Aab Cardiovascular Research Institute
University of Rochester Medical Center

Annual Report
July 2016

Table of Contents

A. Overview

From the Director

The Aab Cardiovascular Research Institute continues to expand: we have strengthened key research teams by hiring four new recruits in 2016.

The newest member of our Vascular Biology Team is Dr. Peng Yao, a new Assistant Professor who trained under Dr. Paul Fox in the Lerner Research Institute at the Cleveland Clinic Foundation. Dr. Yao studies pathways of translational repression that regulate gene expression. He discovered novel proteins that bind to RNA transcripts and control their translation during hypoxia. He joins our well established Vascular Biology Team that includes Dr. Zhang-Gen Jin, Dr. Joe Miano, Dr. Brad Berk, Dr. Jinjiang Pang, Dr. Slava Korshunov, Dr. Jane Sottile, and Dr. Charles Lowenstein.

We have also expanded our Cardiac Biology Team, hiring Dr. Doug Anderson, a new Assistant Professor who trained under Dr. Eric Olson at the University of Texas Southwestern. Dr. Anderson discovered a family of micropeptides that are encoded by long RNA transcripts previously thought not to encode proteins. This particular set of micropeptides regulate calcium signaling and muscle contractility, revealing a novel pathway of muscle regulation. Dr. Anderson joins our Cardiac Biology Team, that includes Dr. Chen Yan and Dr. Eric Small.

Our Platelet Biology Team has hired a new member, Dr. Scott Cameron. Dr. Cameron trained in the laboratory of Dr. Craig Morrell at the University of Rochester. He studies pathways of platelet activation during vascular stress. Dr. Cameron discovered a novel redox sensor in platelets that controls thrombosis. As a cardiologist in the Coronary Care Unit, Dr. Cameron also brings a translational perspective to the CVRI with numerous clinical studies of platelets in cardiovascular diseases. He joins our Platelet Biology Team that includes Dr. Craig Morrell and Dr. Charles Lowenstein.

We have expanded our Ion Channel Team as well. Our medical center is home to the world's largest and most prominent research program in sudden death, the Multicenter Automatic Defibrillator Implantation Trials (MADIT). We have expanded our CVRI translational research team that interacts with MADIT by hiring Dr. David Auerbach. He trained with Dr. José Jalife at the State University of New York and Dr. Lori Isom at the University of Michigan, before joining the lab of Dr. Robert Dirksen at the University of Rochester. As a new Assistant Professor, Dr. Auerbach has discovered a set of ion channel mutations that lead to both seizures and cardiac arrest. He joins our Ion Channel Biology Team that includes Dr. Coeli Lopes and collaborates with Dr. Robert Dirksen.

In addition to our new members hired this year, our recruits hired over the past 5 years have continued to develop their own research programs while expanding contacts throughout our larger research community.

Dr. Craig Morrell who was hired in 2010 leads our Platelet Biology Team. In addition to his research program in platelets and inflammation, he now works with Dr. Lowenstein in GWAS identification of novel regulators of thrombosis, with Dr. Scott Cameron on redox regulation of platelet activation, and with Dr. Sanjay Maggiwar of the Center for AIDS Research on Platelets and Neuroinflammation in AIDS. Dr. Morrell also leads our Animal Microsurgery Core.

Dr. Eric Small who was hired in 2011 has established a program in cardiac fibrosis. He also has a multiple investigator NIH grant with Dr. Richard Phipps of Environmental Science which explores pathways of multi-organ fibrosis, a pilot grant studying fibrosis in patients with mechanical assist devices in partnership with Dr. Jeffrey Alexis in the Division of Cardiology, and a multiple investigator NIH grant with Dr. Mario Delmar at the New York School of Medicine studying fibrosis in arrhythmogenic cardiomyopathy.

Our recruits old and new have enhanced our research programs in Vascular Biology, Cardiac Biology, Platelet Biology, and Ion Channel Biology, leading to new collaborations, new training opportunities, and new discoveries.

CVRI Facts Fiscal Year 2016

Personnel

Faculty		10
Research Faculty	3	
Postdoctoral Fellows	13	
Graduate Students	5	
Technical & Administrative Staff	24	

Scientific Publications

Publications Academic Year 2016: 37

Seminar Series Speakers

Richard Aab Cardiovascular Seminar Series: 12

B. Faculty Appointments

Faculty

Douglas Anderson, Ph.D.
Assistant Professor, Department of Medicine, Aab CVRI

David Auerbach, Ph.D.
Senior Instructor, Department of Medicine, Aab CVRI

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

Scott James Cameron, Ph.D., M.D.
Senior Instructor, Department of Medicine, Aab CVRI

***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.**
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

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

***Chen Yan, Ph.D.**
Associate Professor, Department of Medicine, Aab CVRI

Peng Yao, Ph.D.
Assistant Professor, Department of Medicine, Aab CVRI

**With tenure*

Research Faculty

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 Appointments

Adjunct Faculty

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

C. Our Research Labs

David S. Auerbach, PhD

Synopsis

Patients with inherited ion channel diseases develop electrical disturbances in the brain (seizures) and heart (arrhythmias) that can lead to sudden death. My lab explores the mechanisms for multisystem genetic ion channel diseases. I previously showed that in severe genetic forms of epilepsy, in addition to seizures, there are alterations in cardiac electrical function, with a high rate of cardiac arrhythmias. Arrhythmias provide one potential mechanism for the high rate of sudden death in epilepsy.

Now approaching these neuro-cardiac investigations in the opposite direction, I am assessing the co-prevalence and severity of seizures and cardiac arrhythmias in a classically studied cardiac disease, called Long QT Syndrome (LQTS.) LQTS is a genetic disease, characterized by cardiac electrocardiographic pathologies, arrhythmias, and a high risk of sudden death. Mutated genes in LQTS1-3 are expressed in the heart and brain, and seizures have been reported in LQTS patients. Ongoing studies using both LQTS patient registries and animal models of LQTS are being used to establish new clinical and mechanistic insights into this dual system disease, and the potential intricate crosstalk between the brain and heart.

The LQTS registry provides a unique and powerful resource to advance LQTS and epilepsy research. The Rochester-based LQTS Registry is the largest (>18,000 subjects) and most deeply annotated LQTS database in the world. It contains detailed clinical and genetic information from LQTS patients, plus affected and unaffected family members. It offers temporal resolution of the disease progression, including the dates of seizures, syncope, arrhythmias, start/end of medications, sudden death, and records/results from clinical and genetic tests.

Rabbits carrying the same mutation as LQTS2 patients with seizures, and state of the art *in vivo/in vitro* techniques (e.g., radiotelemetry ECGs & single cell electrophysiology), provide excellent tools to interrogate direct vs. indirect mechanisms for the neuro-cardiac disease manifestations and progression.

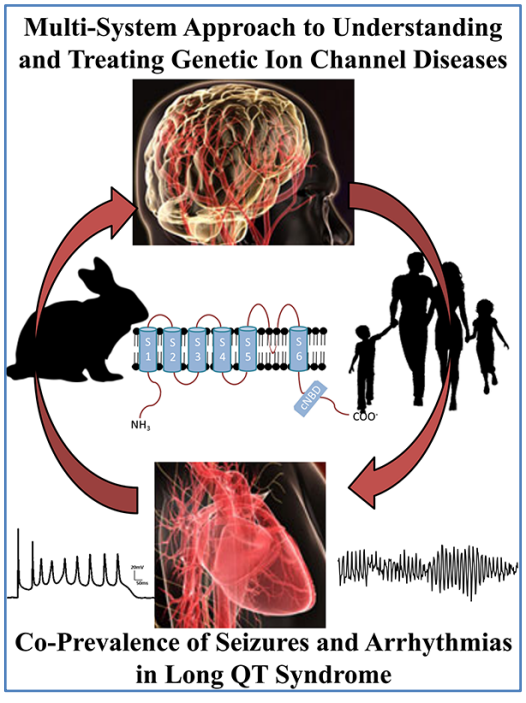
Project 1: Co-prevalence, severity, and disease progression of seizures and arrhythmias in LQTS patients.

Project 2: Pro- vs. anti-arrhythmic effects of anti-epileptic drugs in LQTS patients.

Project 3: Heart rate and QT variability parameters as biomarkers for arrhythmias and seizures in LQTS patients.

Project 4: Construction of the first knockin rabbit model of LQTS2 to investigate the direct vs. indirect mechanisms for seizures and cardiac arrhythmias.

a) Quantification of the LQTS2 mutant gene/protein expression patterns in the hearts and brains of WT and LQTS2 rabbits.
b) Effects of a LQTS2 mutation on single myocyte and whole heart electrophysiological properties.
c) Conscious *in vivo* simultaneous video/EEG/ECG recordings to investigate the incidence, dynamics, and types of seizures and arrhythmias in LQTS2 rabbits



