

Contacts

If you would like to be added to the CBAC email list to receive information on upcoming seminars, events, and news, or to be added to the CBAC mailing list to receive future newsletters, email cbac@biomed.wustl.edu or call 314.935.7887.

Contact Information:

Cardiac Bioelectricity and Arrhythmia Center (CBAC)

Washington University in St. Louis
Whitaker Hall, Room 290A
1 Brookings Drive, Campus Box 1097
St. Louis, MO 63130-4899, USA
Phone: 314.935.7887
Fax: 314.935.8168
www.cbac.edu
www.rudylab.edu



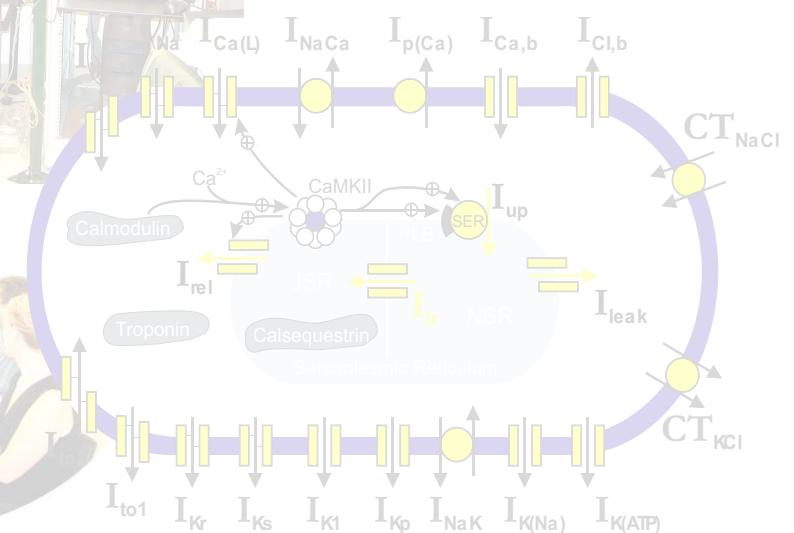
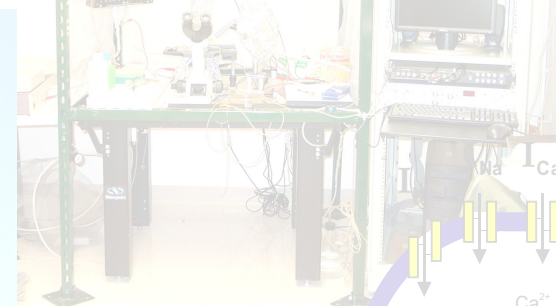
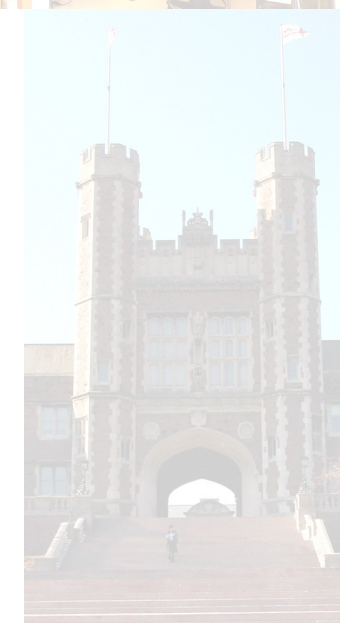
Whitaker Hall Atrium, home to the Department of Biomedical Engineering and the CBAC.



Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S., Director



An interdisciplinary approach to
studying and treating rhythm
disorders of the heart



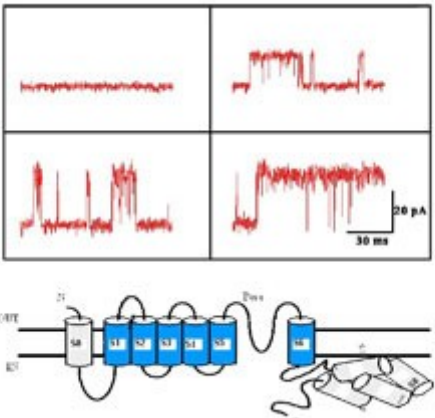
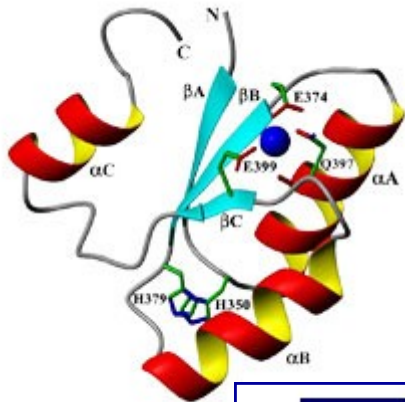
Cardiac Bioelectricity and Arrhythmia Center (CBAC)



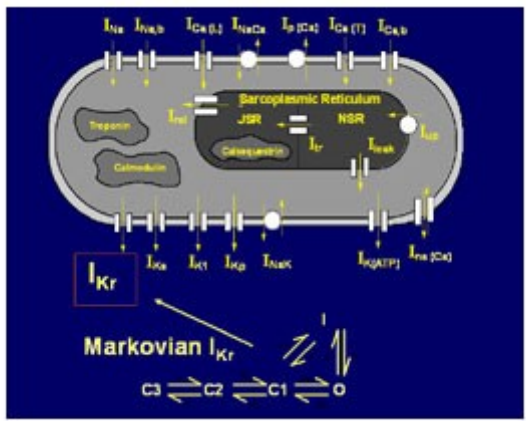
The **Cardiac Bioelectricity and Arrhythmia Center, CBAC**, is an interdisciplinary center whose goals are to study the mechanisms of rhythm disorders of the heart (cardiac arrhythmias) and to develop new tools for their diagnosis and treatment. Cardiac arrhythmias are a major cause of death (over 300,000 deaths annually in the US alone; estimated 7 million worldwide) and disability, yet mechanisms are poorly understood and treatment is mostly empirical. Through an interdisciplinary effort, CBAC investigators apply molecular biology, ion-channel and cell electrophysiology, optical mapping of membrane potential and cell calcium, multi-electrode cardiac electrophysiological mapping, Electrocardiographic Imaging (ECGI) and other noninvasive imaging modalities, and computational biology (mathematical modeling) to study mechanisms of arrhythmias at all levels of the cardiac system. Our mission is **to battle cardiac arrhythmias and sudden cardiac death through scientific discovery and its application in the development of mechanism-based therapy.**

Visit the CBAC website at <http://cbac.wustl.edu/> to get more information about the research, CBAC members and seminars. There is also a video archive from past seminars that is updated following each season of seminars that is available for viewing.

