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AAB CARDIOVASCULAR RESEARCH INSTITUTE
Department of Medicine

CVRI Beat

UNIVERSITY of ROCHESTER MEDICAL CENTER
MEDICINE of THE HIGHEST ORDER

Upcoming Scientific Events:

ATVB Scientific Sessions 2011 in Chicago, IL on April 28-30 2011
International Society on Thrombosis and Haemostasis in Kyoto, Japan on July 23-28, 2011

Director's Column

Winter is almost over! Soon, flowers will be in bloom ushering in warmer weather and the anticipation of children finishing their school year.

Meanwhile, the Aab CVRI continues to grow in important ways. This past January, Alberti & Associates successfully oversaw the installation of a new fly wheel Uninterrupted Power Supply (or UPS). The addition of this state-of-the-art device will ensure continuous electrical power during a power outage for all equipment plugged into red emergency outlets. We thank the University and Alberti & Associates for making this much-anticipated installation a reality. Recently, work has been initiated to complete the "shelled" rooms within our vivarium. We are grateful that all three rooms will be completed at once to meet the growing demand of our research and, at the same time, minimize future disruption to our precious mouse colony. We expect that completion of the vivarium-shelled space will be in mid-May. Speaking of the vivarium, we welcome Dr. Kyung ae Ko who has been hired to further augment our animal surgery core. Kyung ae is a veterinarian trained in Korea and brings her clinical and surgical skills to the surgery core. Kyung ae can now perform carotid ligations and hindlimb ischemia and is rapidly making progress towards adding TAC to her repertoire.

We are expanding the capacity of the CVRI in significant new ways. We have bought a new confocal microscope that will be available for all of us to image our cells and tissues and acquire more data. We are able to make this new purchase because of the generosity of Mr. Richard Aab. Read the accompanying article by Keigi Fujiwara to learn why our new confocal microscope is more colorful than the old one!

Beginning this month, we will be interviewing a number of prospective tenure track faculty candidates. All are encouraged to attend the seminars as we work towards a modest expansion of our research faculty. We have encouraged applications from investigators with accomplishments in the following areas: Atherosclerosis, Vascular Inflammation, Thrombosis, and Heart Failure. Our guest speakers are from a variety of labs at a range of top-notch institutions.

The Aab CVRI continues to thrive with the generous gifts from Mr. Aab, institutional support from the University of Rochester, and with your good ideas and hard work. Thank you for making the Aab CVRI an exciting place to work!
-- Charlie Lowenstein, MD

Technical Corner

Keigi Fujiwara, PhD

An image we observe in an ordinary microscope contains both in-focus and out-of-focus images. The latter reduces the contrast of the in-focus image and creates 'softness' of the image. These features reduce the resolution of microscope images. Light carrying out-of-focus information is particularly disturbing for fluorescence microscopy of thick specimens, as it becomes general background fluorescence against which in-focus images are embedded. Microscopists were wondering if there was a way to remove the out-of-focus images, and in 1957, a theoretical solution to this problem was proposed by a postdoctoral fellow at Harvard. It took 30 more years to make a microscope that could do the job, for which high intensity monochromatic light sources (laser),

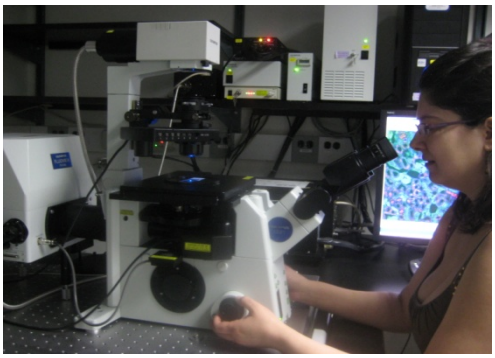
Technical Corner continued…

precise scanning mechanisms, highly sensitive photo detectors, and computers that can rapidly process acquired images were necessary. The first commercial laser scanning confocal (confocal: having the same focus) microscope (LSCM) unit was manufactured by BioRad, and quickly all major microscope companies built their own LSCMs. Laser scanning confocal microscopy indeed eliminates out-of-focus images providing crisp optical sections of the specimen and is now a standard technique for localizing proteins inside cells and tissues. Because images are digitized, one can easily create 3-dimensional images of the specimen by stacking optical sections generated by this opto-electronic device.