Lab Members

- Samuel Kashtan – Project Assistant

Publications

1. **AUERBACH DS**, McNitt S, Gross RA, Zareba W, Dirksen RT, Moss AJ. Genetic Biomarkers for the Risk of Seizures in Long QT Syndrome. Neurology. July 27 2016. doi 10.1212/WNL.0000000000003056. PubMed ID: 27466471
2. Carrell S, **AUERBACH DS**, Dirksen RT, Thorton C Dmpk Gene Deletion or Antisense Knockdown Does Not Compromise Cardiac or Skeletal Muscle Function in Mice. Human Molecular Genetics. 2016 *In Press*
3. Stables CL, **AUERBACH DS**, Whitesall SE, D'Alecy LG, Feldman EL. Differential impact of type-1 and type-2 diabetes on control of heart rate in mice. Auton Neurosci. Jan 2016. doi: 10.1016/j.autneu.2015.12.006. PubMed PMID: 26725752.
4. Lin X, O'Malley H, Chen C, **AUERBACH D**, Foster M, Shekhar A, Zhang M, Coetzee W, Jalife J, Fishman GI, Isom L, Delmar M. Scn1b deletion leads to increased tetrodotoxin-sensitive sodium current, altered intracellular calcium homeostasis, and arrhythmias in murine hearts. J Physiol. March 2015. doi: 10.1113/jphysiol.2014.277699. PubMed PMID: 25772295.
5. **AUERBACH DS**, Jones J, Clawson BC, Offord J, Lenk GM, Ogiwara I, Yamakawa K, Meisler MH, Parent JM, Isom LL. Altered Cardiac Electrophysiology and SUDEP in Dravet Syndrome. PLoS One, October 14, 2013, 8(10): e77843. PMID: 24155976
6. Milstein ML, Musa H, Balbuena DP, Anumonwo JMB, **AUERBACH DS**, Furspan PB, Hou L, Hu B, Schumacher SM, Vaidyanathan R, Martens JR, Jalife J. Dynamic Reciprocity of Sodium and Potassium Channel Expression in a Macromolecular Complex Controls Cardiac Excitability and Arrhythmia. PNAS 2012 April 16: 109 E2134-E2143. PMID: 22509027
7. Noujaim SF, Kaur K, Milstein M, Jones JM, Furspan P, Jiang D, **AUERBACH DS**, Herron T, Meisler MH, Jalife J. A null mutation of the neuronal sodium channel Nav1.6 disrupts action potential propagation and excitation-contraction coupling in the mouse heart. FASEB January 2012 26:63-72. PMID: 21948246
8. **AUERBACH DS**, Jalife J. “Substrates and Triggers for the Initiation of Arrhythmias” Physiology News. Winter 2011. 85: 15–17
9. **AUERBACH DS**, Grzęda KR, Furspan PB, Sato PY, Mironov S, Jalife J “Structural Heterogeneity Promotes Triggered Activity, Reflection and Arrhythmogenesis in Cardiomyocyte Monolayers”. J. Physiology 2011 May 1: 589(9) 2363-81. PMID: 21486795

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:

Project 1: The mechanisms by which the biomechanical force generated by blood flow (shear stress) contributes to CVD. When blood flow is turbulent or disturbed (d-flow) there is a predilection for endothelial dysfunction and atherosclerosis. 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 by blood flow and modulate atherosclerosis. Of the 13 PB1 domain proteins in the human genome, 7 play a role in the biomechanical transduction pathway. S-flow stimulates an atheroprotective pathway that involves MEKK3 (PB1)-MEK5(PB1)-ERK5-KLF2. We showed that PKCz inhibited the pathway by phosphorylating ERK5. 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 hypertension. We are currently studying the downstream mechanisms responsible for these phenotypes and developing reagents to inhibit these proteins.

Project 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 the pro-inflammatory and pro-apoptotic effects of CypA. Based on our previous work it is logical that CypA would be a potential pathogenic mediator of PAH. We found a 2-fold increase in circulating CypA in patients with PAH. CypA expression is enhanced in lungs of PAH patients. To strengthen our hypothesis that CypA is a novel mediator of PAH, we generated cell-specific CypA over-expressing transgenic mice (ecCypA-tg and smcCypA-tg). The exciting result was the EC specific ecCypA-tg mice developed pulmonary hypertension at 3 months of age. We are now investigating the role of extracellular (eCypA) as a novel mediator of PAH based on two mechanisms: vascular remodeling and inflammation.

Project 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 (*Im*1 on chromosome 2, *Im*2 on chromosome 11 and *Im*3 on chromosome 18, that regulate intimal thickening. We found using congenic mice that genomic material on *Im*1 and *Im*3 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 *Im*3, 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 *Im*1 and *Im*3 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

- Chao Xue, Graduate Student
- Mark Sowden – Research Assoc. Professor
- Martha Zettel – Technical Associate

Publications

Project 1: Fluid Shear Stress and Endothelial Biology

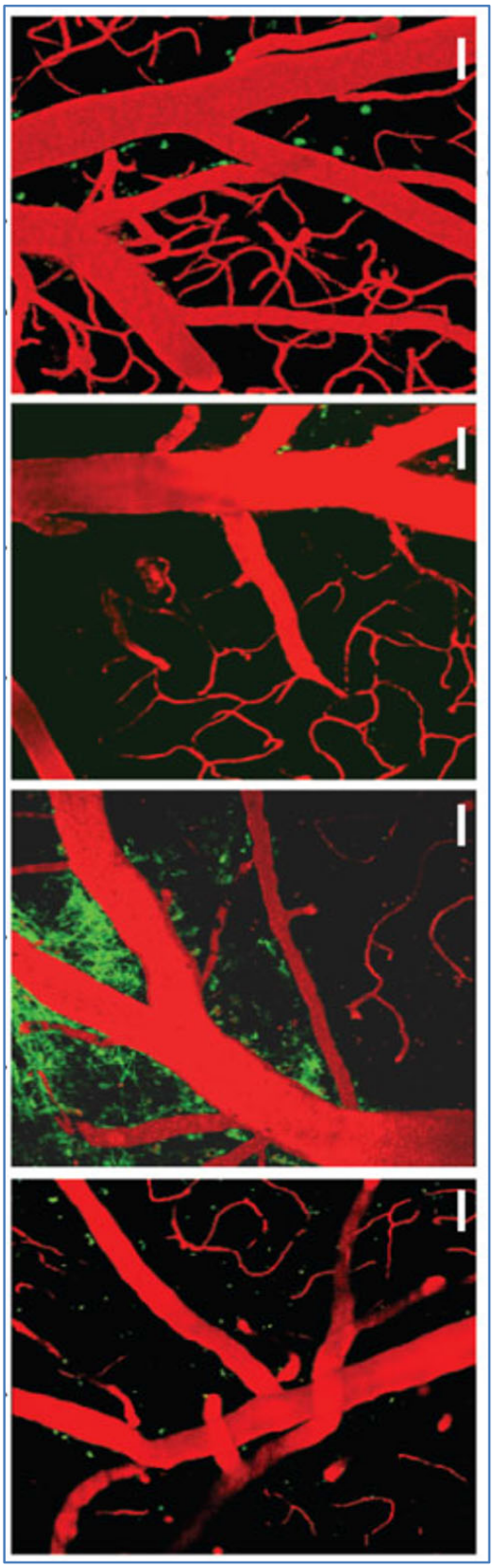
1. Nigro P, Abe J, Woo CH, Satoh K, McClain C, O'Dell MR, Lee H, Lim JH, Li JD, Heo KS, Fujiwara A, Berk BC. PKCzeta decreases eNOS protein stability via inhibitory phosphorylation of ERK5. *Blood;* 2010, 116:1971-1979.
2. Heo KS, Lee H, Nigro P, Thomas T, Le NT, Chang E, McClain C, Reinhart-King CA, King MR, Berk BC, Fujiwara K, Woo CH, Abe J. PKCζ mediates disturbed flow-induced endothelial apoptosis via p53 SUMOylation. J Cell Biol. 2011;193:867-84.
3. Kim GY, Nigro P, Fujiwara K, Abe J, Berk BC. p62 binding to protein kinase C ζ regulates tumor necrosis factor α-induced apoptotic pathway in endothelial cells. Arterioscler Thromb Vasc Biol. 2012;32:2974-80.
4. Abe J, Berk BC. Atheroprone flow activation of the sterol regulatory element binding protein 2 and nod-like receptor protein 3 inflammasome mediates focal atherosclerosis. Circulation. 2013 Aug 6;128(6):579-82.
5. Spindel ON, Burke RM, Yan C, Berk BC. Thioredoxin-interacting protein is a biomechanical regulator of Src activity: key role in endothelial cell stress fiber formation. Circ Res. 2014 Mar 28;114(7):1125-32.

Project 2: Cyclophilin A and Pulmonary Hypertension

1. Satoh, K., Nigro, P., Matoba, T., O'Dell, M.R., Cui, Z., Shi, X., Mohan, A., Yan, C., Abe, J., Illig, K.A. & Berk, B.C. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. Nat Med 15, 649-656 (2009).
2. Nigro P, Satoh K, O'Dell MR, Soe NN, Cui Z, Mohan A, Abe J, Alexis JD, Sparks JD, Berk BC. Cyclophilin A is an inflammatory mediator that promotes atherosclerosis in apolipoprotein E-deficient mice. J Exp Med. 2011 Jan 17;208(1):53-66. Epub 2010 Dec 20. PMID: 21173104 8.
3. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, Holtzman DM, Betsholtz C, Armulik A, Sallstrom J, Berk BC, Zlokovic BV. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature. 2012 May 16;485(7399):512-6. PMID: 22622580
4. Soe NN, Sowden M, Baskaran P, Kim Y, Nigro P, Smolock EM, Berk BC. Acetylation of cyclophilin A is required for its secretion and vascular cell activation. Cardiovasc Res. 2014 Mar 1;101(3):444-53.
5. Wang L, Soe NN, Sowden M, Xu Y, Modjeski K, Baskaran P, Kim Y, Smolock EM, Morrell CN, Berk BC. Cyclophilin A is an important mediator of platelet function by regulating integrin αIIbβ3 bidirectional signalling. Thromb Haemost. 2014 May 5;111(5):873-82.