Molecular Structure of Cardiac Ion Channels



Structure/Function of Cardiac Ion Channels



Mathematical Modeling of Cardiac Cells and Tissue

More Publications Fall 2007-Spring 2008



- * Marionneau, C., Aimond, F., Brunet, S., Niwa, N., Finck, B., Kelly, D.P., and **Nerbonne, J.M.** PPARα-mediated remodeling of repolarizing voltage-gated K⁺ (Kv) channels in a mouse model of metabolic cardiomyopathy. *Journal of Molecular and Cellular Cardiology*, in press (2008).
- * **Y. Rudy**, "Molecular Basis of Cardiac Action Potential Repolarization", *Annals of the New York Academy of Sciences* 2008;1123:113-118.
- * Y. Wang, Li Li, P.S. Cuculich, **Y. Rudy**, "Electrocardiographic Imaging of Ventricular Bigeminy in a Human Subject", *Circulation Arrhythmia and Electrophysiology* 2008;1:74-75.
- * N. Varma, P. Jia, **Y. Rudy**, "Placebo CRT", *J Cardiovasc Electrophysiol* 2008; 19:878.
- * S. Ghosh, J.N. Avari, E.K. Rhee, P.K. Woodard, **Y. Rudy**, "Noninvasive Electrocardiographic Imaging (ECGI) of a Univentricular Heart with Wolff-Parkinson-White Syndrome", *Heart Rhythm* 2008; 5: 605-608.
- * S. Ghosh, J.N. Avari, E.K. Rhee, P.K. Woodard, **Y. Rudy**, "Noninvasive Electrocardiographic Imaging (ECGI) of Epicardial Activation before and after Ablation of Accessory Pathway in a Patient with Ebstein's Anomaly", *Heart Rhythm* 2008;5:857-860.
- * M. Bebarova, T. O'Hara, J.L.M.C. Geelen, R.J. Jongbloed, C. Timmermans, Y.H. Arens, L.M. Rodriguez, **Y. Rudy**, P.G. Volders, "Subepicardial phase-0 block and discontinuous transmural conduction underlie right-precordial ST-segment elevation by a SCN5A loss-of-function mutation", *Am J Physiol Heart Circ Physiol* 2008;295:H48-H58.
- * S. Ghosh, J.N. Avari, E.K. Rhee, P.K. Woodard, **Y. Rudy**, "Hypertrophic Cardiomyopathy with Pre-excitation: Insights from Noninvasive Electrocardiographic Imaging (ECGI) and Catheter Mapping", *J Cardiovasc Electrophysiol* 2008 (in press).
- * T.J. Hund, K.F. Decker, E. Kanter, P.J. Mohler, P.A. Boyden, R.B. Schuessler, K.A. Yamada, **Y. Rudy**, "Role of activated CaM-KII in abnormal calcium homeostasis and I_{Na} remodeling after myocardial infarction: Insights from mathematical modeling", *J of Molecular and Cellular Cardiology* 2008 (in press).
- * S. Ghosh, E.K. Rhee, J.N. Avari, P.K. Woodard, **Y. Rudy**, "Cardiac Memory in WPW Patients: Noninvasive Imaging of Activation and Repolarization before and after Catheter Ablation", *Circulation* 2008;118:907-915.
- * A. Nekouzadeh, J. Silva, **Y. Rudy**, "Modeling subunit cooperativity in opening of tetrameric ion channels" *Biophysical Journal* 2008 (in press)
- * Y. Wang and **Y. Rudy**, "Electrocardiographic Imaging (ECGI) of Normal Human Atrial Repolarization" *Heart Rhythm Journal* 2008 (in press)
- * **Y. Rudy**, M.J. Ackerman, D. M. Bers, C. E. Clancy, S. R. Houser, B. London, A. D. McCulloch, D. A. Przywara, R. L. Rasmusson, R. J. Solaro, N. A. Trayanova, D. R. Van Wagoner, A. Varró, J. N. Weiss, D. A. Lathrop, "Systems Approach to Understanding Electromechanical Activity in the Human Heart" *Circulation* 2008; 118: 1202-1211.
- * J Silva and **Y. Rudy**, "Ionic Mechanisms of Ventricular Action Potential Excitation" In: *Cardiac Electrophysiology: From Cell to Bedside*, 5th edition, Eds. D.P. Zipes and J. Jalife. Elsevier Science Publisher, 2008 (in press).
- * **Y. Rudy**, C. Ramanathan, S. Ghosh, "Noninvasive Electrocardiographic Imaging (ECGI): Methodology and Excitation of the Normal Human Heart" In: *Cardiac Electrophysiology: From Cell to Bedside*, 5th edition, Eds. D.P. Zipes and J. Jalife. Elsevier Science Publisher, 2008 (in press).
- * **Y. Rudy**, Y. Wang, P. Cuculich, "Noninvasive Electrocardiographic Imaging (ECGI): Examples of Clinical Applications" In: *Cardiac Electrophysiology: From Cell to Bedside*, 5th edition, Eds. D.P. Zipes and J. Jalife. Elsevier Science Publisher, 2008 (in press).
- * N. Varma, P. Jia, **Y. Rudy**, "Electrocardiographic Imaging of Heart Failure Patients with Left Bundle Branch Block. Effects of Right Ventricular Pacing and Cardiac Resynchronization Therapy" In: *Cardiac Mapping*, 3rd edition, Eds. M. Shenasa, G. Hindricks, M. Borggreffe, G. Breithardt. Blackwell Publishing, 2008 (in press).
- * N. Varma, P. Jia, **Y. Rudy**, "The Role of Electrocardiographic Imaging in Cardiac Resynchronization Therapy" In: *Cardiac Resynchronization Therapy in Heart Failure* Eds. W. T. Abraham and R.R. Baliga. Lippincott Williams & Wilkins, 2008 (in press).

