Aab Cardiovascular Research Institute (CVRI)

University of Rochester Medical Center

Annual Report 2014 – 2015

June 2015
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A. Overview

From the Director

The Aab Cardiovascular Research Institute completed an exciting transition in 2015: we have returned to the main campus of the medical center! Our faculty and staff welcome the increased opportunities to interact with our scientific colleagues and clinical collaborators at the medical center. Our move has strengthened our links to clinical research and increases the available cardiovascular training programs for graduate students and research fellows centered at the main campus.

The Aab Cardiovascular Research Institute has a long tradition of collaborations with scientists at the medical center – and our move to the medical center has strengthened the community of scientists across the medical center. We now offer our colleagues new opportunities for interactions:

- Our vascular biologists study the cells of the vessel wall – endothelial cells, smooth muscle cells, pericytes, and fibroblasts – and their role in angiogenesis and vascular inflammation.
- Our thrombosis team at the Aab Cardiovascular Research Institute has identified a novel protein that regulates thrombosis in humans, and has discovered a new role for platelets in the regulation of inflammation.
- Our cardiac researchers explore the effect of ischemia and reperfusion upon the heart; and they examine the process of fibrosis as the heart responds to injury. We are recruiting additional cardiac biologists who not only lead their own research programs but also can interact with our clinical cardiac programs, including our Advanced Heart Failure team and our Electrophysiology Section.

Our return to the medical center strengthens our close links with our clinical colleagues in the Cardiology Division. Our cardiologists at the medical center lead a world famous study that explores the causes and treatments of sudden cardiac death; at the CVRI we study mutations in ion channels that cause electrical abnormalities leading to sudden death. Our cardiologists also study the impact of mechanical assist devices in patients with advanced heart failure; at the CVRI we study the effect of mechanical assist devices upon thrombosis, diabetes, and fibrosis in our patients with advanced heart disease. And we are studying the effect of hypoxia on blood vessel development in the lungs of infants. Our move enhances connections and collaborations between our cardiovascular scientists and clinicians.

Our move to the medical center also increases the opportunities for training the next generation of cardiovascular scientists. We are the center for a training grant from the National Institutes of Health that supports graduate students and postdoctoral fellows who explore mechanisms of preventive cardiology. Our trainees now have increased exposure to the top notch researchers and outstanding seminars and advanced facilities available at the medical center. In turn, the trainees already at the medical center have increased access to our training programs, research seminars, and mentors.

Philanthropic funds raised over the last few years are being used to support collaborative research projects between teams of scientists at the Aab Cardiovascular Research Institute and at the medical center. Our return to the medical center forges stronger bonds between collaborators supported by philanthropic funds. The Aab Cardiovascular Research Institute is grateful to our community for their generous support of cardiovascular research.
CVRI Facts Fiscal Year 2015

Personnel

- Faculty Tenure Track: 10
- Faculty Research Track: 4
- Post Doctoral Fellows: 13
- Graduate Students: 7
- Staff: 25

Finances

- NIH Grant Funding: $3.3 M
- Other Funding: $2.4 M
- Total Operating Revenue: $5.7 M
- Salary & Benefits: $3.8 M
- Supplies & Equipment: $1.5 M
- Total Expenses: $5.3 M

Scientific Publications

- Publications Fiscal Year 2015: 25

Seminar Series Speakers

- Richard Aab Cardiovascular Seminar Series: 16

Training Programs

- NIH T32 Training Grant in Preventive Cardiology
B. Faculty Appointments

Tenure Track Faculty (12)

Bradford C. Berk, M.D., Ph.D.
Distinguished University Professor in Medicine/Cardiology, Neurology, Pathology, and Pharmacology & Physiology
Director, University of Rochester Neurorestoration Institute

Zheng-Gen Jin, Ph.D.
Associate Professor, Department of Medicine, Aab CVRI

Vyacheslav (Slava) Korshunov, Ph.D.
Associate Professor, Department of Medicine, Aab CVRI and Department of Biomedical Genetics

Charles J. Lowenstein, M.D.
Paul N. Yu Professor in Cardiology, Department of Medicine
Chief, Division of Cardiology and Director, Aab Cardiovascular Research Institute

Joseph M. Miano, Ph.D.
Associate Professor Department of Medicine, Aab CVRI and Pathology and Laboratory Medicine
Associate Director, Aab CVRI

Craig N. Morrell, D.V.M., Ph.D.
Associate Professor, Department of Medicine, Aab CVRI

Jinjiang Pang, B. Med., Ph.D.
Assistant Professor, Department of Medicine, Aab CVRI (part-time, non-tenure track)

Eric M. Small, Ph.D.
Assistant Professor, Department of Medicine, Aab CVRI and Department of Pharmacology and Physiology

Jane Sottile, Ph.D.
Associate Professor, Department of Medicine, Aab CVRI

Mark B. Taubman, M.D.
Professor of Medicine/Cardiology
Dean, School of Medicine & Dentistry, University Vice-President for Health Sciences

R. James White, M.D., Ph.D.
Associate Professor of Medicine/Pulmonary and Critical Care

Chen Yan, Ph.D.
Associate Professor, Department of Medicine, Aab CVRI
Research Faculty (4)

Coeli Lopes, Ph.D.
Research Associate Professor, Department of Medicine, Aab CVRI

Mark Sowden, Ph.D.,
Research Associate Professor, Department of Medicine, Aab CVRI

Jian Fu, B. Med., Ph.D.
Research Assistant Professor, Department of Medicine, Aab CVRI

Maria Garcia-Hernandez, Ph.D.
Senior Associate, Department of Medicine, Aab CVRI

Other Faculty Appointments (4)

Secondary Faculty
George A. Porter, M.D., Ph.D.
Assistant Professor, Pediatrics
URMC

Alan V. Smrcka, Ph.D.
Professor and Louis C. Lasagna Professor of Experimental Therapeutics
URMC

Adjunct Faculty
Xiaochun Long, Ph.D.
Associate Professor, Albany Medical College

Guoyong Yin, B. Med., Ph.D.
Professor, First Affiliated Hospital of Nanjing Medical University
Bradford C. Berk, M.D., Ph.D.