Project 3: Genetics of Intima Formation

1. Smolock EM, Korshunov VA, Glazko G, Qui X, Gerloff J, and Berk BC. Ribosomal protein L17, RpL17, is an inhibitor of vascular smooth muscle growth and carotid intima formation. Circulation. 2012,126: 2418-2427. PMID: 23065385.
2. Pang J, Xu X, Wang X, Majumder S, Wang J, Korshunov VA, Berk BC. G-protein-coupled receptor kinase interacting protein-1 mediates intima formation by regulating vascular smooth muscle proliferation, apoptosis, and migration. Arterioscler Thromb Vasc Biol. 2013 May;33(5):999-1005.
3. Smolock EM, Machleder DE, Korshunov VA, and Berk BC. Identification of a genetic locus on chromosome 11 that regulates leukocyte infiltration in mouse carotid arteries. Arterioscler Thromb Vasc Biol. 2013, 33: 1014-1019. PMID: 23448970.
4. Smolock EM, Burke R, Wang F, Batchu SN, Qui X, Thomas T, Zettel M, Fujiwara K, Berk BC, and Korshunov VA. Intima modifier locus 2 controls endothelial cell activation and vascular permeability. *Physiological Genomics*, 2014.



Scott Cameron, M.D., Ph.D.

Synopsis

Platelets are small anucleate blood particles which play an important role in thrombosis, hemostasis, and inflammation. Patients with ischemic and thrombotic disease of the coronary and peripheral vasculature are treated with anti-platelet drugs, yet some patients do not derive benefit from these drugs or they experience unexpected, off-target adverse events.

We aim to better define platelet function in disease states, paying particular attention to post-receptor signal transduction pathways. Our overall goal is to evaluate gaps in clinical care, then identify viable signaling pathways in human tissue for drug intervention, and finally to utilize animal models to test the hypothesis.

Project 1: The role of platelet ERK5 in myocardial infarct expansion. We recently identified a novel role for the protein ERK5 (also known as Big Map Kinase 1), a MAPK family member which is expressed in human and murine platelets. We discovered that ERK5 regulates platelet activation, heart function, and scar size after a heart attack. We found that ERK5 changes the expression of platelet proteins during ischemia. We are now collaborating with colleagues in protein biochemistry at Johns Hopkins to identify platelet ERK5 targets with a highly-sensitive mass spectrometer. Since ERK5 is exquisitely sensitive to reactive oxygen species, our observations have important implications for ischemic diseases such as heart attack, stroke, and peripheral vascular disease.

Project 2: The role of platelets in the progression of peripheral vascular disease. We have discovered that atherosclerosis and ischemia in mice and in humans dramatically changes platelet protein expression, altering the activation state of the platelet and the risk for thrombosis. We are now characterizing the platelet signaling pathways which are activated in conditions of acute and chronic ischemia. We are working with our colleagues in vascular surgery and will characterize these signaling pathways in patients with peripheral vascular disease (chronic limb ischemia, chronic venous insufficiency, and aortic aneurysms). This will allow us to determine which medications will be most efficacious in controlling these vascular diseases.

Project 3: The role of platelet gap junction proteins in thrombosis. Platelets contain gap junction proteins which may be important for platelet activation and thrombosis. Gap junction proteins mediate physical communication and exchange of cellular material between cells. We recently developed an assay which can assess communication between mouse and human platelets, and we have already observed that some drugs modulate this communication. Using a mouse model which is deficient in a gap junction protein, we found that thrombosis and platelet activation are altered after myocardial infarction. This project has the potential to develop new anti-platelet medications for myocardial infarction, stroke, and peripheral vascular disease.

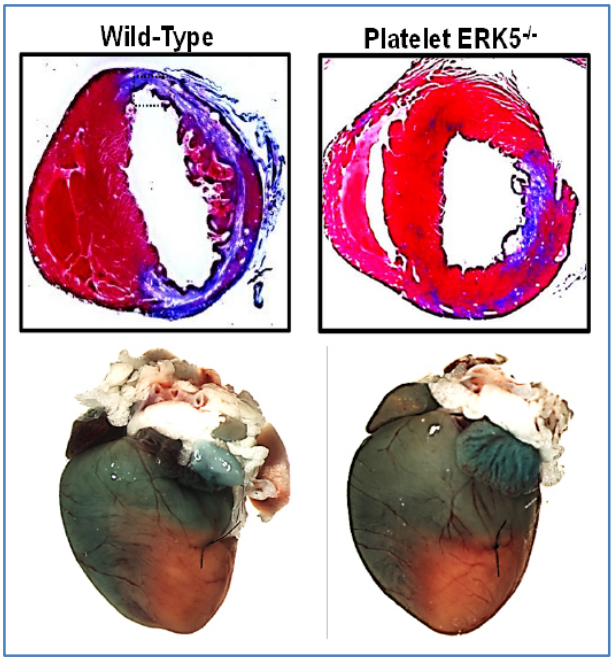


Figure: (Top) Size of myocardial infarction is smaller in mice lacking ERK5 in platelets, as shown by Masson trichrome stain for fibrosis in cross section of hearts. (Bottom) Ischemic area at risk in hearts is similar. Ischemic area at risk is red, perfused region is blue.

Publications

1. Cameron SJ, Morrell CN, Bao C, Lowenstein CJ. A Novel Anti-inflammatory Function for High Density Lipoprotein. *PLOS One*. 2015 Dec 17;10(12).
2. Cameron SJ, Ture SK , Modjeski KL, Mickelsen D, Chakrabarti E, Seaberry M, Field DJ , Le N, Abe J, Morrell, CN. Platelet ERK5 is a Redox Switch and Triggers

Maladaptive Platelet Responses and Myocardial Infarct Expansion. *Circulation*. 2015 Jul 7;132(1):47-58
3. Cameron SJ, Laskurain E, Holcman K, Richeson JF, Mieszczanska H. Treacherous Travelers: thrombi. *Am J Med.* 2015 Jul;128(7):695-8
4. Cameron SJ, Usama D, Block R. A case of abdominal pain with dyslipidemia: difficulties diagnosing cholesterol ester storage disease *Eur Rev Med Pharmacol Sci.* 2015 Jul;19(14):2628-33.
5. Cameron, SJ. Vascular Medicine: the eye cannot see what the mind does not know. *JACC*. 2015 Jun 30;65(25):2760-3.
6. Fernandez G, Cameron SJ, Nayda J, Cove C. A Family of Aortic Dissections. American Journal of Medicine. *Am J Med.* 2015; 128(11).
7. Holcman K, Cameron SJ, Laskurain E, Massey HT, Trawick DR and Mieszczanska H. Breathtaking: platypnea-orthodeoxia syndrome. *Am J Med.* 2014 Jun;127(6):491-3.
8. Gardner B, Ling, FL Hopke PK, Frampton MW, Utell MJ, Zareba W, Cameron SJ, Chalupa D, Kane C, Kulandhaisamy S, Topf M, Rich, DQ. Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST-elevation myocardial infarction: a case-crossover study. *Part Fibre Toxicol*. 2014 Jan 2;11(1):1
9. Cameron SJ, Block R, Richeson JF. Severe Coronary Disease in an Adult Considered at Low Cardiovascular Disease Risk with a Healthy Lifestyle. *J Clin Lipidol*. 2013 Sep-Oct;7(5):526-30.
10. Cameron SJ, Goulopoulo, S, Weil B, Kanaley, JA. Regulation of arterial blood flow by aspirin following ischemia is a function of plasma HDL. *Eur Rev Med Pharmacol Sci.* 2012 Feb;16(2):143-50.

Jian Fu, B. Med., Ph.D.

Synopsis

My research focuses on the role of SM20, the ortholog of EGLN3, with a specific emphasis on deciphering the effect of SM20 on the development of skeletal muscle. Towards this end, we have been using pharmacological inhibitors to repress the activity of the prolyl hydroxylase, siRNAs to knock down SM20 expression level, and transient transfection strategy to overexpress SM20 to reveal a role for SM20 in the differentiation of cultured skeletal myoblasts. Strikingly, our preliminary results suggest that SM20 is involved in myogenesis.

Myogenic differentiation is orchestrated by a family of muscle regulatory factors including MyoD, myogenin, Myf-5, and MRF4. We are now exploring the impact of SM20 on these master muscle-specific molecules. We are creating SM20 knock-out mice to understand how SM20 regulates myogenesis. Our study will generate novel insights into the regulation of myogenic differentiation. Current projects include:

Project 1: Role of EGLN3 in Vascular Inflammation and Remodeling. EGLN3 was first cloned from vascular smooth muscle cells. It is also expressed in endothelial cells and macrophages. Our previous studies showed that EGLN3 is an inhibitor of NFκB, a master regulator of inflammation. However, it remains to be determined whether EGLN3 is involved in vascular inflammation. Our ongoing project is to uncover the role of EGLN3 in vascular inflammation and remodeling.

Project 2: EGLN3 Signaling Pathways. EGLN3 (also known as PHD3, HPH1, and SM-20) belongs to the *C. elegans gene egl-9* (EGLN) family of prolyl hydroxylases that require oxygen, iron and α-ketoglutarate for their enzymatic activity. EGLN hydroxylases are best known for the ability to catalyze the hydroxylation of HIF1α (hypoxia-inducible factor 1α). However, the role and mechanism for EGLN3 in other signaling pathways are poorly understood. We are now identifying novel vascular targets of EGLN3.

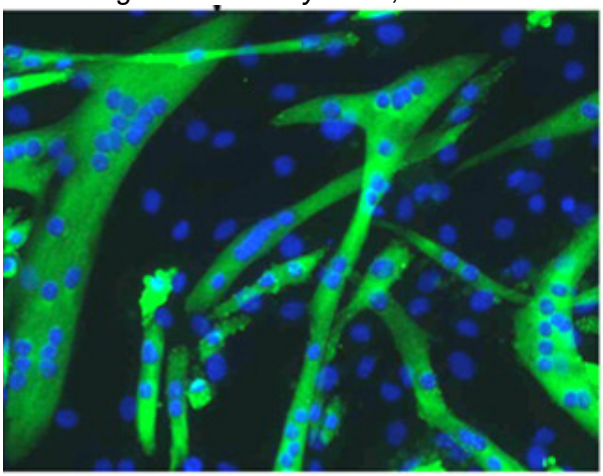
Project 3: Protein Ubiquitination and Vascular Inflammation. Protein ubiquitination is a post-translational modification involved in all facets of cell signaling and cell function. Ubiquitination not only influences the fate of the substrate but also has non-degradative functions such as signaling. We are exploring the role of protein ubiquitination in vascular inflammation.

