

AAB CARDIOVASCULAR RESEARCH INSTITUTE

Department of Medicine

UNIVERSITY of
ROCHESTER
MEDICAL CENTER

MEDICINE of THE HIGHEST ORDER

CVRI**Beat**

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Directors' Column

Our two year anniversary at the Aab CVRI was this fall, on October 22, 2009. Our Cardiovascular Research Institute continues to expand, with new faculty, new staff, and new ideas.

We have a lot to be proud of. We now have 15 tenured faculty and 13 non-tenured faculty. Our University of Rochester Medical Center is in the top 30 medical centers for NIH funding, and we are number 12 among private institutions receiving federal research funds. Our own CVRI grant funding last year topped \$8 million!

During the last summer, we have met with two distinguished groups, our Scientific Advisory Board, and our Aab CVRI Advisory Board. Our Scientific Advisory Board gathered here on June 10, 2009 to review our progress and help us chart out our future. Dr. Edward Fisher from the New York University School of Medicine, Dr. Jose "Pepe" Jalife from the University of Michigan Medical Center, Dr. Aldon "Jake" Lulis from the University of California at Los Angeles Medical Center, and Dr. Alain Tedgui from Institut National de la Santé et de la Recherche Médicale in France, all met at the Aab CVRI. The Scientific Advisory Board listened to our presentations of our studies and gave us advice on developing our research programs.

This fall in October 7, 2009, we met with the Aab CVRI Advisory Board, which includes Mr. Richard Aab, Mr. Tansukh Ganatra, and Dr. Louis Lange. Dr. Berk, Dr. Taubman, and I spoke to our Advisory Board about the challenges and opportunities that lie ahead for all of us at the CVRI. Our Advisory Board helped us plan our strategies for future growth.

My goal is for our Aab CVRI to be one of the top 10 cardiovascular research institutes in the United States within the next five years. After listening to the advice from our Advisory Boards, here is an outline of my plans. I want to build several research programs which can help us focus our efforts. These programs will include a Thrombosis Center, a Peripheral Vascular Disease Center, and a Cardiomyopathy Center. We will construct these centers with faculty and staff already at the CVRI, with colleagues within our URM community, and with new recruits from the outside. Each center will develop a program project grant (PPG) application to help fund its activities. We will develop links between each research center and our clinical colleagues at the medical center. And each center will help train junior investigators. Collaborative work will help all of us develop new ideas, make new discoveries, and translate our findings into clinical applications. I am looking forward to a productive future! --- Charlie Lowenstein, M.D.

Howard Hughes Medical Institute (HHMI)

The Howard Hughes Medical Institute (HHMI) has awarded the University of Rochester School of Medicine and Dentistry \$700,000 to support a new program to train graduate students for a biomedical research career in cardiovascular sciences with an emphasis on translating laboratory discoveries into treatments and diagnostics.

The School of Medicine and Dentistry is one of 23 schools in the country selected by the Howard Hughes Institute to receive a grant. In total, HHMI is awarding \$16 million through its “Med into Grad Initiative,” which encourages schools to integrate medical knowledge and an understanding of clinical practice into biomedical Ph.D. programs.

The Rochester program will give students the knowledge and methodology necessary for basic research, and also will teach students about the clinical aspects of cardiovascular disease, the current limitations of its diagnosis and treatment, and the approaches to translate basic research. Graduate students, for example, will accompany clinical cardiologists as they examine, diagnose and treat a variety of patients with acute and chronic cardiovascular diseases in outpatient clinics and critical care units in the hospital. “The goal of this clerkship with cardiologists is to expose students to clinical issues and to inspire them to explore the scientific basis of medical problems,” said Charles J. Lowenstein, M.D., chief of the Division of Cardiology. “We expect that a combined medical and scientific background will prepare our graduates to pursue clinically important research topics.”

Elizabeth R. McAnarney, M.D., acting dean of the School of Medicine and Dentistry, said the HHMI grant will support a significant addition to the degree programs offered by the School. “This new program will provide graduate students with extensive education in basic research but will also give them valuable insights into clinical problems,” McAnarney said. “This will benefit our students immediately but, in the long term, it also will enhance patient care because we expect our students to initiate discoveries that will improve the treatment of cardiovascular diseases.”

Rochester’s five-year program will include a new three-semester course in cardiovascular sciences that will cover scientific principles of cardiovascular molecules and cells, physiology and pathophysiology. Students also will have courses and lab sessions in biomedical engineering.

The plan calls for approximately 20 students in the program—four students for each of the five years. The Aab Cardiovascular Research Institute (CVRI), where the program will be based, and the Medical Center will fund some of the positions. Lowenstein and Burns C. Blaxall, Ph.D., associate professor of Medicine, are co-directors of the new program.