Synopsis

My laboratory investigates fundamental and clinical mechanisms of signal transduction in blood vessels that contribute to cardiovascular diseases (CVD) such as atherosclerosis, aneurysms, hypertension and stroke. Current projects include:

1. **The mechanisms by which the biomechanical force generated by blood flow (shear stress) contributes to CVD.** Specifically when blood flow is turbulent or disturbed (d-flow) there is a predilection for atherosclerosis and endothelial dysfunction. In contrast, steady flow (s-flow) stimulates a canonical atheroprotective pathway. We have discovered that a family of proteins that contain the protein binding motif termed (PB1 domain) are regulated both by expression and activity depending on blood flow pattern. PB1 domain proteins are dramatically overexpressed in the biomechanical transduction pathway. Of the 13 PB1 domain proteins in the human genome, 7 play a role in this pathway. S-flow stimulates an atheroprotective pathway that involves MEKK3 (PB1)-MEK5(PB1)-ERK5-KLF2 transcription factor. We showed that PKCz inhibited the pathway by phosphorylating ERK5. Using an antibody to the specific ERK5 phospho-serine we showed increased phosphorylation in d-flow regions. Furthermore, we have shown an absolute requirement for another PB1 protein, p62 that regulates PKCz activity and location. Recently we developed mouse models with altered levels of PKCz and p62 in a tissue specific manner that exhibit important phenotypes such as atherosclerosis and aneurysm formation. Likely pathogenic mechanisms include our data which demonstrated that CypA had pro-inflammatory and pro-apoptotic effects on endothelial cells (EC) and stimulated SMC proliferation, MMP activation, and migration. Based on our previous work it is logical that CypA would be a potential pathogenic mediator of PAH. Therefore, we first measured plasma CypA in PAH patients. There was a 2-fold increase in circulating CypA. Expression of CypA assayed by immunohistochemistry was also enhanced in lungs of PAH patients, as well as in the rat PAH model of pneumonectomy and monocrotaline (pMCT) treatment. To strengthen our hypothesis that CypA is a novel mediator of PAH, we generated cell-specific CypA over-expressing transgenic mice (ecCypA-tg and smCypA-tg). The exciting result was the EC specific ecCypA-tg mice developed pulmonary hypertension at 3 months of age. Based on these findings, we will investigate the role of extracellular (eCypA) as a novel mediator of PAH based on two mechanisms: vascular remodeling (EC apoptosis, EC-transdifferentiation, SMC proliferation and migration) and inflammation.

2. **The role of Cyclophilin A (CypA) in pulmonary arterial hypertension (PAH).** We have previously established that CypA is secreted from all cell types present in vessels; and participates in a positive feedback loop in Smooth Muscle Cells (SMC) generating reactive oxygen species (ROS) by binding p47phox and translocating it to the membrane. Most importantly, we used several mouse models of CypA deletion and over-expression to demonstrate a pathogenic role for CypA in atherosclerosis and aneurysm formation. Likely pathogenic mechanisms include our data which demonstrated that CypA had pro-inflammatory and pro-apoptotic effects on endothelial cells (EC) and stimulated SMC proliferation, MMP activation, and migration. Based on our previous work it is logical that CypA would be a potential pathogenic mediator of PAH. Therefore, we first measured plasma CypA in PAH patients. There was a 2-fold increase in circulating CypA. Expression of CypA assayed by immunohistochemistry was also enhanced in lungs of PAH patients, as well as in the rat PAH model of pneumonectomy and monocrotaline (pMCT) treatment. To strengthen our hypothesis that CypA is a novel mediator of PAH, we generated cell-specific CypA over-expressing transgenic mice (ecCypA-tg and smCypA-tg). The exciting result was the EC specific ecCypA-tg mice developed pulmonary hypertension at 3 months of age. Based on these findings, we will investigate the role of extracellular (eCypA) as a novel mediator of PAH based on two mechanisms: vascular remodeling (EC apoptosis, EC-transdifferentiation, SMC proliferation and migration) and inflammation.