Lab Members

- Ying Jin, Staff Scientist

Publications

1. Fu J. Catalytic-independent inhibition of cIAP1-mediated RIP1 ubiquitination by EGLN3. *Cellular Signaling* 2016, 28:72-80.
2. Fu J, Taubman MB. EGLN3 inhibition of NF-κB is mediated by prolyl hydroxylase-independent inhibition of IκB kinase γ ubiquitination. *Molecular and Cellular Biology* 2013, 33: 3050-61
3. Fu J, Taubman MB. Prolyl hydroxylase EGLN3 regulates skeletal myoblast differentiation through an NF-κB-dependent pathway. *Journal of Biological Chemistry* 2010, 285: 8927-893
4. Jian Fu, Menzies K, Freeman RS, Taubman MB. EGLN3 prolyl hydroxylase regulates skeletal muscle differentiation and myogenin protein stability. *Journal of Biological Chemistry* 2007, 282: 12410-8.



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
- Suowen Xu – Postdoctoral Associate
- Yanni Xu, Visiting Scientist

Publications

1. Xu S, Ha CH, Wang W, Xu X, Yin M, Jin FQ, Mastrangelo M, Koroleva M, Fujiwara K, Jin ZG. PECAM1 regulates flow-mediated Gab1 tyrosine phosphorylation and signaling. *Cell Signal*. 2016 Mar;28(3):117-24.
2. Zhao J, Yin M, Deng H, Jin FQ, Xu S, Lu Y, Mastrangelo MA, Luo H, Jin ZG. Cardiac Gab1 deletion leads to dilated cardiomyopathy associated with mitochondrial damage and cardiomyocyte apoptosis. *Cell Death Differ*. 2015 Oct 30.
3. Kwon IS, Wang W, Xu S, Jin ZG. Histone deacetylase 5 interacts with Kruppel-like factor 2 and inhibits its transcriptional activity in endothelium. *Cardiovasc Res*. 2014.
4. Jhun BS, J OU, Wang W, et al. Adrenergic signaling controls RGK-dependent trafficking of cardiac voltage-gated L-type Ca2+ channels through PKD1. *Circ. Research*. 2012;110(1):59-70.
5. Zhao J, Wang W, Ha CH, et al. Endothelial Grb2-associated binder 1 is crucial for postnatal angiogenesis. *Arterioscler Thromb Vasc Biol*. 2011;31(5):1016-1023.
6. Ha CH, Kim JY, Zhao J, et al. PKA phosphorylates histone deacetylase 5 and prevents its nuclear export, leading to the inhibition of gene transcription and cardiomyocyte hypertrophy. *Proc Natl Acad Sci U S A*. 2010;107(35):15467-15472
7. Wang W, Ha CH, Jhun BS, Wong C, Jain MK, Jin ZG. Fluid shear stress stimulates phosphorylation-dependent nuclear export of HDAC5 and mediates expression of KLF2 and eNOS. *Blood*. 2010;115(14):2971-2979.

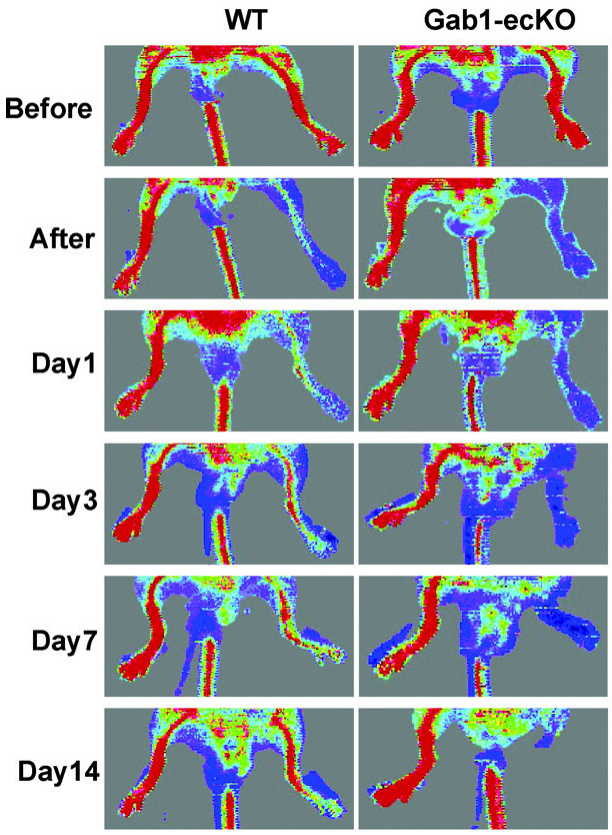


Figure: Hind limb ischemia is more severe in the absence of Gab1 from endothelial cells.

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:

Project 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 also found that Axl regulates vascular remodeling by promoting immune activation of smooth muscle cells in a mouse model of vein graft (**Figure**). Our most recent paper shows that Axl requires for survival of adaptive immune cells and vascular remodeling in hypertension

Project 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 biomechanical pathways through which this gene regulates pathological remodeling.

Project 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 and vascular remodeling. Our most recent findings suggest that autonomic dysfunction is crucial for stress-induced vascular inflammation in mice. We are studying candidate genes within chromosome 7 locus that control hemodynamic parameters and vascular inflammation.

Lab Members

- George Dugbartey - *Postdoctoral Associate*

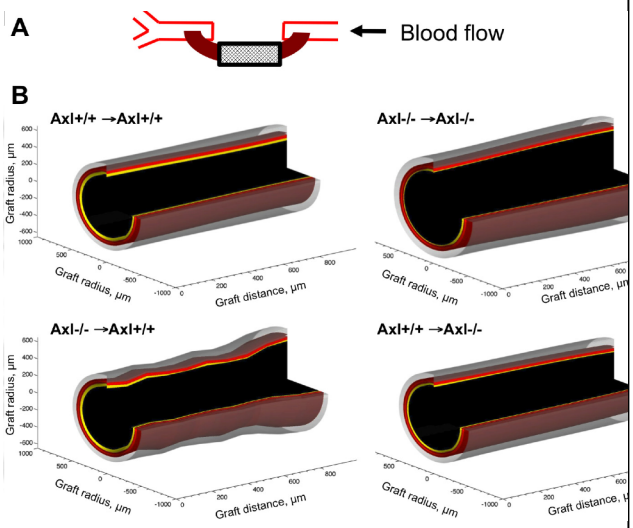


Figure. Axl contributes to vein graft thickening in mice. **A**: schematic representation of the vein-to-carotid grafting. Only the boxed area was used for morphometric analyses of a series of cross-sections marked with the cross-hatched pattern. Arrow shows the direction of blood flow. **B**: three-dimensional reconstruction of vein graft vessel compartments based on a series of histological sectioning over 800-µm length. Graft compartments are color-coded: black - lumen area, yellow - intima area, red - media area, and transparent - adventitia area..
From *Batchu et al, Am J Physiol Heart Circ Physiol* 2015

Publications

Project 2 publications

1. Batchu SN, Hughson A, Wadosky KM, Morrell CN, Fowell DJ, Korshunov VA. Role of Axl in T-lymphocyte survival in salt-dependent hypertension. *Arterioscler Thromb Vasc Biol* 2016;36(8):1638-46.
2. Batchu SN, Xia J, Ko KA, Doyley MM, Abe J, Morrell CN, Korshunov VA. Axl modulates immune activation of smooth muscle cells in vein graft remodeling. *Am J Physiol Heart Circ Physiol* 2015;309(6):H1048-58.
3. Batchu SN, Hughson A, Gerloff J, Fowell DJ, Korshunov VA. Role of Axl in early kidney inflammation and development of salt-dependent hypertension. *Hypertension* 2013;62(2):302-309.
4. Gerloff J and Korshunov VA. Immune modulation of vascular resident cells by Axl orchestrates carotid intima-media thickening. *Am J Pathol* 2012;180(5):2134-43.

Project 2 publications

1. Smolock EM, Burke R, Wang C, Batchu SN, Qiu X, Thomas T, Zettel M, Fujiwara K, Berk BC, Korshunov VA. Intima modifier locus 2 controls endothelial cell activation and vascular permeability. *Physiol Genomics* 2014;46(17):624-633.
2. Smolock EM, Machleder DE, Korshunov VA, Berk BC. Identification of a genetic locus on chromosome 11 that regulates leukocyte infiltration in mouse carotid. *Arterioscler Thromb Vasc Biol* 2013;33:1014-1019.
3. Smolock EM, Korshunov VA, Glazko G, Qiu X, Gerloff J, Berk BC. Genetic analysis of carotid intima formation identifies Rpl17 as a vascular smooth muscle growth inhibitor. *Circulation* 2012;126:2418-2427.

Project 3 publications

1. Batchu SN, Smolock EM, Dyachenko IA, Murashev AN, Korshunov VA. Autonomic dysfunction determines stress-induced cardiovascular and immune complications in mice. *J Am Heart Assoc* 2015;4:e001952.
2. Smolock EM, Ilyushkina IA, Ghazalpour A, Gerloff J, Murashev AN, Lusis AJ, Korshunov VA. Genetic locus on mouse chromosome 7 controls elevated heart rate. *Physiol Genomics* 2012;44(13):689-98.