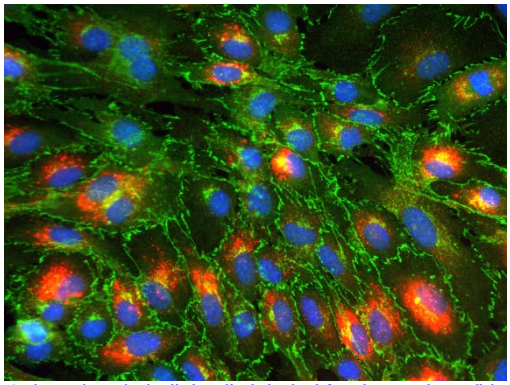
Our LSCM was purchased more than 10 years ago, and in recent years, its capabilities have become a limiting factor, given the ever-increasing demand for more sophisticated and precise bioimaging. However, a state-of-the-art LSCM has a price tag of several hundred thousand dollars.

With the generous gift of Mr. Aab, we were able to upgrade our old LSCM to the top-of-the-line Olympus model. The Fluoview 1000 is configured to accommodate the needs of the current Aab CVRI investigators but is also configured to meet future needs. It is mounted on a computer controlled inverted microscope (Olympus IX81) equipped with epi-fluorescence capability for blue (DAPI), green (FITC, GFP, EGFP, Alexa 488), and red (Texas Red, rhodamine, Alexa 556) fluorescence viewing and DIC optics. Our new LSCM has several unique features. (1) It has 7 laser lines (405, 440, 458, 488, 515, 559, and 635 nm), which enables us to use a variety of fluorescent dyes in various combinations. (2) Instead of the standard filter detection system, it is equipped with a spectral detection system. While the filter-based detection system is limited to detecting a set of preselected (this is done at the time of purchase) wavelengths determined by the transmission characteristics of the filters, spectral detection allows us to "design personalized barrier filters" so that we can image specimens using any wavelength of fluorescent light. (3) The Fluoview 1000 is capable of imaging the same specimen in a set of up to 4 different fluorescent wavelengths. These features make our LSCM very versatile and present a platform for creative confocal fluorescence imaging. In addition, the software of Fluoview 1000 comes with FRAP (fluorescence recovery after photo-bleaching) capability. This imaging technique allows us to study dynamic movements of molecules within cells.

This gift of Mr. Aab is timely as increasing numbers of PIs want to do multi-color fluorescence imaging with precise Z-axis resolution. It is also timely as high impact journals demand increasingly sophisticated analyses and presentations of image data. Using the new scope, we will be able to meet the challenge. Indeed, the new LSCM fulfills the long-standing need for improved confocal imaging here at the Aab CVRI. If you are interested in using this instrument, please contact Keigi Fujiwara and Tamlyn Thomas for training.

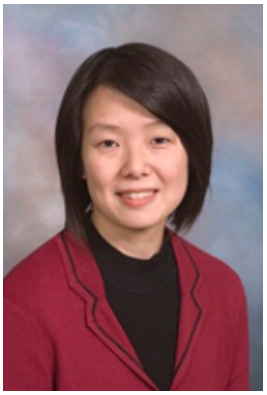


Tamlyn Thomas operating Fluoview 1000.



Cultured endothelial cells labeled for the nucleus (blue), LDL uptake (red) and VE-cadherin (green) for cell border identification.

"In Focus"



Chen Yan, PhD

Cyclic nucleotides, cAMP and cGMP, are critical intracellular second messengers involved in many fundamental biological processes in the cardiovascular system, ranging from acute effects on cellular contraction/relaxation to chronic effects on gene expression and tissue remodeling. The versatility and specificity of cyclic nucleotide function is dependent on the organization of multiple divergent macromolecular complexes containing unique cyclases, phosphodiesterases (PDEs), kinases, and anchoring proteins. PDEs, by catalyzing the

In Focus continued...

hydrolysis of cAMP and cGMP, play very important roles in the regulation of the amplitude, duration, and compartmentalization of intracellular cyclic nucleotide signaling. Dysregulation of PDE activity/expression has been closely associated with various diseases and several PDE inhibitors such as Viagra are currently available or in development for treatment of these pathological conditions. Therefore, we are particularly interested in defining and characterizing the specific PDE isoform that is dysregulated and contributes significantly to the pathological vascular and cardiac remodeling in diseases such as atherosclerosis, aneurysm, and heart failure.

Recently, we have found that the PDE1C isoform is specifically expressed in growing vascular smooth muscle cells (SMCs) in vascular lesions, while is not expressed in normal quiescent SMCs. PDE1C plays important roles in aberrant SMC activation and in injury-induced mouse carotid artery remodeling. We are currently determining the role and underlying mechanism of PDE1C action and signaling in SMC pathogenesis and vascular diseases such as atherosclerosis and aneurysm using PDE1C knockout mice and PDE1C-selective pharmacological inhibitors. Thus, our studies may lead to the novel discovery of PDE1C as an important therapeutic target for these vascular diseases. In addition, we have also demonstrated that PDE1A isoform is highly induced in cardiac myocytes and activated cardiac fibroblasts in diseased rodent and human hearts. PDE1A plays critical roles in cardiac myocyte hypertrophy as well as in cardiac fibroblast activation and ECM production. Our results suggest that upregulated PDE1A contributes significantly to the pathological cardiac remodeling, and targeting PDE1A may represent a potential therapeutic strategy to regress the adverse cardiac remodeling associated with various cardiac diseases.