3. **The genetic basis for vascular intima inflammation, a predictor of cardiovascular mortality.** A long-term goal in treating atherosclerosis and hypertension is to understand the mechanisms that regulate the structure of blood vessels, a process termed “vascular remodeling.” An important predictive phenotype for human cardiovascular disease is vascular remodeling in the carotid artery, represented by the measurement termed intima-media thickening (IMT). Clinical studies of atherosclerosis and coronary artery disease have yet to identify single gene candidates that could be targeted to treat IMT. In this project we will gain insight into the genetic mechanisms responsible for IMT by a systems biology approach that involves genome wide association studies combined with congenic mouse strains, which differ in vascular remodeling phenotypes. Previously we
performed a quantitative trail locus (QTL) analysis of vascular remodeling alleles in a backcross of C3HeB/FeJ (C3H/F) and SJL/J (SJL) mouse strains and identified three QTLs, termed Intima modifier loci (Im1 on chromosome 2, Im2 on chromosome 11 and Im3 on chromosome 18, that regulate intimal thickening. We found using congenic mice that genomic material on Im1 and Im3 from SJL on the C3H/F background promoted intimal thickening in response to carotid injury (low flow). Our major hypothesis is that genetic elements within these two loci, Im1 and Im3, work via a cooperative mechanism (trans-acting) to regulate intimal thickening. Based on our preliminary data our goal is to employ an integrative genomic approach to identify elements critical to the regulatory network between Im1 and Im3 loci. Using a combination of analyses including congenic fine mapping, genome-wide association with the Hybrid Mouse Diversity Panel (HMDP), RNA sequencing, biological pathway and network we will identify the cooperative regulation of these genomic regions. We will map the intimal regulatory locus using Im1/Im3 double congenic mouse lines; perform genome-wide association mapping of the intima trait using the HMDP combined with SJLxC3H/F backcross; and establish intima regulatory networks based on deep sequencing data in the Im1/Im3 congenic mouse lines.

**Lab Members**

- Ryan Burke – Postdoc
- Chao Xue, Graduate Student
- Amy Mohan – Senior Technical Associate
- Elaine Smolock – Research Asst. Professor
- Mark Sowden – Research Assoc. Professor
- Yingqian Xu – Laboratory Technician
- Martha Zettel – Technical Associate
**Publications**

**Project 1 Fluid Shear Stress and Endothelial Biology**


**Project 2 Cyclophilin A and Pulmonary Hypertension**


Zheng-Gen Jin, Ph.D.

Synopsis

Atherosclerosis, the formation of plaque inside arterial wall, is the leading cause of death and disability in the United States and throughout the world. Atherosclerotic lesions develop in the regions of curvature, bifurcation, and branching of vessels, where fluid shear stress is low. In contrast, steady laminar flow associated with high fluid shear stress within the large straight arteries is atheroprotective.

Our research goal is to elucidate the molecular mechanisms of atherosclerosis and to identify the key molecules and signal pathways in the atheroprotective programs of laminar flow. Our recent studies have demonstrated that histone deacetylase 5 (HDAC5) plays an important role in regulation of laminar flow-sensitive genes. Current projects focus on exploring the mechanisms by which HDAC5 and other chromatin-modifying enzymes control gene transcription in vascular endothelial cells in response to laminar flow. Our studies may provide insights into the pathogenesis of atherosclerosis and lead to the development of new therapies to prevent/treat atherosclerotic disease.

Lab Members

• Marina Koroleva – Laboratory Technician
• Michael Mastrangelo – Tech Associate
• Suowen Xu – Postdoctoral Associate
• Ying Yang – Postdoctoral Associate
• Meimei Yin – Postdoctoral Associate

Publications


Figure: Hind limb ischemia is more severe in the absence of Gab1 from endothelial cells.
Vyacheslav Korshunov, Ph.D.

Synopsis

Understanding the mechanisms that regulate the structure of blood vessels will decrease cardiovascular morbidity and mortality in humans. My current research focuses on immune mechanisms of cardiovascular disorders that affect vascular remodeling.

My laboratory research has three programs:

1. We are working on a project that explores the role of Axl, a receptor tyrosine kinase, in regulation of the immune responses in hypertension. Using state-of-the-art flow cytometry techniques we found that expression of Axl affected accumulation of leukocytes in the kidneys and determined pathogenesis of early phase of deoxycorticosterone-acetate and salt hypertension in mice. We showed that Axl regulates reactive oxygen species production in kidney's leukocytes in hypertension (brown staining, Figure).

2. We study genetic mechanisms that lead to differences between physiological and pathological carotid artery remodeling. We discovered a new candidate gene that regulates arterial rigidity and arterial stenosis; we are currently defining the pathway through which this novel gene regulates remodeling.

3. We used a combined genetic approach of genome-wide linkage and association analyses to identify a novel locus on mouse chromosome 7 that controls elevated heart rate. We are studying candidate genes within chromosome 7 locus that control hemodynamic parameters and vascular inflammation.

Lab Members

- Alex Xia - Postdoctoral Associate
- Kathy Donlon - Laboratory Technician

Publications


role of redox-dependent association of Axl with non-muscle myosin IIB. *Hypertension* 2010;56(1):105-11.


**Project 2 publications**


**Project 3 publications**


Coeli Lopes, Ph.D.

Synopsis

We study the regulation of ion channels by diverse G-protein signaling pathways in normal and pathological states.

One major focus of our current work is the changes in function and regulation of cardiac ion channels that cause the most common form of inherited cardiac arrhythmia, Long QT syndrome. Our work translates channel dysfunction and dysregulation at the cellular level to clinical phenotype and patient’s response to treatment. A second focus of our current research is the study of pathological remodeling of the slow delayed rectifier-like current (IKs) in heart failure. Our current research focus on stress signals caused by chronic stimulation of kinase signaling pathways, and their consequence for ion channel function and membrane trafficking. We explore novel antiarrhythmic treatments to reverse IKs pathological remodeling during heart failure.

Lab Members

Elsa Ronzier, Ph.D., Postdoctoral Associate
Xiaorong Parks, Ph.D., Staff Scientist

Publications


Figure: Schematic of mutations in KCNQ1 ion channel.
Charles J. Lowenstein, M.D.