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, Postdoctoral Associate
- Xiaorong Parks, Staff Scientist
- Chen Kaplan, Graduate Student

Publications

1. Ruwald MH, Xu Parks X… and Lopes CM. Stop-codon and C-terminal nonsense mutations are associated with a lower risk of cardiac events in patients with long QT syndrome type 1. *Heart Rhythm*. 2016 Jan;13(1):122-31.
2. O-Uchi J, Sorenson J… and Lopes CM. Isoform-specific dynamic translocation of PKC by α1-adrenoceptor stimulation in live cells. *Biochem Biophys Res Commun*. 2015 Sep 25;465(3):464-70.
3. O-Uchi J, Rice JJ… and Lopes CM. Impaired IKs channel activation by Ca(2+)-dependent PKC shows correlation with emotion/arousal-triggered events in LQT1. *J Mol Cell Cardiol*. 2015Feb;79:203-11.
4. Mathias A, Moss AJ, Lopes CM… and Goldenberg I. Prognostic implications of mutation-specific QTc standard deviation in congenital long QT syndrome. *Heart Rhythm*. 2013 May;10(5):720-5.
5. Mullally J, Goldenberg I, Moss AJ, Lopes CM… and Barsheshet A. Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations. *Heart Rhythm*. 2013 Mar;10(3):378-82.
6. Hoefen R, Reumann M,… and Lopes CM. In silico cardiac risk assessment in patients with long QT syndrome: type 1: clinical predictability of cardiac models. *J Am Coll* Cardiol. 2012 Nov 20;60(21):2182-91.
7. Couderc JP, Xia … and Lopes CM. Genotype- and Sex-Specific QT-RR Relationship in the Type-1 Long-QT Syndrome. *J Am Heart Assoc*. 2012 Apr;1(2):e000570.
8. Barsheshet A, Goldenberg I… and Lopes CM. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to β-blocker therapy in type 1 long-QT syndrome. *Circulation*. 2012 Apr 24;125(16):1988-96.
9. Costa J, Lopes CM… and Goldenberg I. Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome. *Heart Rhythm*. 2012 Jun;9(6):892-8.

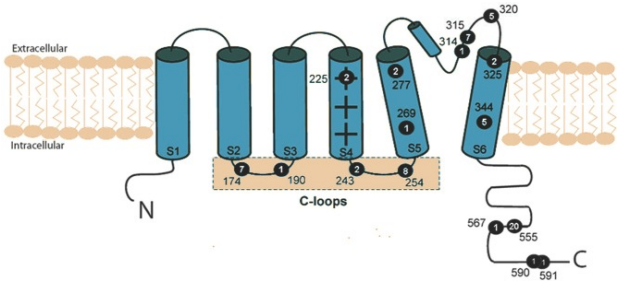


Figure: Schematic of mutations in KCNQ1 ion channel.

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.

Lab Members

- John Allen Bennett, Postdoctoral Fellow
- Maria de la Luz Garcia-Hernandez – Senior Associate
- Michael Mastrangelo – Technical Associate

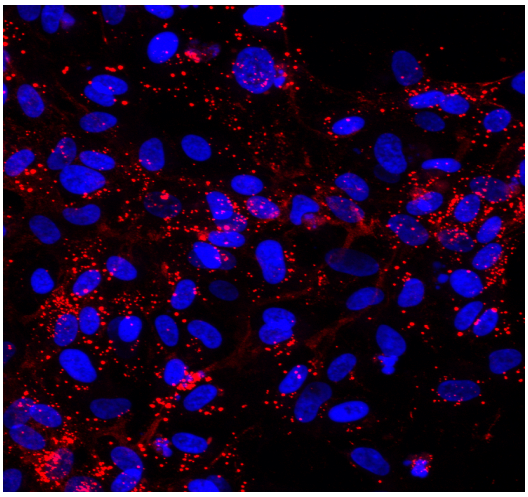


Figure: Endothelial cells grown on a defined matrix express granules containing VWF (red).

Publications

1. Miano JM, Zhu QM, Lowenstein CJ, A CRISPR Path to Engineering New Genetic Mouse Models for Cardiovascular Research., *Arterioscler Thromb Vasc Biol*. 2016 Jun;36(6):1058-75.
2. Cameron SJ, Morrell CN, Bao C, Swaim AF, Rodriguez A, Lowenstein CJ. A Novel Anti-Inflammatory Effect for High Density Lipoprotein. *PLoS One*. 2015 Dec 17;10(12):e0144372.
3. Zhu Q, Yamakuchi M, and Lowenstein CJ. SNAP23 Regulates Endothelial Exocytosis of von Willebrand Factor. *PLoS One*. 2015 Aug 12;10(8):e0118737.
4. Zhu Q, Yamakuchi M, Ture S... and Lowenstein CJ. Syntaxin binding protein STXBP5 inhibits endothelial exocytosis and promotes platelet secretion. *The Journal of Clinical Investigation*. 2014;124(10):4503–4516
5. LoMonaco MB and Lowenstein CJ. Enhanced assay of endothelial exocytosis using extracellular matrix components. *Anal Biochem*. 2014;452:19-24.
6. Jeong Y, Du R.… and Lowenstein CJ. Histone deacetylase isoforms regulate innate immune responses by deacetylating mitogen-activated protein kinase phosphatase-1. *J Leukoc Biol*. 2014;95(4):651-659.

7. Huang J, Huffman JE, Yamakuchi M, et al. Genome-wide association study for circulating tissue plasminogen activator levels and functional follow-up implicates endothelial STXBP5 and STX2. *Arterioscler Thromb Vasc Biol*. 2014;34(5):1093-1101.

Joseph Miano, Ph.D.

Synopsis

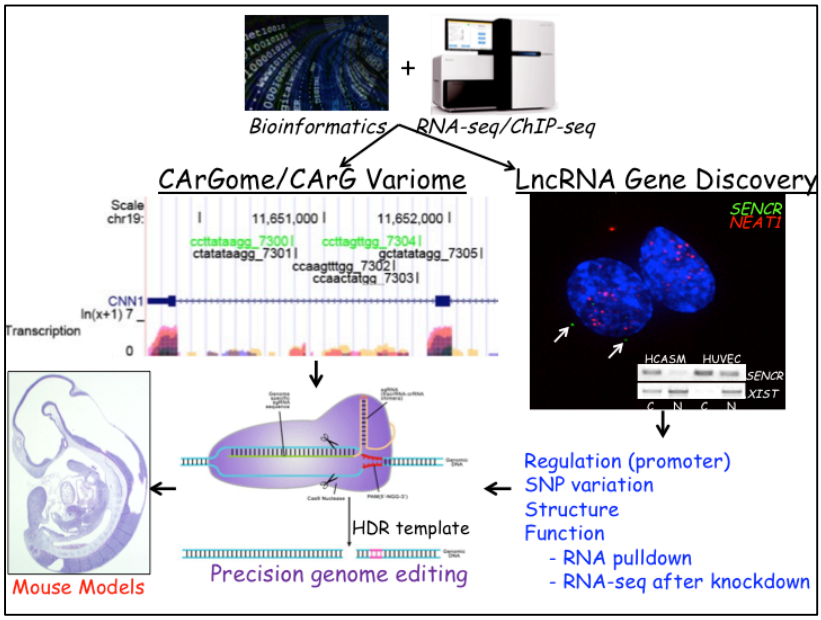
The notion of "junk DNA" has been debunked with the realization that the human genome is punctuated with millions of regulatory codes and undergoes pervasive transcription, particularly with respect to the emerging class of long noncoding RNA (lncRNA) genes, which already outnumber all protein-coding 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 genomic sequences once thought to be genomic refuse.

The Miano Lab uses tools in bioinformatics and genomics to study functional regulatory elements and lncRNA genes that affect 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 lncRNA genes, and we recently published the first novel, human vascular cell-restricted lncRNA called *SENCR*. This lncRNA appears to fine tune the program of vascular smooth muscle cell gene expression including that of Myocardin (MYOCD) 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 lncRNA genes, some of which are highly enriched in vascular smooth muscle. We are in the process of working up new and recently annotated lncRNA 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 lncRNA 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 lncRNA genes) and variant sequences therein that are associated with, but not limited to, cardiovascular disease.



Lab Members

- Christine Christie, *Lab Technician*
- Qing (Rex) Lyu, *Postdoctoral Associate*
- Orazio Slivano – *Technical Associate*
- Michael Wilson – *Postdoctoral Associate*
- Mary Wines-Samuelson – *Staff Scientist*