More Publications
Fall 2007-Spring 2008



- * Nassir, F., Wilson, B., Han, X., **Gross, R.W.**, and Abumrad, N.A. CD36 is important for fatty acid and cholesterol uptake by the proximal but not distal intestine. *J. Biol. Chem.* 2007, 282:19493-19501.
- * Han, X., Yang, J., Yang, K., Zhao, Z., Abendschein, D.R., and **Gross, R.W.** Alterations in myocardial cardiolipin content and composition occur at the very earliest stages of diabetes: A shotgun lipidomics study. *Biochemistry* 2007, 46:6417-6428.
- * Yang, J., Sambandam, N., Han, X., **Gross, R.W.**, Courtois, M., Kovacs, A., Febbraio, M., Finck, B.N. and Kelly, D.P. CD36 deficiency rescues lipotoxic cardiomyopathy. *Circulation Research* 2007, 100:1208-1217.
- * Sun, G., Yang, K., Zhao, Z., Guan, S., Han, X., and **Gross, R.W.** Shotgun metabolomics approach for the analysis of negatively charged water-soluble cellular metabolites from mouse heart tissue. *Anal. Chem.* 2007, 79:6629-6640.
- * Burkard, E.M., Sambandam, N., Han, X., **Gross, R.W.**, Courtois, M., Gierasch, C.M., Shoghi, K. Welch, M.J., and Kelly, D.P. The nuclear receptors PPARb/d and PPARa direct cardiac metabolic regulatory program. *J. Clin. Invest.* 2007, 117:3930-3939.
- * Jiang, X., Cheng, H., Yang, K., **Gross, R.W.**, and Han, X. Alkaline methanolysis of lipid extracts extends shotgun lipidomics analyses to the low abundance regime of cellular sphingolipids. *Anal. Biochem.* 2007, 371:135-145.
- * Malik, I., Turk, J., Mancuso, D.J., Montier, L., Wohltmann, M., Wozniak, D.F., Schmidt, R.E., **Gross, R.W.**, and Kotzbauer, P.T. Disrupted membrane homeostasis and accumulation of ubiquitinated proteins in a mouse model of infantile neuroaxonal dystrophy due to PLA2G6 mutations. *Am. J. Pathol.* 2007, 172:406-416.
- * Yang, K., Zhao, Z., **Gross, R.W.**, and Han, X. Shotgun lipidomics identifies a paired rule for the presence of isomeric ether phospholipid molecular species. *PLoS ONE* 2007, 12:e1368.
- * Han, X. and **Gross, R.W.** Free fatty acids and lipids. In *Choice of Ionization for Analysis of Various Substances* (Vol. 6 of Encyclopedia of Mass Spectrometry), 2007, 876-889, Elsevier Ltd.
- * **Gross, R.W.** and Han, X. Lipidomics in Diabetes and the Metabolic Syndrome. In *Methods Enzymology. Lipidomics and Bioactive Lipids: Specialized Analytical Methods and Lipids in Disease*, (H. Alex Brown, editor), 2007, Vol. 433C:73-90, Elsevier Inc.

.....