Synopsis

Venous thromboembolism (VTE) is a major cause of morbidity and mortality, with an annual incidence of over 900,000 in the USA. Elevated plasma levels of Von Willebrand factor (VWF) are a risk factor for venous thrombosis, but the genetic factors that regulate VWF levels are not well understood.

VWF is a glycoprotein that mediates platelet adhesion to the vascular wall and also platelet aggregation with other platelets. VWF is synthesized by endothelial cells and platelets, stored inside intracellular granules, and then released into the blood by a process called exocytosis.

The overall goal of my lab is to understand pathways of exocytosis in the human vasculature. Our general approach is to use genetic studies of humans to identify gene products that are potential regulators of exocytosis, and then to use cells and mice to characterize the role of these candidates in exocytosis.

We identified several key components of the exocytic machinery in endothelial cells, including VAMP8, SNAP23, and STX4. We then characterized the molecular motor, NSF, that controls endothelial secretion. Next, we found that nitric oxide regulates endothelial exocytosis.

We are currently using genome-wide association studies to identify novel regulators of exocytosis. For example, a recent genome wide association of patients with altered VWF levels identified 6 novel genetic loci. We are now studying the candidate genes within these loci, and determining how mutations affect their expression and function.

These approaches will increase our understanding of endothelial pathways that increase the risk of diseases such as venous thromboembolism, and they will identify new therapeutic targets for the prevention and treatment of thromboembolic diseases.

Figure: Endothelial cells grown on a defined matrix express granules containing VWF (red).

Lab Members

- Maria de la Luz Garcia-Hernandez – Senior Associate
- Michael Lomonaco – Technical Associate
- Qiuyu (Martin) Zhu – Graduate Student

Publications


Joseph Miano, Ph.D.

Synopsis

The notion of “junk DNA” has been debunked with the realization that the human genome is punctuated with millions of regulatory codes and undergoes pervasive transcription, particularly with respect to the emerging class of long noncoding RNA (lncRNA) genes, which already outnumber all protein-coding genes. Most of the so called “dark matter” in our genome is, from a functional standpoint, poorly characterized. Moreover, most sequence variations associated with human diseases fall within genomic dark matter. Thus, there is urgent need to elucidate the function (or dysfunction) of the estimated 2.4 billion nucleotides of human sequences once thought to be genomic refuse.

The Miano Lab uses tools in bioinformatics and genomics to elucidate functional regulatory elements and lncRNA genes that effect transcriptional and post-transcriptional regulation of gene expression, especially as they relate to vascular smooth muscle cell (VSMC) differentiation. For example, we have computationally defined over 3.6 million regulatory elements called CArG boxes that bind the SRF transcription factor. This so-called CArGome has allowed for the discovery of over 140,000 CArG-SNPs, many of which appear to effect neighboring gene expression. We have started to validate these elements and sequence variants therein using next generation sequencing assays (RNA-seq and ChIP-seq) coupled to conventional luciferase, gel shift, and ChIP experiments. The goal of what we refer to as the CArG Variome Project is to pinpoint CArG-SNPs within haplotype blocks linked to human diseases.

The CArGome initiative has also led us to delve deep into the world of lncRNA genes. Accordingly, we have been mining the human genome for unannotated IncRNA genes, and we recently published the first novel, human vascular cell-restricted IncRNA called SENCR. This IncRNA appears to fine tune the program of vascular smooth muscle cell gene expression including that of Myocardin (MYOC) which we first showed functions as a molecular switch for the smooth muscle cell differentiation program. Recent RNA-seq experiments have uncovered numerous Myocardin-dependent IncRNA genes, some of which are highly enriched in vascular smooth muscle. We are in the process of working up new and recently annotated IncRNA genes using modern tools in molecular biology, biochemistry, genetics, and cell biology.

Another focus of the lab is utilizing the revolutionary CRISPR/Cas9 system of genome editing to engineer mice carrying precision-guided mutations in key CArG elements or clinically relevant CArG-SNPs or deletions of conserved IncRNA genes.

In summary, work in the Miano Lab spans the gamut from computer to cell to genetically-altered mouse models in order to understand noncoding sequences (e.g., CArG boxes and IncRNA genes) and variant sequences therein that are associated with, but not limited to, cardiovascular disease.
Lab Members

- Christine Christie, Lab Technician
- Bing Guo, Postdoctoral Associate
- Yu Han – Staff Scientist
- Pengtao Jiang – Postdoctoral Associate
- Orazio Slivano – Technical Associate

Publications


Craig Morrell, D.V.M., Ph.D.

Synopsis

My lab focuses on the role of platelets in vascular inflammation and platelet regulation of immune responses. Platelets are best known as the cellular mediator of thrombosis, but platelets also have a major role in the initiation and regulation of inflammation and immune responses. An understanding of platelets in immunity is rapidly expanding and our lab is a leader in this field. We have discovered that platelets play a central role in innate immune responses. We found that platelets also control the development of acquired immune cells, including T-helper cell differentiation and B cell development. This places platelets at the center of inflammatory processes that have a direct effect on vascular disease such as atherosclerosis, myocardial infarction and transplant rejection. We have recently identified a novel platelet mediated mechanism for the regulation of T-helper cell development and differentiation. Using mouse models of cardiac transplantation we have demonstrated that the platelet derived chemokine PF4/CXCL4 limits the T-helper 17 (Th17) type of CD4+ T-cell response. We are now actively expanding this work to determine how platelets and PF4 interact with developing T helper cells and the signaling mechanisms involved in PF4 limiting Th17 differentiation. We have now identified novel mechanisms for PF4 mediated B cell development that is now being actively pursued.