Publications

1. Chettimada S, Joshi SR, Dhagia V, Aiezza A 2nd, Lincoln TM, Gupte R, **Miano** JM, Gupte SA., Vascular smooth muscle cell contractile protein expression is increased through PKG-dependent and -independent pathways by G6PD inhibition and deficiency, Am J Physiol Heart Circ Physiol. 2016 Aug 12.
2. Zhao J, Zhang W, Lin M, Wu W, Jiang P, Tou E, Xue M, Richards A, Jourd'heuil D, Asif A, Zheng D, Singer HA, **Miano** JM, Long X., MYOSLID Is a Novel Serum Response Factor-Dependent Long Noncoding RNA That Amplifies the Vascular Smooth Muscle Differentiation Program. Arterioscler Thromb Vasc Biol. 2016 Jul 21.
3. **Miano** JM, Zhu QM, Lowenstein CJ, A CRISPR Path to Engineering New Genetic Mouse Models for Cardiovascular Research., Arterioscler Thromb Vasc Biol. 2016 Jun;36(6):1058-75.
4. Ballantyne MD, Pinel K, Dakin R, Vesey AT, Diver L, Mackenzie R, Garcia R, Welsh P, Sattar N, Hamilton G, Joshi N, Dweck MR, **Miano** JM, McBride MW, Newby DE, McDonald RA, Baker AH., Circulation. 2016 May 24;133(21):2050-65,
5. Boulberdaa M, Scott E, Ballantyne M, Garcia R, Descamps B, Angelini GD, Brittan M, Hunter A, McBride M, McClure J, **Miano** JM, Emanueli C, Mills NL, Mountford JC, Baker AH., A Role for the Long Noncoding RNA SENCR in Commitment and Function of Endothelial Cells., Mol Ther. 2016 May;24(5):978-90.
6. Ackers-Johnson M, Talasila A, Sage AP, Long X, Bot I, Morrell NW, Bennett MR, Miano JM, Sinha S. Myocardin regulates vascular smooth muscle cell inflammatory activation and disease. Arterioscler Thromb Vasc Biol. 2015 Apr;35(4):817-28.
7. Han Y, Slivano OJ, Christie CK, Cheng AW, Miano JM. CRISPR-Cas9 genome editing of a single regulatory element nearly abolishes target gene expression in mice--brief report. Arterioscler Thromb Vasc Biol. 2015 Feb;35(2):312-5.
8. Fisher EA, Miano JM. Don't judge books by their covers: vascular smooth muscle cells in arterial pathologies. *Circulation*. 2014;129(15):1545-1547.
9. Shi F, Long X, Hendershot A, Miano JM, Sottile J. Fibronectin matrix polymerization regulates smooth muscle cell phenotype through a Rac1 dependent mechanism. *PLoS One*. 2014;9(4):e94988.
10. Bell RD, Long X, Lin M, et al. Identification and initial functional characterization of a human vascular cell-enriched long noncoding RNA. *Arterioscler Thromb Vasc Biol*. 2014;34(6):1249-1259.
11. Long X, Miano JM. Myocardin: new therapeutic agent in vascular disease? *Arterioscler Thromb Vasc Biol*. 2013;33(10):2284-2285.

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

Synopsis

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. My lab focuses on the role of platelets in vascular inflammation and platelet regulation of 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 also found that platelets 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 exploring how platelets and PF4 interact with developing T helper cells and the signaling mechanisms involved in PF4 limiting Th17 differentiation. This work has expanded to investigate the role of platelet activation and T cell differentiation in other inflammatory diseases including inflammatory bowel disease (IBD).

We have also recently identified novel mechanisms for PF4 mediated B cell differentiation that is now being actively pursued, in addition to identifying alternative, non-megakaryocyte and platelet derived sources of PF4.

New studies in our lab are focusing on how platelets contribute to neurovascular inflammation and injury in chronic HIV infection that leads to cognitive decline. Even with current anti-retroviral therapies and undetectable viral loads there is still evidence of ongoing platelet activation and vascular inflammation that correlates with increased thrombotic risk and neurovascular injury that precedes a neurocognitive decline. We are now exploring platelet mediated mechanisms for neurovascular inflammation and the decline in memory and learning associated with chronic HIV infection.

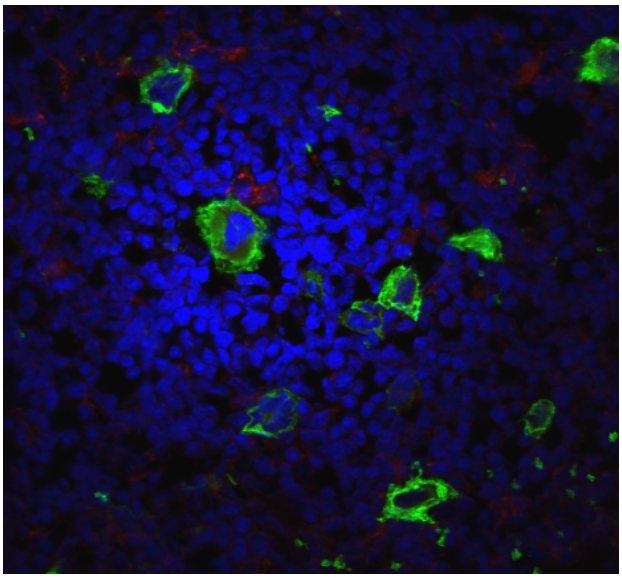


Figure: Megakaryocytes staining green in mouse bone marrow.

Lab Members

- Zachary T. Hilt– Graduate Student
- Daphne N. Pariser – Graduate Student
- Sara Ture – *Laboratory Technician*

Publications

1. Modjeski KL, Levy SC, Ture SK, Field DJ, Shi G, Ko K, Zhu Q, Morrell CN. Glutamate receptor interacting protein 1 regulates CD4(+) CTLA-4 expression and transplant rejection. Am J Transplant. 2015 Nov 25.
2. Cameron SJ, Ture SK, Mickelsen D, Chakrabarti E, Modjeski KL, McNitt S, Seaberry M, Field DJ, Le NT, Abe J, Morrell CN. Platelet Extracellular Regulated Protein Kinase 5 Is a Redox Switch and Triggers Maladaptive Platelet Responses and Myocardial Infarct Expansion. Circulation. 2015 Jul 7;132(1):47-58.
3. Wang L, Soe NN, Sowden M, et al. Cyclophilin A is an important mediator of platelet function by regulating integrin alphaIIbbeta3 bidirectional signalling. *Thromb Haemost*. 2014;111(5):873-882.

4. Shi G, Field DJ, Ko KA, et al. Platelet factor 4 limits Th17 differentiation and cardiac allograft rejection. *J Clin Invest*. 2014;124(2):543-552.
5. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune and inflammatory cells. *Blood*. 2014;123(18):2759-2767.
6. Morrell CN. Understanding platelets in malaria infection. *Curr Opin Hematol*. 2014;21(5):445-449.
7. Modjeski KL, Morrell CN. Small cells, big effects: the role of platelets in transplant vasculopathy. *J Thromb Thrombolysis*. 2014;37(1):17-23.
8. Metcalf Pate KA, Lyons CE, Dorsey JL, et al. TGFbeta-Mediated Downregulation of Thrombopoietin Is Associated With Platelet Decline in Asymptomatic SIV Infection. *J Acquir Immune Defic Syndr*. 2014;65(5):510-516.
9. Shi G, Field DJ, Long X, et al. Platelet factor 4 mediates vascular smooth muscle cell injury responses. *Blood*. 2013;121(21):4417-4427.
10. Metcalf Pate KA, Lyons CE, Dorsey JL, et al. Platelet activation and platelet-monocyte aggregate formation contribute to decreased platelet count during acute simian immunodeficiency virus infection in pig-tailed macaques. *J Infect Dis*. 2013;208(6):874-883
11. Aggrey AA, Srivastava K, Ture S, Field DJ, Morrell CN. Platelet induction of the acute-phase response is protective in murine experimental cerebral malaria. *J Immunol*. 2013;190(9):4685-4691.
12. Kuo HH, Morrell CN, Baldwin WM, 3rd. Alloantibody induced platelet responses in transplants: potent mediators in small packages. *Hum Immunol*. 2012;73(12):1233-1238.
13. Chapman LM, Aggrey AA, Field DJ, et al. Platelets present antigen in the context of MHC class I. *J Immunol*. 2012;189(2):916-923.

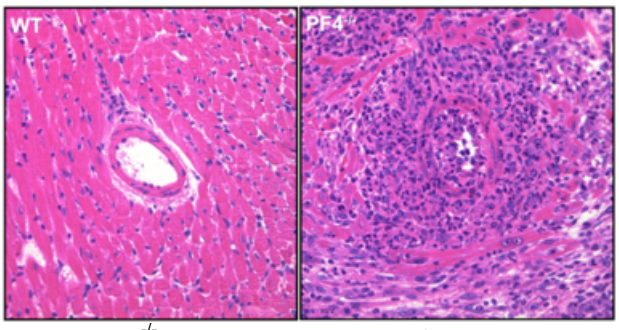


Figure. $PF4^{-/-}$ mice have severe graft vasculopathy. WT and $PF4^{-/-}$ mice were given BM12 heart allografts and transplants harvested 35 days later. $PF4^{-/-}$ mice have extensive leukocyte and neutrophil infiltrates.

Jinjiang Pang, B. Med., 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 involve in mitochondrial biogenesis during cardiac development and diseases.

Lab Members

- Sharon Senchanthisai, ***Laboratory Technician***
- Mark Sowden, *Research Associate Professor*
- Guofu (Nathan) Zhu, *Visiting Student in Residence*

Publications

1. Yin G, Sheu TJ, Menon P, et al. Impaired angiogenesis during fracture healing in GPCR kinase 2 interacting protein-1 (GIT1) knock out mice. *PLoS One*. 2014;9(2):e89127.
2. Majumder S, Sowden MP, Gerber SA, et al. G-protein-coupled receptor-2-interacting protein-1 is required for endothelial cell directional migration and tumor angiogenesis via cortactin-dependent lamellipodia formation. *Arterioscler Thromb Vasc Biol*. 2014;34(2):419-426.
3. Zhang L, Malik S, Pang J, et al. Phospholipase Cepsilon hydrolyzes perinuclear phosphatidylinositol 4-phosphate to regulate cardiac hypertrophy. *Cell*. 2013;153(1):216-227.
4. Park SY, Shi X, Pang J, Yan C, Berk BC. Thioredoxin-interacting protein mediates sustained VEGFR2 signaling in endothelial cells required for angiogenesis. *Arterioscler Thromb Vasc Biol*. 2013;33(4):737-743.
5. Pang J, Xu X, Wang X, et al. G-protein-coupled receptor kinase interacting protein-1 mediates intima formation by regulating vascular smooth muscle proliferation, apoptosis, and migration. *Arterioscler Thromb Vasc Biol*. 2013;33(5):999-1005.
6. Pang J, Xu X, Getman MR, et al. G protein coupled receptor kinase 2 interacting protein 1 (GIT1) is a novel regulator of mitochondrial biogenesis in heart. *J Mol Cell Cardiol*. 2011;51(5):769-776.
7. Wang J, Yin G, Menon P, et al. Phosphorylation of G protein-coupled receptor kinase 2-interacting protein 1 tyrosine 392 is required for phospholipase C-gamma activation and podosome formation in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2010;30(10):1976-1982.