- * London, B., Baker, L.C., Petkova-Kirova, P., **Nerbonne, J.M.**, Choi, B.-R., and Salama, G. Dispersion of repolarization and refractoriness are determinants of arrhythmogenic phenotype in transgenic mice with long QT. *Journal of Physiology* 578: 115-129 (2007).
- * Laezza, F., Gerber, B.R., Lou, J.-L., Kozel, M., Hartman, H., Craig, A.M., Ornitz, D.O., and **Nerbonne, J.M.** The FGF14^{F145S} mutation disrupts the interaction of FGF14 with voltage-gated Na⁺ channels and impairs neuronal excitability. *Journal of Neuroscience* 27: 2033-2044 (2007).
- * Lehnart, S.E., Ackerman, M.J., Benson, D.W. Jr., Brugada, R., Clancy, C.E., Donahue, J.K., George, A.L. Jr., Grant, A.O., Groft, S.C., January, C.T., Lathrop, D.A., Lederer, W.J., Makielski, J.C., Mohler, P.J., Moss, A., **Nerbonne, J.M.**, Olson, T.M., Przywara, D.A., Towbin, J.A., Wang, L.H., and Marks, A.R. Inherited Arrhythmias: A National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 116: 2325-2345 (2007).
- * Li, J., Marionneau, C., Koval, D., Zingman, L., Mohler, P., **Nerbonne, J.M.**, and Anderson, M.E. Calmodulin kinase II inhibition enhances ischemic preconditioning by augmenting ATP-sensitive K⁺ current. *Channels* 1: 387-394 (2008).
- * Niwa, N., Wang, W., Sha, Q., and **Nerbonne, J.M.** Kv4.3 is not required for the generation of functional I_{to,f} channels in adult mouse ventricles. *Journal of Molecular and Cellular Cardiology* 44: 95-104 (2008).
- * **Nerbonne, J.M.**, Gerber, B., Mellor, R.L., and Burkhalter, A. Electrical remodeling maintains firing properties in cortical pyramidal neurons lacking KCND2-encoded A-type K⁺ currents. *Journal of Physiology* 586: 1565-1579 (2008).
- * Marionneau, C., Brunet, S., Flagg, T.P., Pilgram, T.K., Demolombe, S. and **Nerbonne, J.M.** Distinct cellular and molecular mechanisms underlie functional remodeling of repolarizing K⁺ currents with left ventricular hypertrophy. *Circulation Research*, in press (2008).

An interdisciplinary approach to studying and treating rhythm disorders of the heart

CBAC HOSTS VISITORS FROM INTERNATIONAL
COLLABORATING UNIVERSITIES

Since May 1, 2008, Jordi Heijman, PhD student at Maastricht University in The Netherlands has been working in the lab of Dr. Yoram Rudy, (the Rudy Lab <http://rudylab.wustl.edu/>) as a next step in the collaboration between Maastricht University and the CBAC. Heijman is interested in using mathematical models to analyze the emergent dynamics arising in the heart from various subcellular (signaling) components. Heijman will work in the Rudy Lab for one year, with the exception of a brief return visit to be a speaker at the “Frontiers in Computational Cardiology” workshop being sponsored by the Departments of Cardiology and Mathematics in Maastricht on September 17, 2008. Jordi provides insight on the CBAC/Maastricht collaboration and his hopes for the future:



Jordi Heijman,
Maastricht University

“The Faculty of Health Medicine and Life Sciences, and the Academic Hospital Maastricht (now together as Maastricht University Medical Centre) have always been very important for Maastricht University. In this group, the field of Cardiology/ Electrophysiology has had a primary position with renowned scientists such as Professor Wellens, Professor Allesie and Professor Reneman, who played a major role in the establishment of the Cardiovascular Research Institute Maastricht (CARIM). However, the computational aspects have not received the same attention and the Department of Mathematics (now Maastricht Information and Communication Technology Competence Centre), is relatively small. Nonetheless it is clear that both computational and experimental techniques have to be combined in order to increase our understanding of a system as complex as the human heart. That is why, in the last few years, two things have happened. On the one hand a closer collaboration between the Department of Mathematics and the Department of Cardiology has arisen. (cont’d on page 4)

Maastricht University, The Netherlands

Maastricht , the capital of the Providence of Limburg is situated at the heart of the Euregion Meuse-Rhine where the borders of The Netherlands, Belgium and Germany meet. Maastricht is a springboard to the cities of Amsterdam, London, Paris and Brussels



Maastricht Skyline



Streets of Maastricht



Maastricht University Visitors Center and
(R) Randwijck Medical Campus.