Our lab is also investigating the role of platelets in myocardial infarction responses. We have discovered unique mechanisms for platelet activation in the ischemic myocardial tissue that leads to inflammation and infarct expansion. We have recently shown that ERK5 is an ‘ischemic sensor’ in platelets that is activated following myocardial infarction. We have also found that platelet protein expression is different pre and post myocardial infarction in an ERK5 dependent manner, indicating that ERK5 has a central role in regulating platelet responses in ischemic environments. This presents a novel pathway to limit platelet responses following heart attack or stroke to preserve organ function that we are actively exploring.

Figure: Megakaryocytes staining green in mouse bone marrow.

Lab Members

- Angela Aggrey – Postdoctoral Associate
- Lesley Chapman – Graduate Student
- David Field – Laboratory Technician
- Kyung Ae Ko – Technical Associate
- Deanne Mickelsen – Technical Associate
- Sara Ture – Laboratory Technician

Publications


Figure. PF4⁻/⁻ mice have severe graft vasculopathy. WT and PF4⁻/⁻ mice were given BM12 heart allografts and transplants harvested 35 days later. PF4⁻/⁻ mice have extensive leukocyte and neutrophil infiltrates.
Jinjiang Pang, Ph.D.

Synopsis

Angiogenesis, the formation of new blood vessels from existing ones, is a critical event for tissue development and repair, as well as being associated with many diseases (e.g. bronchopulmonary dysplasia, pulmonary artery hypertension, ischemic cardiomyopathy, retinopathy and tumor growth).

The long-term goal of our lab is to identify the critical targets that regulate angiogenesis under physiological and pathological conditions. We also focus on molecular mechanisms involved cardiac metabolism.

Current project goals are to:

1. Define the role of Dll4-Notch signaling in postnatal lung vasculature development and lung vascular diseases.
2. Determine the therapeutic effect of a cell permeable Ankyrin repeat peptides on prostate cancer.
3. Determine the molecular mechanisms involved in mitochondrial biogenesis during cardiac development and diseases.

Lab Members

- Lin Gao, Postdoctoral Associate

Publications


Figure: Imaging shows reduced vasculature in lungs of GIT1 KO mice.
Eric Small, Ph.D.

Synopsis

The transition to heart failure (HF) following an initial insult is partially caused by the development of cardiac fibrosis. Fibrosis is a form of scarring that increases the rigidity of muscular tissue, decreases cardiac contractility and can lead to lethal arrhythmias. Cardiac fibrosis arises from the aberrant and persistent stimulation of fibroblasts, the main source of extracellular matrix in the heart, in a pathological attempt to repair damaged tissue. Although current therapeutic strategies improve contractility by targeting the cardiomyocyte, without a complementary approach to block or reverse the development of fibrosis and regenerate functioning myocardium, treatment options often represent a bridge to cardiac transplantation.

The Small Lab uses mouse genetics, cell biology and biochemical approaches to define the molecular mechanisms that control fibroblast plasticity and progenitor cell differentiation during development and disease with the ultimate goal of developing novel therapeutic approaches to block or reverse the progression of HF. The first focus of my lab revolves around our recent finding that cardiac fibroblasts exhibit distinct gene expression programs (GEP) in physiological (exercise training/sustained cardiac function) versus pathological (disease states/deterioration of cardiac function) remodeling. We are currently using mouse genetics and cell biological approaches to test the hypothesis that some genes that are expressed in fibroblasts specifically during exercise might abrogate the development of cardiac fibrosis. A related project is aimed at identifying novel small molecules that might block pathological fibroblast activation and the development of cardiac fibrosis.

The second major focus my lab is aimed at defining the gene regulatory mechanisms leading to the mobilization and differentiation of an important population of cardiovascular progenitors, called epicardium-derived progenitor cells (EPDCs). EPDCs give rise to fibroblasts and perivascular cells in the embryo and can repopulate damaged myocardium in the adult. We have recently found that Myocardin-related transcription factors drive EPDC motility, pericyte differentiation and coronary vessel maturation. This study is expected to accelerate the development of strategies to stimulate progenitor cell mobilization for neovascularization and cardiac regeneration.

Taken together, our lab is well positioned to define the cellular and molecular mechanisms that regulate cardiac progenitor cell differentiation and fibroblast plasticity and use this knowledge to devise novel and innovative therapeutic strategies to reduce cardiac fibrosis and promote regeneration in HF patients.

Figure: Epicardium-derived cells undergoing epithelial-mesenchymal transition (EMT) exhibit Vinculin-positive focal adhesions (green) and smooth muscle actin-positive stress fibers (red).

Lab Members

- Ron Dirkx – Technical Associate
• Janet Lighthouse – Postdoctoral Associate
• Michael Trembley – Graduate Student
• Lissette Velasquez– Technical Associate

Publications

Figure: Epicardium-derived cells (green) undergoing EMT and migrating into the compact myocardium in the developing heart. Endothelial cells are stained with PECAM1 (red).
Jane Sottile, Ph.D.

**Synopsis**

Fibrosis is a progressive and often fatal disease that can develop in many organs, including the heart, liver, skin, lungs, and kidneys. During fibrosis, there is abnormal accumulation of proteins in the tissues, which contributes to impaired organ function. The goal of our research is to understand the processes that control the development of fibrosis, and to develop reagents to inhibit the progression of fibrosis.