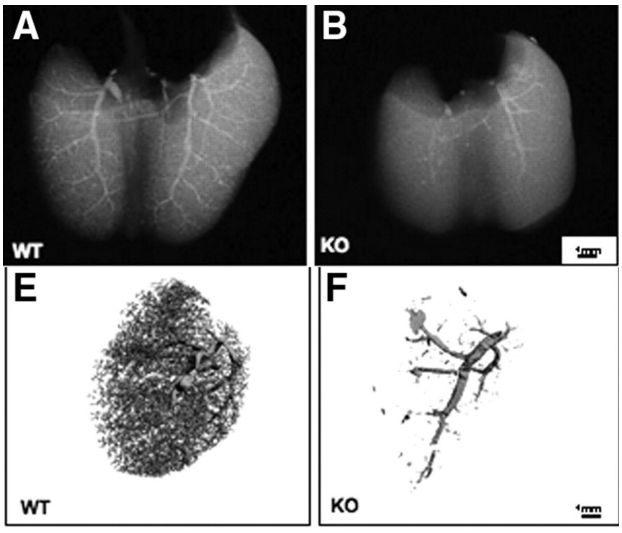


Figure: Imaging shows reduced vasculature in lungs of GIT1 KO mice.

Eric Small, Ph.D.

Synopsis

The transition to heart failure (HF) following an ischemic event is the result of irreversible cardiomyocyte loss and the development of cardiac fibrosis. 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 heart development and disease with the ultimate goal of developing novel therapeutic approaches to block or reverse the progression of heart failure. We have recently found 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.

We have also made advances in 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.

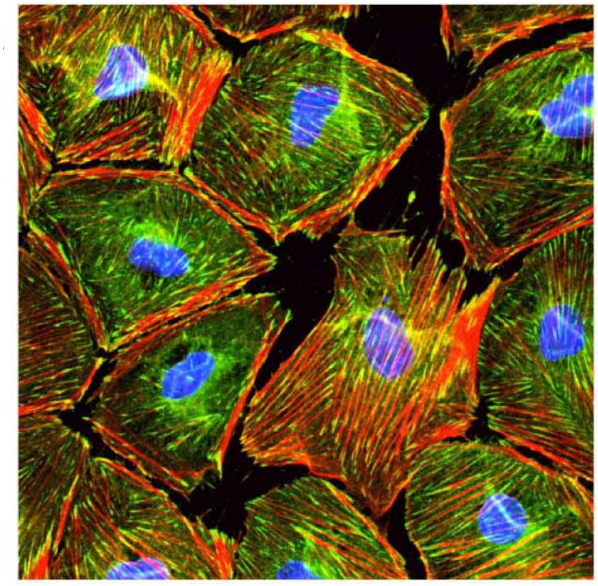


Figure: Epicardium-derived cells undergoing epithelial- mesenchymal transition (EMT) exhibit Vinculin-positive focal adhesions (green) and smooth muscle actin-positive stress fibers (red).

Lab Members

- Ryan Burke, Postdoctoral Associate
- Ron Dirkx – Technical Associate
- Janet Lighthouse – Postdoctoral Fellow
- Pearl Quijada – Postdoctoral Fellow
- Michael Trembley – Graduate Student

Publications

1. Trembley MA, Velasquez LS, Small EM. Epicardial outgrowth assay and ex vivo assessment of epicardial-derived cell migration. J Vis Exp. 2016 Mar 18; (109).
2. Luna-Zurita L, Stirnimann CU, Glatt S, Kaynak BL, Thomas S, Baudin F, Samee MA, He D, Small EM, Mileikovsky M, Nagy A, Holloway AK, Pollard KS, Müller CW, Bruneau BG. Complex Interdependence Regulates Heterotypic Transcription Factor Distribution and Coordinates Cardiogenesis. *Cell*. 2016 Feb 10. pii: S0092-8674(16)00005-2.

3. Lighthouse JK, Small EM. Transcriptional control of cardiac fibroblast plasticity. *J Mol Cell Cardiol*. 2016 Feb;91:52-60.
4. Trembley MA, Velasquez LS, de Mesy Bentley KL, Small EM. Myocardin-related transcription factors control the motility of epicardium-derived cells and the maturation of coronary vessels. *Development*. 2015 Jan 1;142(1):21-30.
5. Velasquez LS, Sutherland LB, Liu Z, Grinnell F, Kamm KE, Schneider JW, Olson EN, Small EM. Activation of MRTF-A-dependent gene expression with a small molecule promotes myofibroblast differentiation and wound healing. *Proc Natl Acad Sci U S A.* 2013;110(42):16850-16855.
6. Rodes-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, Costa MA, Mega JL, O'Donoghue ML, Ohman EM, Becker RC. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. J Am Coll Cardiol. 2013;62(25):2349-59.
7. Small EM. The actin-MRTF-SRF gene regulatory axis and myofibroblast differentiation. *J Cardiovasc Transl Res.* 2012;5(6):794-804.
8. Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. *Nature*. 2011;469(7330):336-342.
9. Miano JM, Small EM. MicroRNA133a: a new variable in vascular smooth muscle cell phenotypic switching. *Circ Res.* 2011;109(8):825-827.
10. Small EM, Thatcher JE, Sutherland LB, et al. Myocardin-related transcription factor-a controls myofibroblast activation and fibrosis in response to myocardial infarction. *Circ Res.* 2010;107(2):294-304.
11. Small EM, Sutherland LB, Rajagopalan KN, Wang S, Olson EN. MicroRNA-218 regulates vascular patterning by modulation of Slit-Robo signaling. *Circ Res*. 2010;107(11):1336-1344.
12. Small EM, O'Rourke JR, Moresi V, et al. Regulation of PI3-kinase/Akt signaling by muscle-enriched microRNA-486. *Proc Natl Acad Sci U S A.* 2010;107(9):4218-4223.
13. Small EM, Frost RJ, Olson EN. MicroRNAs add a new dimension to cardiovascular disease. *Circulation*. 2010;121(8):1022-1032.

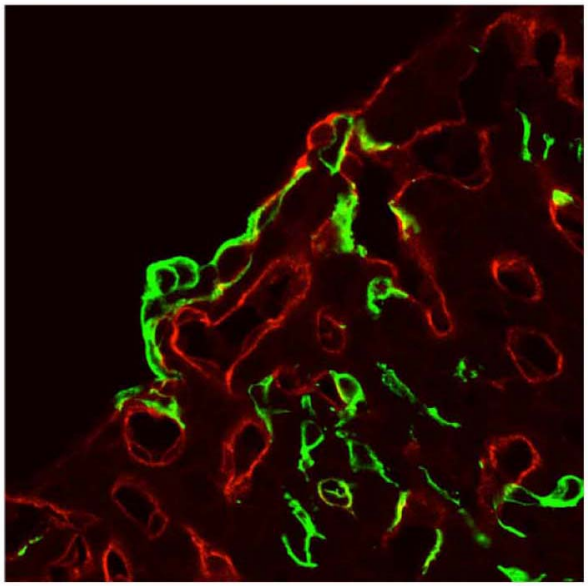


Figure: Epicardium-derived cells (green) undergoing EMT and migrating into the compact myocardium in the developing heart. Endothelial cells are stained with PECAM1 (red).

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.

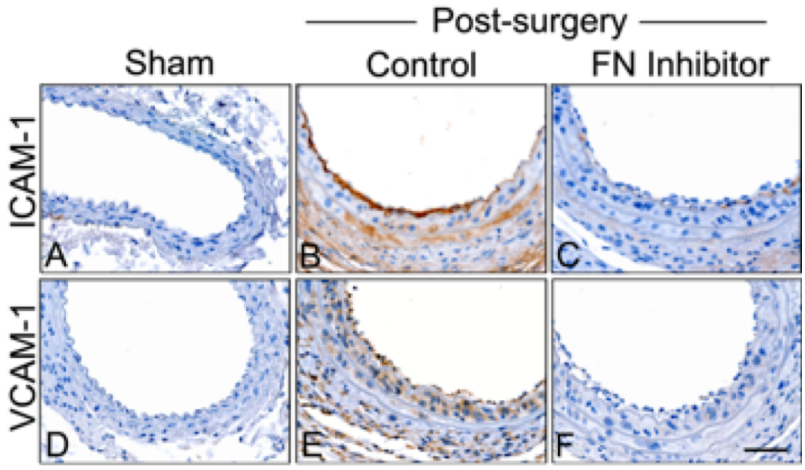


Figure. The pUR4 fibronectin inhibitor decreases ICAM-1 and VCAM-1 levels in the vessel wall in an animal model of flow-induced vascular remodeling. Sections of the left carotid artery were stained with antibodies to ICAM-1 (A-C) or VCAM-1 (D-F) seven days after surgery. Bar, 20 μm.

Lab Members

- Allison Hendershot – *Lab Technician*
- *Mary Wines-Samuelson – Staff Scientist*

Publications

1. Lee, T.-H, Sottile, J., Chiang, H.-Y. 2015. Collagen Inhibitory Peptide R1R2 Mediates Vascular Remodeling by Decreasing Inflammation and Smooth Muscle Cell Activation. PLoS One. Feb 12;10(2):e0117356;
2. Altrock E, Sens C, Wuerfel C, Vasel M, Kawelke N, Dooley S, Sottile J. 2014. Nakchbandi IA Inhibition of fibronectin deposition improves experimental liver fibrosis. J Hepatol. Jun 16. pii: S0168-8278(14)00405-X.
3. Shi F, Long X, Hendershot A, Miano JM, Sottile J. 2014. Fibronectin matrix polymerization regulates smooth muscle cell phenotype through a Rac1 dependent mechanism. PLoS One. Apr 21;9(4):e94988.
4. Shi, F., and Sottile, J. 2011 MT1-MMP regulates the turnover and endocytosis of extracellular matrix fibronectin J. Cell Sci. 124:4039-5.
5. Shi, F., Harman, J., Fujiwara, K., and Sottile, J. 2010. Collagen I matrix turnover is regulated by fibronectin polymerization. Am J Physiol Cell Physiol, 298:C1265-75.