Recent Publications

Kamal, F.A., Smrcka, A.V., Blaxall, B.C.. Taking the heart failure battle inside the cell: Small molecule targeting of Gβγ. Journal of Melecular and Cellular Cardiology. 2011.

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Miano, JM. Dicing up microRNA gene expression profiles in normal and neoplastic muscle cells. Am J Pathol. 177(2):541-543. 2010

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New Grants/Awards

Dr. Brad Berk was awarded funding by the NIH for his R01 entitled, *Flow Responsive Mediators of Inflammation and Survival*.

Dr. Keigi Fujiwara was awarded an AHA Grant-in-Aid for his application, *Mechanism of PECAM-1 Tyrosine Phosphorylation.*

Dr. Slava Korshunov received his first NIH R01 Award entitled, *The Role of Immune Response in Vascular Dysfunction in Hypertension*. As a new investigator he is funded for a full 5 years.

Dr. Jane Sottile received funding from the AHA for her Grant-in-Aid, *Regulation of SMC Differentiation and Inflammation by Fibronectin.*

Dr. Mark Taubman received funding from the NIH for his R01 entitled, *Smooth Muscle Cell Tissue Factor and Cardiovascular Disease.*

Dr. Jun-ichi Abe received the prestigious Vascular Biology Special Recognition award from ATVB.

Dr. Burns Blaxall was elected to the Editorial Board of Circulation Research.

Comings and Goings

Welcome to our newest Aab CVRI Personnel:

Dr. Padmamalini Baskaran
Research Assistant Professor
Berk Lab

Dr. Jin Man Cho
Visiting Research Associate Professor
Berk Lab

Sarah Cowan
Lab Technician
Miano Lab

Dr. Amit Dhamoon
Postdoctoral Research Associate
Lowenstein Lab

Mike Getman
Technical Associate
Berk Lab

Alison Hobbins
Lab Technician
Berk Lab

Dr. Zhao-Yang Hu
Postdoctoral Research Associate
Blaxall Lab

Cheryl Hurley
Lab Technician
Abe Lab

Dr. Fadia Kamal
Postdoctoral Research Associate
Blaxall Lab

Dr. Kyung Ae Ko
Technical Associate
Animal Surgical Core

Mike Mastrangelo
Technical Associate
Jin Lab

Dr. Shin-Young Park
Postdoctoral Research Associate
Berk Lab

Dr. Mark Sowden
Research Associate Professor
Berk Lab

Allison Hendershot
Technical Associate III
Sottile Lab

Best Wishes and a Fond Farewell to:

Dr. Takashi Ito is currently in Kagoshima, Japan working as an Assistant Professor at Kagoshima University.

Clint Miller completed his graduate studies at the Aab CVRI and will be relocating to California to pursue his postdoctoral fellowship.

Dr. Patrizia Nigro is currently in Milan, Italy working at the Laboratorio di Biologia Vascolare e Medicina Rigenerativa and is busy preparing for her wedding in July.

Masayoshi (Masa) Oikawa will be leaving us this month and returning to Fukushima Medical University, Fukushima, Japan, where he will return to practice medicine. We wish Masa and his family safe travel back to Japan.

Dr. Shi Pan joined the lab of Dr. Shey-Shing Sheu in the Center for Translational Medicine at Thomas Jefferson University in Philadelphia.

Chelsea Wong is enjoying being a stay-at-home mom. Chelsea, Bently and baby Caleb are doing well.

Dr. Chang-Hoon Woo is working in the Department of Pharmacology at Yeungnam University College of Medicine in Korea.

Congratulations!

CVRI members Craig Morrell and Joe Miano with their Red Bull Cup

The extra ice time at the CVRI's ice rink came in handy on the weekend of February 12-13 as CVRI Faculty, Craig Morrell and Joe Miano (above), won the over 35 division in the annual Red Bull Pond Hockey Tournament held in Churchville. Burns Blaxall, who was to have played but had been injured in a separate hockey game, showed great team spirit in making the trek out and providing support. The team, named "Jeff is Back", in honor of teammate Jeff MacInnes who dislocated his elbow in last year's tournament but came back to play this year, was awarded a Red Bull Cup (held up by Miano and teammates in photo above). All players received a case of Red Bull and the Captain, Dr. Morrell, was given a new hockey helmet he donated to charity (his brother, also a teammate). Let's see if they can repeat at next year's tournament!