Lowenstein, director of the CVRI, said the new curriculum will become a model for other Ph.D. programs at the University that develop disease-oriented degrees.

“We anticipate an increase in the number of projects that have direct clinical relevance,” Lowenstein said. “A long-term outcome of our new program will be an increase in publications and funding of our graduates. Researchers who have exposure to clinical clerkships will be able to select projects with high levels of significance.”

Any university in the United States that offers Ph.D. training in a biomedical science was eligible to apply for a four-year Med into Grad grant. A panel of graduate educators, biomedical researchers, and physician-scientists selected the 23 awardees from among 103 applications submitted by 92 institutions. HHMI began the Med into Grad Initiative in 2005 as an experiment to find out how graduate schools could provide doctoral students the skills necessary to investigate the scientific mechanisms of disease and translate scientific discoveries into clinically relevant treatments, diagnostics, and public health practices—and whether such programs would attract students. As a result of the initial competition, 13 schools were awarded a total of \$10 million.

The Med into Grad Initiative has been a resounding success, said Peter J. Bruns, HHMI’s vice president for grants and special programs. Participating schools are attracting top graduate students from within their departments and students are applying to some of these schools because they have a Med into Grad program.

“We’ve found this is something students are really hungry for. And it’s interesting because most of the programs require that students do work above and beyond the normal graduate curriculum, adding an extra measure of effort without eliminating anything from the basic curriculum,” Bruns said.

“In Focus”

Platelets have two major functions: hemostasis/thrombosis and an immune regulatory function. We actively study both important platelet functions.

Pathways of Platelet Activation and Thrombosis: We have recently discovered that platelets express ionotropic glutamate receptors including the AMPA and KA receptors. When stimulated, platelets release glutamate that can mediate membrane depolarization, increase GPCR signaling, and thus make platelet activation and thrombosis more efficient. We have also recently discovered that platelet glutamate receptor signaling drives COX activation and the elaboration of thromboxane, contributing to a pro-thrombotic and inflammatory vascular environment. Based on these findings we are now better defining glutamate mediated pathways of platelet activation. In collaboration with Dr. Lowenstein we are also in the initial stages of establishing a small clinical study for the use of glutamate receptor antagonists as anti-thrombotic agents.



Craig Morrell PhD DVM

Immune Regulatory Role of Platelets: Platelets have an important immune regulatory role that is not well defined. We have two main projects related to this key platelet function; the role of platelets in transplant rejection and cerebral malaria.

We have established a skin transplant model to study platelet interactions with endothelial cells and leukocytes in transplant rejection. We have found that platelets accelerate vascular damage and leukocyte trafficking across transplant endothelium in response to alloantibody. This work is being expanded to more closely examine platelet interactions with T-cells and the role of platelet-derived chemokines in transplant rejection.

Our lab is actively studying the role of platelets in cerebral malaria. Cerebral malaria is a complication of severe malaria, primarily in children, that has a vascular inflammation-based pathogenesis. Using a mouse model, we have established an important role for platelets and the platelet-derived chemokine, Platelet Factor 4 (PF4/CXCL4), in the development of experimental cerebral malaria. We are now dissecting the molecular signaling events between platelets and monocytes that promote the cerebral immune response. We are also exploring the role of platelets in stimulating the acute phase response very early in infection and how this may assist in clearing infected red blood cells.

Upcoming Scientific Events

ATVB Annual Conference in San Francisco, CA; April 8-10, 2010.

International Vascular Biology Meeting, Los Angeles, CA; June 20-24, 2010.

Comings and Goings

Welcome to our newest Aab CVRI Personnel (new arrivals since Spring Issue):

*Takashi Ito (Lowenstein Lab)
Samantha Lomber (Blaxall Lab)
Mike LoMonaco (Morrell Lab)
Craig Morrell (Morrell Lab)
Weike Mao (Alexis Lab)
Deanne Mickelsen (Microsurgical core)
Rashmi Ram (Blaxall Lab)
Leisha Robert (Shared Tech)
Vivek Nanda (Miano Lab)
Nwe Nwe Soe (Berk Lab)
Kalyan Srivastava (Morrell Lab)
Shusiuke, Yagi (Lowenstein Lab)
Munekazu Yamakuchi (“Kazu”) (Lowenstein Lab)
Guanfang Shi (Morrell Lab)
David Field (Morrell Lab)
Qizhi Chen (Taubman Lab)
Asad Zeidan (Berk Lab)*

Best Wishes and a Fond Farewell to:

Mary Georger (Miano Lab)
Chris Kovacs (Berk Lab)
Brooke Krovic (Fujiwara Lab)
Min Hur (Berk Lab)
Jaime Sorenson (Lopes Lab)

Recent Publications

Pan S, et al. (Berk BC). Glucose 6-phosphate dehydrogenase is regulated through c-Src-mediated tyrosine phosphorylation in endothelial cells. *ATVB*. 29(6); 895-901. 2009

Satoh K, et al. (Berk BC). Cyclophilin A enhances vascular oxidative stress and the development of Angiotensin II-induced aortic aneurysms. *Nature Medicine*. 15(6); 649-656. 2009

Masset MP, et al. (Berk BC). Quantitative trait loci for exercise training responses in FVB/NJ and C57BL/6J mice. *Physiol Genomics*. 2009.

Zhang N, et al. (Berk BC). GIT1 is a novel MEK1-ERK1/2 scaffold that localizes to focal adhesions. *Cell Biol Int*. 34(1); 41-47. 2009.

Pang, J, et al, (Berk, BC.) G-Protein Receptor Kinase Interacting Protein-1 Is Required for Pulmonary Vascular Development. *Circulation*. 119(11):1524-32. 2009

Miller CL, et al. (Blaxall BC). Role of Ca²⁺/calmodulin-stimulated cyclic nucleotide phosphodiesterase 1 in mediating cardiomyocyte hypertrophy. *Circ Res*. 105(10); 956-964. 2009

Cordes K.R. et al, (Miano JM.) miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. *Nature*. 460(7256); 705-710. 2009

Long X, et al. (Miano J.M.) The Smooth Muscle Cell-restricted KCNMB1 Ion Channel Subunit Is a Direct Transcriptional Target of Serum Response. *Journal of Biological Chemistry*. 284(48); 33671-33682. 2009

Lee T.H, et al. (Miano JM). Functional Characterization of a Putative Serine Carboxypeptidase in Vascular Smooth Muscle Cells. *Circ. Res*. 105:271-278. 2009

Sun Q, et al. (Miano JM). Myocardin-dependent Activation of the CARG Box-rich Smooth Muscle γ -Actin Gene. *Journal of Biological Chem*. 284(47); 3582-32590. 2009

Sun H, et al. (Morrell CN). Platelet kainate receptor signaling promotes thrombosis by stimulating cyclooxygenase activation. *Circulation Research*. 105(6):595-603. 2009

Smyth SS, Et al. (Morrell CN; for the 2009 Platelet Colloquium Participants. Platelet functions beyond haemostasis. *Journal of Thrombosis and Haemostasis*. 7(11); 1759-1766. 2009.

Wehner JR, et al. (Morrell CN). Immunological Challenges of Cardiac Transplantation: The need for Better Animal Models to Answer Current Clinical Questions. *Journal of Clinical Immunology*. 2009.

Steele BM, et al. (Morrell CN). Canonical Wnt signaling negatively regulates platelet function. *Proceedings National Academy of Science*. 106(47); 19836-19841. 2009

Pan S. Molecular Mechanisms Responsible for the Atheroprotective Effects of Laminar Shear Stress. *Antioxidants & redox signaling*. 11(7); 1669-1682. 2009

Chiang, H-Y. et al, (Sottile, J.) Fibronectin Is an Important Regulator of Flow-Induced Vascular Remodeling. *ATVB*. 29:1074-1079. 2009

Miller C.L, et al. (Yan C). Role of Ca²⁺/calmodulin-stimulated cyclic nucleotide phosphodiesterase 1 in mediating cardiomyocyte hypertrophy. Circ Res. 105(10):931-3. 2009

Grants/Awards

Stephen Belmonte, *Functional Implication of Mena and its Modulation in the Heart* (AHA)

Burns Blaxall, *A role for Mena in the heart* (NIH, R01)

Burns Blaxall, *Visualsonics Vevo 2100* (NIH, S10 equipment grant)

Latika Dhawan, *Regulation of MCP-1 mRNA stability in smooth muscle cells* (AHA-SDG National)

Patrizia Nigro received the ATVB Travel Award for the November AHA 2009 meeting

Jin O-Uchi, *Isoform-specific PKC modulation of IKs channel in Long QT syndrome* (AHA Post-Doc)

American Reinvestment and Recovery Act (ARRA) Awards

Burns Blaxall; Zheng-Gen Jin; Craig Morrell; Jane Sottile

Promotions

Staff Promotions:

To Tech Associate I
Chelsea Wong, B.S.

Faculty Promotions:

To- Associate Professor
Burns Blaxall, PhD