The major goal of my laboratory is to determine the mechanisms that regulate extracellular matrix (ECM) remodeling, and the role of fibronectin in promoting ECM remodeling. ECM remodeling plays an important role in a number of pathologies, including vascular remodeling following arterial injury, and fibrosis.

My laboratory has discovered that the deposition and polymerization of fibronectin into the ECM plays an important role in regulating ECM remodeling in vitro and in vivo. We have been exploring both the mechanisms by which fibronectin regulates ECM remodeling, as well as the physiological consequences of fibronectin-dependent ECM remodeling. We and others have shown that the polymerized form of fibronectin has distinct functions from the soluble form of fibronectin, and can trigger distinct intracellular signaling pathways. Our data show that the pUR4 fibronectin polymerization inhibitor blocks many processes that contribute to vascular remodeling and fibrosis, including excess deposition of type I collagen, inflammation, cell migration, and cell growth. In addition, our in vivo data show that pUR4 administration can inhibit vascular remodeling, cardiac fibrosis, and liver fibrosis. We are currently investigating the mechanisms by which fibronectin inhibitors block pathologic ECM remodeling and attenuate inflammation.

**Lab Members**

- Allison Hendershot – *Lab Technician*
- Feng Shi – *Staff Scientist*
- Mary Wines-Sameulson – *Staff Scientist*

**Publications**


4. Shi, F., and Sottile, J. 2011 MT1-MMP regulates the turnover and endocytosis of


Mark B. Taubman, M.D.

Synopsis

My laboratory investigates the role of vascular smooth muscle cells (SMC) in regulating inflammation and thrombosis in the arterial wall. Current projects include:

1. **The regulation of tissue factor expression.** Tissue factor, the initiator of coagulation, is highly regulated by growth factors in SMC and is induced in the arterial wall after balloon injury. Ongoing studies involve the regulation of tissue factor expression in SMC culture and the regulation of tissue factor expression and activity in the injured vessel wall and in animal models of atherosclerosis. Recent data has shown that tissue factor can be released from the cell wall in microparticles and that these particles retain the ability to activate coagulation. In addition, there is an alternatively spliced form of tissue factor that is soluble and circulates in the blood. We are defining the role of these forms of circulating tissue factor in mediating arterial thrombosis using mice with tissue-specific tissue factor deletions and mice expressing only full-length or alternative-spliced forms of tissue factor.

2. **Mechanisms controlling MCP-1 expression.** Monocyte chemotactic protein 1 (MCP-1 or CCL2) encodes a monocyte chemoattractant that, like tissue factor, is regulated by growth factors in SMC culture and in the vessel wall after balloon injury. Ongoing studies involve examination of MCP-1 regulation in cell culture and in animal models of arterial disease. A particular focus has been the regulation of MCP-1 mRNA stability by PDGF and glucocorticoids. Studies are focused on identifying the proteins and signaling pathways that regulate MCP-1 mRNA stability. Such studies may provide novel approaches to attenuate the inflammatory process.

3. **The role of EGLN3 in muscle cell differentiation and cardiac ischemia.** EGL9 homolog 3 (EGLN3 or PHD3) encodes an intracellular prolyl hydroxylase that regulates the response of cells to hypoxia. We have recently determined that EGLN3 also plays a key role in muscle cell differentiation and are currently exploring the mechanism underlying this finding. Studies are ongoing to elucidate the function of this gene using muscle cell cultures and by generating an EGLN3 knockout mouse. EGLN3 is also being analyzed using in vitro and in vivo models to examine its regulation in response to ischemia.
Lab Members

- Jian Fu – Research Asst. Professor
- Bin Liu – Research Asst. Professor
- Michael Mastrangelo – Tech Associate

Publications


R. James White M.D., Ph.D.

Synopsis

Pulmonary arterial hypertension (PAH) is a rare but devastating disease: five-year survival is dismal, and patients often die from decompensated right ventricular (RV) failure. Effective medical therapies are needed – but therapeutic advances will require a more advanced understanding of pulmonary vascular remodeling and of RV failure.

Since human lung tissue is not available until transplant or autopsy, new mechanistic insight into PAH requires rigorous animal models with high fidelity to human disease. Over the last 10 years, we have developed a novel rodent model involving pneumonectomy and hypoxia which causes severe PAH and RV dysfunction. This model displays all the features of advanced human PAH, including proliferative vascular cell lesions, extensive vascular pruning of the lung circulation, and decompensated RV failure. Our model is particularly useful for preclinical testing of new therapeutic compounds.

We are now using this model to develop new drugs for PAH, in collaboration with industry partners. Our first task is to understand how our model performs with FDA-approved drugs currently used in disease management. We have discovered the benefit of combination drug therapy over single agent therapy. We have also defined sex specific differences in responses to treatment. are also comparing treatment responses between the two sexes. Male animals are more ‘treatment resistant’ than female animals to a combination of oral therapy (ambrisentan and tadalafil); we are now measuring the male response to an advanced infusion therapy (treprostinil). Our advanced animal model has enabled discoveries that are highly relevant to preclinical drug research.

We are also using our models to develop drugs that target RV failure in the setting of PAH. The goal of our ex vivo working heart experiments is to measure the RV function (and dysfunction) which develops in the PAH animal under the carefully controlled conditions of the Langendorff model. We will vary preload, afterload, and metabolic substrates to understand pathways of RV dysfunction, and to test therapies that might improve RV performance and decrease RV injury in the setting of PAH.