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:

- Guangze Jin – *Postdoctoral Associate*
- Walter Knight – *Graduate Student*
- Sharon Senchanthisai – ***Lab Technician***
- Jian Xiong – *Visiting Postdoctoral Fellow*
- Yishuai Zhang – *Postdoctoral Associate*
- Qian Zhou – *Staff Scientist*

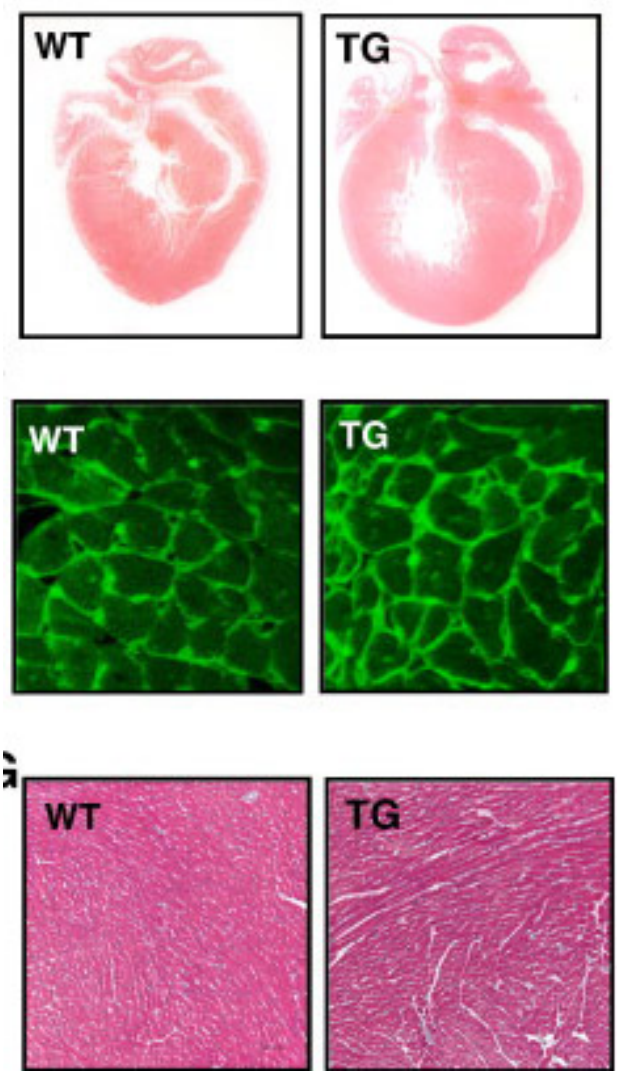


Figure: Transgenic mouse with cardiac expression of PDE3A1 have myocardial hypertrophy with larger cardiac myocytes and larger hearts.

Publications

1. Wu MP, Zhang YS, Zhou QM, Xiong J, Dong YR, Yan C. Higenamine protects ischemia/reperfusion induced cardiac injury and myocyte apoptosis through activation of β2-AR/PI3K/AKT signaling pathway. Pharmacol Res. 2016 Feb;104:115-23.
2. Cai Y, Nagel DJ, Zhou Q, Cygnar KD, Zhao H, Li F, Pi X, Knight PA, Yan C. Role of cAMP-phosphodiesterase 1C signaling in regulating growth factor receptor stability, vascular smooth muscle cell growth, migration, and neointimal hyperplasia. Circ Res. 2015 Mar 27;116(7):1120-32.
3. Yin G, Sheu TJ, Menon P, et al. Impaired angiogenesis during fracture healing in GPCR kinase 2 interacting protein-1 (GIT1) knock out mice. *PLoS One*. 2014;9(2):e89127.
4. Spindel ON, Burke RM, Yan C, Berk BC. Thioredoxin-interacting protein is a biomechanical regulator of Src activity: key role in endothelial cell stress fiber formation. *Circ Res*. 2014;114(7):1125-1132.
5. Park SY, Shi X, Pang J, Yan C, Berk BC. Thioredoxin-interacting protein mediates sustained VEGFR2 signaling in endothelial cells required for angiogenesis. *Arterioscler Thromb Vasc Biol*. 2013;33(4):737-743.
6. Oikawa M, Wu M, Lim S, et al. Cyclic nucleotide phosphodiesterase 3A1 protects the heart against ischemia-reperfusion injury. *J Mol Cell Cardiol*. 2013;64:11-19.
7. Knight W, Yan C. Therapeutic potential of PDE modulation in treating heart disease. *Future Med Chem*. 2013;5(14):1607-1620.
8. Cai Y, Li JD, Yan C. Vinpocetine attenuates lipid accumulation and atherosclerosis formation. *Biochem Biophys Res Commun*. 2013;434(3):439-443.
9. Wang XQ, Nigro P, World C, Fujiwara K, Yan C, Berk BC. Thioredoxin interacting protein promotes endothelial cell inflammation in response to disturbed flow by increasing leukocyte adhesion and repressing Kruppel-like factor 2. *Circ Res*. 2012;110(4):560-568.
10. Spindel ON, Yan C, Berk BC. Thioredoxin-interacting protein mediates nuclear-to-plasma membrane communication: role in vascular endothelial growth factor 2 signaling. *Arterioscler Thromb Vasc Biol*. 2012;32(5):1264-1270.
11. Silva J, Polesskaya O, Knight W, et al. Transient hypercapnia reveals an underlying cerebrovascular pathology in a murine model for HIV-1 associated neuroinflammation: role of NO-cGMP signaling and normalization by inhibition of cyclic nucleotide phosphodiesterase-5. *J Neuroinflammation*. 2012;9:253.
12. Le NT, Takei Y, Shishido T, et al. p90RSK targets the ERK5-CHIP ubiquitin E3 ligase activity in diabetic hearts and promotes cardiac apoptosis and dysfunction. *Circ Res*. 2012;110(4):536-550.
13. Knight WE, Yan C. Cardiac cyclic nucleotide phosphodiesterases: function, regulation, and therapeutic prospects. *Horm Metab Res*. 2012;44(10):766-775.
14. Cai Y, Knight WE, Guo S, Li JD, Knight PA, Yan C. Vinpocetine suppresses pathological vascular remodeling by inhibiting vascular smooth muscle cell proliferation and migration. *J Pharmacol Exp Ther*. 2012;343(2):479-488.

D. 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.

- **Dr. George Dugbartey** is a Postdoctoral Associate in the laboratory of Dr. Slava Korshnuov. Dr. Dugbartey received his Ph.D. in pharmacology from the University Medical Center Groningen, Netherlands in 2015. He is studying the role of immune response in vascular dysfunction in hypertension.

- **Dr. John Allen Bennett** is a Postdoctoral Associate in the laboratory of Dr. Charles Lowenstein. Dr. Bennett received his Ph.D. in Pharmacology from the University of Rochester School of Medicine in 2015. He is studying the genetics of thrombosis.

- **Dr. Guangze Jin** is a Postdoctoral Associate in the laboratory of Dr. Chen Yan. Dr. Jin received his Ph.D. from the University of Rochester in 2015 and is now studying the role and underlying mechanism of cyclic nucleotide phosphodiesterase in vascular biology and disease.

- **Dr. Janet Lighthouse** is a Postdoctoral 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 and is the recipient of a 2-year postdoctoral fellowship from the American Heart Association.

- **Dr. Qing (Rex) Lyu** is a Postdoctoral Associate in the laboratory of Dr. Joseph Miano. Dr. Lyu received his Ph.D. from the School of Life Sciences, Tsinghua University, Beijing and is now studying the long non-coding RNA discovery and use of CRISPR-Cas9 for genome editing of cells and mice.

- **Dr. Pearl Quijada** is a Postdoctoral Fellow in the laboratory of Dr. Eric Small. Dr. Quijada received her Ph.D. in biology from the University of California, San Diego. She is studying the role of epicardium-derived progenitor cells in patterning the coronary vasculature during embryonic development. She is also evaluating novel signals originating from the epicardium that might stimulate regeneration of lost or damaged cardiac tissue and restore normal function after a myocardial infarction.

- **Dr. Elsa Ronzier** is a Postdoctoral Associate 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.

- **Jian Xiong, Ph.D.** is a Visiting Postdoctoral 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 Postdoctoral Associate 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. Michael Wilson** is a Postdoctoral Associate in the laboratory of Dr. Joseph Miano. Dr. Wilson received his Ph.D. from the University of Rochester in 2015 and is now studying SRF-dependent genes.

- **Dr. Yishuai Zhang** is a Postdoctoral Associate 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.

University of Rochester Graduate Students at the CVRI

- **Xue Chao** is a predoctoral student in the laboratory of Dr. Brad Berk. He is studying the role of CyclophilinA (CypA) and acetylated CypA in endothelial to mesenchymal transition in promoting pulmonary hypertension.

- **Chen Kaplan** is a predoctoral student in the lab of Dr. Coeli Lopes. She received her B.Sc. in biotechnology engineering from ORT Braude College, Karmiel, Israel in 2012.

- **Michael Trembley** is a predoctoral student in the laboratory of Dr. Eric Small. Mike received his B.S. in biochemistry from St. Lawrence University, Canton, NY. He is studying the role of epicardial cells in the regeneration of cardiac tissue.

- **Guofu Zhu** is a visiting student in residence in the lab of Dr. Jinjiang Pang. He is a second year graduate student visiting from Tongji University.

E. 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, 2011for $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.