

**SUMMER 2012 OPPORTUNITIES
IN CARDIOVASCULAR RESEARCH
FOR UW MEDICAL STUDENTS**
UW Cardiovascular Research Center
5710 Medical Sciences Center
www.cvrc.wisc.edu
608-263-2266

The UW Cardiovascular Research Center sponsors summer internships for UW medical students between years I and II who are interested in cardiovascular sciences. This program offers approximately a \$400/week stipend for a minimum 8 weeks to a maximum of 12 weeks for medical student interns. Jonathan Makielski, MD, Professor of Medicine (Cardiovascular) and Director of the UW Cardiovascular Research Center Training Programs, coordinates this activity.

The laboratories listed below are from mentors who have specific projects for students. Students should contact these mentors, and then apply for summer research through the Herman Shapiro Summer Research Award Program. Information about the Shapiro Program is at:

<http://www.med.wisc.edu/education/md/curriculum/year-1/student-research/211>

The UW Cardiovascular Research Center will provide matching funding for successful applicants in cardiovascular research settings. The application deadline for the Shapiro Program is March 15, 2012, with notification by early April, 2012. Please contact the UW Cardiovascular Research Center, info@cvrc.wisc.edu or Barbara Weitz, Assistant Director, 263-2266, or brweitz@wisc.edu for more information.

1. William G. Schrage, PhD, Assistant Professor, Kinesiology, Room 1149A Nat/Gym Unit II, 2000 Observatory Dr., wschrage@education.wisc.edu, 262-7715

Our lab studies vascular function of the skeletal muscle and cerebral circulation of humans. We determine the ability to respond to stressors like hypoxia or exercise, and whether this ability is altered by conditions like obesity or pre-diabetes. Most of our studies involve beat-to-beat measures of muscle or cerebral blood flow using ultrasound at rest and during exercise or environmental stressors.

Ongoing projects include: 1) Cerebral blood flow responses in younger obesity and metabolic syndrome, 2) Effects of diet and exercise on muscle blood flow and cerebral blood flow responses in middle-aged metabolic syndrome patients, 3) Sympathetic adrenergic control of muscle blood flow in metabolic syndrome, 4) Endothelial function in younger obese adults. We will also be developing methods to assess protein expression in endothelial cells from obese and metabolic syndrome patients.

Project availability will depend on several factors. You will conduct a key role in one project, and assist with others. We expect at least a 10-week commitment during summer. You will work alongside the PI, 2 doctoral students, several undergraduates, a research technician, and 3 physician-scientist collaborators. A variety of techniques are used, and depending on the project, you may learn hands-on techniques, including: Doppler ultrasound, leg or arm exercise models, blood and biochemical assays, as well as helping with arterial drug infusions to manipulate vascular signaling pathways. For the full experience, you will also be expected to contribute to research design, IRB applications, data collection and analysis and writing research abstracts. Dedicated involvement could lead to the potential for writing and presenting your results as a poster submitted to a national meeting (Experimental Biology, etc).

2. Jonathan C. Makielski, MD, Professor, Medicine (Cardiovascular), H4/530 CSC, 600 Highland Avenue, Jcm@medicine.wisc.edu, 263-9648

The Cellular and Molecular Arrhythmia Research Program (CMARP) located in the basement of MSC (SMI 24) at 1300 University Avenue is a cooperative laboratory founded by faculty Makielski, January, and Kamp and now includes Lee Eckhardt and Ravi Balijepalli. It has core labs and over 20 investigators studying basic mechanisms of cardiac disease with an emphasis on arrhythmia.

The Makielski lab uses recombinant DNA technology and other biomolecular techniques to study cardiac ion channels. He has NIH funded programs to study the cardiac sodium channel, including mutations in the channel that cause arrhythmia syndromes responsible for the congenital long QT syndrome (LQT3), Brugada Syndrome, and Sudden Infant Death Syndrome (SIDS). An additional major interest funded by the NIH is the study of the ATP sensitive potassium channel (KATP) in heart and other tissues, including mitochondrial KATP using transgenic mouse models to delineate the role of KATP in ischemia and ischemic preconditioning. This project focuses on a subunit of the channel called SUR2. These basic studies have clinical implications for patients with both congenital and acquired rhythm problems, and also for myocardial protection in ischemia and during cardiac bypass. A third major project investigates the role of mutations in the inward rectifier potassium channel complex on calcium-mediated arrhythmias such as catecholaminergic polymorphic ventricular tachycardia.