Lab Members

- Deborah Haight – Lab Technician

Publications


7. Ferrantino M, White RJ. Inhaled treprostinil sodium for the treatment of


Figure: Effect on lung vasculature of tadalafil (left) and tadalafil and ambrisentan (right) in a rodent model of pulmonary artery hypertension.
Chen Yan, Ph.D.

**Synopsis**

The second messengers cAMP and cGMP contribute to both normal physiological functions and cardiovascular diseases. Cyclic nucleotide phosphodiesterases (PDEs) that catalyze the degradation of cAMP and cGMP are essential for maintaining homeostasis, compartmentalization, and specificity of cyclic nucleotides. Increasing evidence has indicated that alterations in the expression and activation of different PDEs cause a number of diseases, many of which have been found to be improved by pharmacologically targeting these PDEs. PDEs are a highly promising class of therapeutic targets for drug development. Thus, defining the specific PDE isoforms responsible for the pathological pathways in cardiovascular diseases is essential for developing novel therapeutic strategies.

Our research program focuses on elucidating the roles and underlying mechanisms of PDE activation or inhibition in cardiovascular diseases, particularly from the perspective of revealing new molecular targets for pharmacologic modulation of cyclic nucleotide signaling in the treatment of cardiovascular diseases. Two primary research areas in our laboratory include:

1. Vascular smooth muscle cell phenotypic modulation and vascular disorders, such as hypertension, intima/media thickening, atherosclerosis and aortic aneurysms; and
2. Pathological cardiac remodeling and heart failure.

For example, we have recently discovered that the PDE1C isozyme is selectively induced in neointimal proliferating smooth muscle cells (SMCs) in disease vessels but not in medial contractile SMCs of normal vessels. Induction of PDE1C is essential for SMC proliferation and migration and neointimal hyperplasia by promoting growth factor receptor stability.

**Lab Members:**

- Yujun Cai – Research Asst. Professor
- Walter Knight – Graduate Student
- Meiping Wu – Postdoctoral Associate
- Jian Xiong – Postdoctoral Associate
- Qian Zhou – Staff Scientist

Figure: Transgenic mouse with cardiac expression of PDE3A1 have myocardial hypertrophy with larger cardiac myocytes and larger hearts.


C. Training

Research Fellows at the CVRI

The CVRI faculty offer mentored research training to medical students, graduate students, and post-doctoral fellows. The CVRI is an outstanding environment for cardiovascular trainees. The CVRI is home to the NIH funded T32 Training Grant in Preventive Cardiology.

Research Fellows at the CVRI

- **Dr. Ryan M. Burke** is a research fellow in the laboratory of Dr. Bradford Berk. Dr. Burke received his Ph.D. from the University of Rochester, Rochester, New York. He studies the effect of tumor-associated macrophages on stromal collagen composition and invasiveness of breast carcinomas.

- **Dr. Bing Guo** is a research fellow in the laboratory of Dr. Joe Miano. Dr. Guo received his M.D. from Huazhong University of Science Tongji Medical College, Wuhan, P.R. China. Dr. Guo is studying noncoding RNA and next generation knockouts.

- **Dr. Janet Lighthouse** is a research fellow in the laboratory of Dr. Eric Small. Dr. Lighthouse received her Ph.D. from Stony Brook University, Stony Brook, New York. She studies novel genes involved in cardiac fibroblast plasticity during pathological remodeling.

- **Dr. Jiang Pengtao** is a research fellow in the laboratory of Dr. Joseph Miano. Dr. Pengtao received his Ph.D. from the Institute of Biophysics, Beijing, China. He studies the involvement of lysosomes in the apoptosis and autophagy in free fatty acids-loaded hepatocytes.

- **Dr. Elsa Ronzier** is a research fellow in the laboratory of Dr. Coeli Lopes. Dr. Ronzier received her Ph.D. from SUPAGRO Montpellier-BPMP, Montpellier, France. She studies genetic mutations that cause ion channel dysfunction and cardiac arrhythmias.

- **Dr. Meiping Wu, B. Med.** is a research fellow in the laboratory of Dr. Chen Yan. Dr. Wu received his Ph.D. from Shanghai University of TCM, Shanghai, China. He studies the mechanisms that underlie heart failure.

- **Dr. Jixiang Xia** is a research fellow in the laboratory of Dr. Slava Korshunov. Dr. Xia received his Ph.D. from the University of Central Florida, Orlando, Florida. His research experience is the development of molecular and cellular imaging tools to evaluate gene and cell based therapeutic strategies in vivo.

- **Jian Xiong, Ph.D.** is a research fellow in the laboratory of Dr. Chen Yan. He received his Ph.D. in molecular biology at Peking Medical College, Beijing, China. Dr. Xiong is studying the role and underlying mechanisms in pathological vascular remodeling and disease using in vitro and in vivo models.
• **Dr. Suowen Xu** is a research fellow in the laboratory of Dr. Zheng-Gen Jin. Dr. Xu received his Ph.D. from Sun Yat-sen University, Guangzhou, China. He studies the effect of atorvastatin on atherosclerotic plaque development in ApoE-/- mice and biochemistry of ADP-ribosylation.

• **Dr. Meimei Yin** is a research fellow in the laboratory of Dr. Zheng-Gen Jin. Dr. Yin received her Ph.D. from the University of Groningen Medical Center, Groningen, Netherlands. She studies the effects of anti-diabetic drugs upon cardiac remodeling.