An interdisciplinary approach to studying and treating rhythm disorders of the heart

CBAC HOSTS VISITORS CONT'D.

On the other hand however, we lack the many years of experience with respect to the modeling of the cardiac system that is available in the CBAC. As a result, the benefit for Maastricht of the CBAC - Maastricht collaboration is to further establish our computational branch of the research in Cardiology/Electrophysiology. For CBAC, one of the advantages could be the strong coupling between basic research in cardiology and clinical and experimental validations and applications. It is clear that the collaboration between CBAC and Maastricht is growing stronger and is very productive. One example is the joint publication of experimental work from Maastricht with a CBAC model (M. Bebarova, T. O'Hara, et al. Am. J. P. Heart 2008). Another example is the visit of a Maastricht Ph.D. student (myself) to the CBAC, and very importantly the appointment of Dr. Rudy as the Hein J. J. Wellens Distinguished Professor 2008-2009 at Maastricht University. Also, the partnering of the Departments of Cardiology and Mathematics to host the "Frontiers in Computational Electrocardiology" workshop where myself, Dr. Rudy and Dr. Philip Cuculich, a Clinical Fellow in the Washington University Cardiovascular Division and a CBAC member, are all speakers illustrates these collaborations." For more information on the "Frontiers in Computational Electrocardiology" workshop visit <http://www.unimaas.nl/computationalelectrocardiology/>.

Page 4

"Personally, I hope to obtain a lot of experience with respect to the modeling of cardiac electrophysiology from the CBAC/ Maastricht collaboration in order to be able to help further establish the computational cardiology research in Maastricht. So far, I have already learned numerous things and I find it very interesting to work in this demanding but exciting environment."

INSIDE THIS ISSUE:

- 2...CBAC Mission
- 3...CBAC Hosts Visitors from International Collaborations
- 5....Collaborations With Taiwan
- 6....From The Director's Desk
- 8....CBAC Special Summer Seminar
- 9....Focus On Dr. Charles Antzelevitch, Guest Speaker for the CBAC Spring '08 Seminars
- 10....Spotlight On "Dr. Jeanne Schaffer"
- 11.....Ph.D.'s on Point: Celine Marionneau, Ph.D.
- 12...Outside the Walls of the CBAC
- 12...Lectures & Presentations
- 15...New CBAC Members
- 16...CBAC Faculty Members
- 18...Announcements & News
- 19...Awards & Honors
- 20...CBAC Fall 2008 Seminar Schedule
- 21...Publications
- 24...CBAC Contact Information

The CBAC hosted many visitors over this past year and we've taken this opportunity to share with you some of the experiences of the scholars who have crossed the continent for the opportunity to do research in the Rudy Lab. On page 3 is Jordi Heijman who will be in the Rudy Lab working on collaborative research until May 2009. Snapshots of his campus, Maastricht and his home in The Netherlands are featured.



(Above) The Sunny city of Perth, Australia. The CBAC had a special guest speaker for a seminar this summer, Dr. Livia Hool from the University of Western Australia, read more on pg.8. (U-R) Dr. Rudy explains the dining etiquette of Ethiopian cuisine during the CBAC dinner with guests from Taiwan; (L-R) Dr. Rudy traveled to the Technion in Israel May, 2008, as the liaison for the McDonnell International Scholars Academy.