The student will be given a subproject of ongoing research and will be assigned to a laboratory mentor in addition to working with Dr. Makielski. Those with little or no lab experience can learn recombinant DNA techniques and other molecular biology techniques to participate in ongoing projects involving the structure and function of ion channels and how they cause disease. For those with a mathematical or engineering background it might be possible to become involved in voltage clamp studies or computer simulations of ion channel function. The project will be tailored to the interest and skills of the student.

3. Gary E. Lyons, PhD, Professor, Anatomy, 318 Service Memorial Institute (SMI), 1300 University Ave., gelyons@wisc.edu, 262-2874

My lab is studying the potential of mouse embryonic stem cell-derived cardiac progenitors to repopulate the heart following myocardial infarction, in collaboration with the lab of Timothy Kamp, MD, PhD. This summer research opportunity will provide a medical student with training in the growth, maintenance and differentiation of mouse ES cells. Our focus is on characterizing multipotent ventricular-specific stem cells. Combined lab meetings with the Kamp lab will provide a venue for learning about human ES cells and their differentiation into cardiomyocytes. Discussions include adult stem cells and induced pluripotent cells. Techniques that the student will learn include cell culture, antibody staining, flow cytometry, cell sorting, RNA/DNA/protein extraction, western blotting and work with transgenic mice.

4. Yin Ge, PhD, Director of Mass Spectrometry, Human Proteomics Program, Cell and Regenerative Biology, 130 Service Memorial Institute (SMI), 1300 University Ave, ge2@wisc.edu, 263-9212

The student will be participating in a project aiming to establish a comprehensive cardiac troponin (cTn) assay for diagnosis of heart diseases with high sensitivity and specificity. cTn is the current biomarker of choice for acute myocardial infarction (AMI). However, commercial ELISA kits from different vendors give widely variable results, in part because antibodies are directed at distinct epitopes on cTn. cTn is known to be subjected to extensive post-translational modification but how these modifications influence clinical detection of cTn by ELISA remains almost completely unknown. Moreover, the state of post-translational modification of cTn is likely to contain additional information related to disease etiology, pathogenesis, and prognosis. Therefore, we propose to develop a simple and unbiased multi-dimensional HPLC/MS method to comprehensively characterize cTn from heart tissues and serum samples of both healthy and diseased individuals. For the summer project, the student will learn how to prepare cTn samples from human heart tissue using homogenization, subfractionation and 2D HPLC separation. The student can also be involved in mass spectrometry analysis if interested.

5. Timothy A. Hacker, PhD, Director of Cardiovascular Physiology Core Facility, Medicine (Cardiovascular), 1671 Medical Science Center (MSC), 1300 University Avenue, th2@medicine.wisc.edu, 263-1539

The Cardiovascular Physiology Core Facility is a surgical and imaging lab which creates and analyzes animal models of cardiovascular disease. The student can expect to learn echocardiography, basic surgical techniques, and general physiology lab work (genotyping, western blots, mouse colony management, data analysis, etc). The specific project for the student will examine the effects of MAPK inhibitors on a mouse model of cardiovascular disease. Activation of the MAPK pathways in various types cardiovascular disease has been established, however, the link between MAPK activation and the subsequent heart failure has not been discovered. We are using a mouse model with a mutation in a gene (*Imna* N195K) which codes for a protein that makes up the nuclear membrane. We have discovered that certain MAPK inhibitors improve cardiac function and can extend lifespan in these mice. Our next step is to figure out how MAPK inhibition works to extend lifespan. Your job will be to test additional drugs and measure pathway intermediates in these *Imna* N195K mice to determine the downstream targets of MAPK activation.

6. Bo Liu, PhD, Associate Professor, Surgery, 5137 Wisconsin Institutes for Medical Research (WIMR), 1111 Highland Avenue, liub@surgery.wisc.edu, 263-5139

The overall research goal of our laboratory is to understand the molecular and cellular mechanisms underlying vascular disease (atherosclerosis, restenosis and aneurysm) and to develop novel therapeutic strategies for vascular patients. One of the primary focuses of the lab is to understand how apoptosis of vascular smooth muscle cells influences the recruitment of inflammatory cells as well as progenitor cells to the injury site. We have identified several chemokines including SDF-1 α and MCP-1 that are upregulated by the apoptotic process. Students are invited to work along the side of graduate students and postdoctoral fellows of our laboratory 1) to define the molecular pathways by which these chemokines are regulated and their relationship with the apoptotic pathways and 2) to understand why apoptotic cells attract progenitor cells in the restenotic model but inflammatory cells in the aneurysm model. While students will primarily use a variety of in vitro approaches due to time limit, they will be exposed to in vivo studies as well.