• **Dr. Yishuai Zhang** is a research fellow in the laboratory of Dr. Chen Yan. Dr. Zhang received his Ph.D. in cardiovascular pharmacology at the School of Pharmaceutical Science of Center South University, Changsha, Hunan, P.R. China. Dr. Zhang is exploring the underlying role and underlying mechanism of cyclic nucleotide phosphodiesterase in pathologic cardiac remodeling and dysfunction.

**Graduate Students at the CVRI**

• **Leslie Chapman** is a predoctoral student in the laboratory of Dr. Craig Morrell. She received her B.S. from Duke University. She is studying the role of microRNA in the pathogenesis of malaria.

• **Walter Knight** is a predoctoral student in the laboratory of Dr. Chen Yan. He received his BS from Cornell University. He is studying the role of phosphodiesterase isoforms in cardiac hypertrophy.

• **Kristina Modjeski** is a predoctoral student in the laboratory of Dr. Craig Morrell. She received her BS from the University of Washington, Seattle and her MS from the University of Rochester Medical Center. She is studying the role of glutamate receptors and accessory proteins in the regulation of adaptive immunity.

• **Michael Trembley** is a predoctoral student in the laboratory of Dr. Eric Small. He is studying the role of epicardial cells in the regeneration of cardiac tissue.

• **Qiuyu (Martin) Zhu** is a predoctoral student working in the laboratory of Dr. Charles Lowenstein. He received his BCM and his MCM from Xi’an Jiaotong University, China. He is studying the regulation of endothelial exocytosis and vascular inflammation.
NIH T32 Research Training in Preventive Cardiology

The goal of this training program, funded by the National Institute of Health, is to train students and fellows to be investigators in risk factors that underlie cardiovascular disease. The program consists of 2 years of mentored research, course work that can lead to a Masters of Clinical Investigation or a Masters in Public Health, a seminar series, and a journal club. The program funds 4 graduate students and 6 postdoctoral fellows per year. Dr. Charles Lowenstein is the Principal Investigator and Dr. Robert Block is the Co-Director.

Research Fellows in NIH T32 Training Grant

- **Angela A. Aggrey, Ph.D.** is a research fellow in the laboratory of Dr. Craig Morrell. Dr. Aggrey received her Ph.D. from the University of Rochester, Rochester, New York. Her research experience is the novel protective role for platelet-mediated immune responses in murine experimental cerebral malaria.

- **David S. Auerbach, Ph.D.** is a research fellow working in the laboratory of Dr. Robert Dirksen, Professor, Pharmacology and Physiology. Dr. Auerbach received his M.S. at Case Western Reserve University, and his Ph.D. at SUNY Upstate Medical University, NY. He is studying genetic diseases that cause both brain seizures and cardiac arrhythmias.

- **Scott Cameron, M.D., Ph.D.** is a research fellow working in the laboratory of Craig Morrell, Ph.D., D.V.M. Dr. Cameron received his B.Sc. at the University of Edinburgh, Scotland; his M.S. in Pharmacology at the University of Rochester; his M.D. at SUNY Upstate Medical University; and his Ph.D. in Pharmacology at the University of Rochester. He is studying the role of platelets in myocardial infarction.

- **Yuriy Shapovalov, M.D., Ph.D.** is a research fellow in the laboratory of Wojciech Zareba, M.D., Ph.D., Director of the Heart Research Follow-up Program at URMC. He received his M.D. at Dnepropetrovsk Medical Academy, Ukraine and his Ph.D. in Neuroscience at the University of Rochester Medical Center. He is studying risks and treatment of sudden cardiac death.
D. Philanthropy

Richard T. Aab is an American entrepreneur and successful businessman. In 2007 he named the Aab Cardiovascular Research Institute with a $5 M gift. The Aab CVRI is grateful to Mr. Aab for his generosity and support.

In 1996, Mr. Aab co-founded and served as Chairman of US LEC Corp., a leading publicly owned telecommunications carrier based in Charlotte, NC, providing integrated voice, data and Internet services to medium and large businesses and enterprise organizations throughout the United States. US LEC served over 28,000 business customers in 115 markets, employed over 1,000 people and had annualized revenues of approximately $425 million in 2006. US LEC merged with PAETEC Corp., a privately owned leading telecommunications carrier in 2007. The combined entity, PAETEC Corp., serviced business customers in 84 of the 100 largest MSA’s, employed 5,000 people and had revenues of over $2.1 billion. Mr. Aab was Vice Chairman and a Director of the combined entity. PAETEC was acquired by Windstream Corp. on November 30, 2011 for $2.1 billion.

Prior to US LEC, Mr. Aab founded and was Chairman and Chief Executive Officer for 14 years of ACC Corp., a highly successful publicly owned telecommunications services company headquartered in Rochester, NY. ACC Corp. was acquired for over $1.1 billion in 1998 and is now part of AT&T. In 2001, Mr. Aab founded and served as Chairman of Ovation Payroll, Inc., a very successful privately held payroll solutions company headquartered in Rochester, New York. When it was acquired by Heartland Payment Systems in December 2012, the company employed approximately 160 people and had annualized revenues approaching $20 million.

Mr. Aab is a Trustee of the University of Rochester as well as a Member of the Board of Governors of the University’s Medical Center, and is the benefactor of its research facility the Aab Institute of Biomedical Sciences in, as well as the Aab Cardiovascular Research Institute, which was named in his honor in August 2007. Mr. Aab also serves as co-chairman of the University of Rochester Medical Center capital campaign whose mission is to raise $650 million for the institution.