dr. Stephen Duncan toward developing induced pluripotent stem cells (iPSCs) from mice, rats, and humans. iPSCs are generated by a process called “genetic reprogramming” whereby specific genes are introduced into a differentiated cell like a skin fibroblast using viruses or transposons to cause them to turn into cells that are highly pluripotent and have the ability to develop into any cell type. These cells may allow for genome engineering in these models. They are being explored for their potential for directed differentiation of cells such as hepatocytes and cardiomyocytes, in order to understand the process by which these highly specialized, organ-specific cells develop from early embryonic precursor cells. ESCs, iPSCs, and the tissues and animals derived from them will be powerful tools for understanding gene function related to human disease, responses to environmental stress and stimuli, and developing therapeutic strategies.

Along with Drs. Geurts, Jacob, and Duncan, investigators such as Drs. Allen Cowley, Andrey Sorokin and Mingyu Liang collaborate to capitalize on these and other technologies by creating genetically modified rat models of hypertension and renal disease to understand how specific genes related to their lab interests play a role.

Together, the members of the CVC Stem Cells & Transgenics affinity group are working through technology to manipulate whole animal and human cell culture model systems to understand disease mechanisms and provide their expertise to other researchers who are interested in developing similar research tools.
Blood vessels are hollow tubes that comprise of two cell types: the outer smooth muscle cells that envelope the endothelial cells on the inside. Blood vessels carry blood to all tissues in the body and form one of the three key components of the cardiovascular system, which in addition includes blood and the heart. Blood vessels are formed by two distinct processes, namely vasculogenesis, which is the process of formation of endothelial tube directly from immature cells, and angiogenesis, which is the formation of endothelial tube via extension of an existing vessel. Vasculogenesis and angiogenesis play critical roles in development and disease. The Vascular Biology group consists 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 the research areas of angiogenesis and vasculogenesis.

Core members of this affinity group are Drs. Andrew Chan, Robert Miao, Ravi Misra, Ramani Ramchandran, Rashmi Sood, George Wilkinson, and Carol Williams. This group meets each week to discuss and share scientific results. A brief description of each of the individual programs of the investigators is provided below.

Dr. Chan’s laboratory explores the signaling events regulated by a Ras-related GTPase, R-Ras protein in vascular smooth muscle cells and endothelial cells and is currently investigating potential angiogenic defects under normal or pathological conditions.

Dr. Miao’s laboratory 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.

Dr. Misra’s laboratory studies are directly related to developing 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. Identifying these cells and defining the mechanisms that regulate normal differentiation of these progenitor cells will lead to new therapeutic modalities for the treatment of congenital and acquired blood vessel diseases related to the pulmonary and cardiac circulations.

Dr. Ramchandran’s program investigates the basic mechanisms of blood vessel formation in vertebrates.
and the contribution of the vasculature to disease states. The program’s focus is primarily on studying genes and pathways that are responsible for cardiovascular development. In addition, tools for performing drug screens using zebrafish embryos are being developed, which will identify targets and potential drug leads for treating embryonic congenital cardiovascular defects.

Dr. Sood’s research 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. These studies directly contribute to our understanding of the vessel tone and function in hypertension-mediated cardiovascular conditions.

Dr. Wilkinson’s research is focused on understanding the molecular cues that guide the developing vasculature. They study novel endothelial gene products, using a combination of zebrafish developmental biology, cell culture models, and mouse genetics to unravel targets responsible for cardiovascular development.

Dr. Williams’s program investigates the mechanisms that cause atherosclerosis and hypertension, with the goal of developing new approaches to treat these diseases. Dr. Williams’s research is defining the abnormal changes that occur in these diseased vascular smooth muscle cells and investigating new strategies to prevent or reverse these pathological changes.

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**Financials**

**Cardiovascular Center — FY 2010**

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<th>Annual Revenue Sources</th>
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The CVC administration group
The total number of CVC affiliated faculty exceeds 170 and includes more than 100 clinicians. Specific ongoing CVC areas of research include atherosclerosis, cardiac regeneration, cardiac transplantation, heart attack, heart development, genetic risk factors of heart malformations, heart failure, vascular biology, development of new blood vessels, chronic renal disease, genetics of hypertension, hypertension, ischemic kidney disease, diabetes, pulmonary vascular diseases, intracellular signaling pathways, stem cells, and cerebral vascular disease.