7. Amish N. Raval, MD, Assistant Professor, Medicine (Cardiovascular), H4/568 Clinical Science Center (CSC), 600 Highland Ave., anr@medicine.wisc.edu, 265-4188

Project 1: Translational Adult Stem Cell Project

My lab has embarked on a large translational adult stem cell project to test a novel double dose, “prime and boost” therapeutic strategy for the treatment myocardial infarction. Cells will be administered intravenously (IV) early post MI and again directly into the heart muscle (IM) two weeks later. We will use a novel interventional imaging system for targeted injection of the stem cells. The goal is to demonstrate the safety and efficacy of the approach, as a prelude toward a first-in-man clinical trial. However, little is known about the acute retention of stem cells when delivered IV versus IM. This has important implications on mechanism of cell homing and effect.

The Shapiro student would consider the following hypothesis: IV administration of adult stem cells offers significantly reduced retention compared to IM administration post myocardial infarction. We have optimized the methods to perform 18F-FDG labeling of these cells. CT-PET imaging and animal protocols are already in place. The student would meet with myself regularly, but have direct supervision of a research associate in the lab.

The student would learn fundamentals of 3D cardiovascular imaging, including CT, PET and MRI. The student would generate data, analyze the data and prepare an abstract with the intent of presenting it at a major national heart society meeting. Depending on the student’s commitment and energy, a 1st author publication is entirely possible for this project.

To enhance the bed-bedside experience, the student will attend my ½ day per week UW OPTIONS clinic for no-option patients with advanced heart and vascular disease. Students will also have the opportunity to observe how stem cell injection procedures are conducted in actual patients.

Project 2: Clinical

ST Elevation Myocardial Infarction is a common and deadly condition. Regional coordination of care is required for efficient symptom recognition, ECG acquisition, inter-hospital transport and cardiac catheterization laboratory response. As part of a national registry, we collect detailed information on response times of every aspect along the chain of survival, including door to balloon time, emergency medical service (EMS) scene arrival to door time etc. Given the large rural population outside of Dane County, UW Med-flight is typically called upon for rapid patient transport. We are piloting a quality improvement where Med-flight is launched based on regional paramedic STEMI activation, based on an ECG acquired in the field. We would like to explore the feasibility of UW Med-flight intercept between the scene and Madison (akin to how we manage trauma victims), to expedite patient transport for lifesaving angioplasty.

The Shapiro student would consider the following hypothesis: A system approach to UW Medflight regional intercepts is feasible, and significantly reduces door to balloon times compared to our current approach. The student would learn about STEMI management and comprehensive data analysis. The student would be expected to prepare a minimal risk IRB protocol to retrospectively and prospectively evaluate the data obtained from the national registry of those cases where Med-flight intercepts were performed. The student would generate data, analyze the data and prepare an abstract with the intent of presenting it at a major national heart society meeting. Depending on the student’s commitment and energy, a 1st author publication is entirely possible for this project. To enhance the clinical research experience, the student will be able to observe actual STEMI cases that come to the cardiac cath-lab.

8. Pamela J. Kling, MD, Associate Professor, Pediatrics, Neonatology, 202 S. Park, Meriter Hospital, pkling@pediatrics.wisc.edu, 417-5867

Iron Deficiency in the Fetus and Newborn

The lab is working on both human samples and studying animals (fetal sheep and newborn rats). Certain fetal and neonatal conditions place infants at risk for iron deficiency. In our human study, we are examining whether it is possible to screen for depleted iron stores earlier than is traditional. Traditionally, screening for iron deficiency does not occur until 1 year of life. We are currently collecting samples at birth and screening newborns for iron status. We are assessing whether a population-based newborn screening is feasible within the construct of existing newborn screening. Certain genes may be altered when iron status is poor at birth, including genes that program asthma and allergy. Other genes that may be programmed include those that control renal development and that involved in programming of hypertension. We using newborn rats and fetal sheep to study the effects of fetal/neonatal iron deficiency on renal development, examining genes involved in the programming of adult hypertension.

9. Nan Shi, PhD, Senior Scientist/Investigator, Medicine (Cardiovascular), 024 Service Memorial Institute (SMI), 1300 University Ave, nqs@medicine.wisc.edu, 263-1172

Gender difference has been reported in key cardiovascular diseases such as ischemia and hypertrophy. I am interested in nuclear receptor biology and hormonal regulation in cardiac ion channel diseases. I have NIH or AHA funded projects studying ion channel structure/function and molecular signaling in hypertrophy cardiomyopathy and ischemia. The training opportunities include short projects using methodologies in molecular biology, animal physiology (using knockout mouse models), small molecule screening and biochemistry to investigate the above diseases. You will be working with a team of young scientists from diverse backgrounds.