Page 21

CBAC Faculty Publications
Fall 2007-Spring 2008



- * Efimov, IR, Nature Versus Nurture in Cardiac Conduction: Toward Integrative Paradigm of Cardiac Tissue Engineering, Circ. Res., Circ. Res. 2008; 103:119-121.
- * Hucker WJ, Fedorov VV, Foyil KV, Moazami N, Efimov, IR, Optical Mapping of the Human Atrioventricular Junction, Circulation, 2008, 117(11): 1474-7.
- * Fedorov VV, Kostecki G, Hemphill M, Efimov, IR, Atria are more susceptible to electroporation than ventricles: Implications for atrial stunning, shock-induced arrhythmia and defibrillation failure, Heart Rhythm J., 2008, 5(4): 593-604.
- * Li J, Greener ID, Inada S, Nikolski VP, Yamamoto M, Billeter R, Efimov IR, Dobrzynski H, Boyett MR, Computer three-dimensional reconstruction of the atrioventricular node, Circ. Res., 2008, 102: 975-985.
- * Hucker WJ, McCain ML, Laughner JI, Iaizzo PA, Efimov IR, Connexin 43 Expression Delineates Two Discrete Pathways in the Human Atrioventricular Junction, Anat. Rec., 2008, 291(2): 204-15.
- * Fedorov VV, Nikolski VP, Efimov IR. Effect of electroporation on cardiac electrophysiology. Methods Mol Biol. 2008; 423: 433-48.
- * Estes NAM, Damiano RJ Jr: Surgery for atrial fibrillation: Current state of the art. J Interv Card Electrophysiol 2007;20:57 (Guest Editor)
- * Schuessler RB, Damiano RJ Jr: Mechanisms of human atrial fibrillation: Lessons learned from 20 years of atrial fibrillation surgery. J Interv Card Electrophysiol. 2007; 20:59-64
- * Lall SC, Damiano RJ Jr. Surgical ablation devices for atrial fibrillation. J Interv Card Electrophysiol 2007;20:73-82
- * Damiano RJ Jr, Voeller, RK: Biatrial lesion sets. J Interv Card Electrophysiol 2007;20:95-99
- * Estes NAM, Damiano RJ Jr: Curing atrial fibrillation: Two decades of progress. J Interv Card Electrophysiol 2007;20:127-131
- * Wang Y, Schuessler RB, Damiano RJ, Woodward PK, Rudy Y: Noninvasive electrocardiographic imaging (ECGI) of scar-related atypical atrial flutter. Heart Rhythm 2007;4:1565-1567
- * Lall SC, Foyil KV, Sakamoto S-I, Voeller RK, Boineau JP, Damiano RJ Jr, Schuessler RP: Pulmonary vein isolation and Cox-Maze procedure only partially denervate the atrium. J Thorac Cardiovasc Surg 2008;135:894-900
- * Voeller RK, Bailey MS, Zierer A, Lall SC, Sakamoto S, Aubuchon K, Lawton JS, Moazami N, Huddleston CB, Munfakh NA, Moon MR, Schuessler RB, Damiano RJ Jr: Isolating the entire posterior left atrium improves surgical outcomes following the Cox-Maze procedure. J Thorac Cardiovasc Surg 2008;135:870-877.
- * Olsen MA, Krauss M, Agniel D, Schootman M, Gentry CN, Yan Y, Damiano RJ Jr, Fraser VJ: Mortality associated with blood-stream infection following coronary artery bypass graft. Clin Infect Dis 2008;46:1537-154.
- * Mancuso, D.J., Han, X., Jenkins, C.M., Lehman, John J., Sambandam, N., Sims, H.F., Yang, J., Yan, W., Yang, K., Green, K., Abendschein, D.R., Saffitz, J.E., and Gross, R.W. Dramatic accumulation of triglycerides and precipitation of cardiac hemodynamic dysfunction during brief caloric restriction in transgenic myocardium expressing human calcium-independent phospholipase A2g J. Biol. Chem. 2007, 282:9216-9227.
- * Mancuso, D.J., Sims, H.F., Han, X., Jenkins, C.M., Guan, S.P., Yang, K., Moon, S.H., Pietka, T., Abumrad, N., Schlesinger, P.H., and Gross, R.W. Genetic ablation of calcium-independent phospholipase a2g leads to alterations in mitochondrial lipid metabolism and function resulting in a deficient mitochondrial bioenergetic phenotype. J. Biol. Chem. 2007, 282:34611-34622.

CBAC Fall 2008 Seminar Schedule

Seminars are hosted on Mondays, 5:30PM–6:30PM unless otherwise noted.
Horsd'oeuvre reception is from 5:00PM–5:30PM
Whitaker Hall, Room 218, Danforth Campus

SAVE THE DATES FOR
CBAC FALL 2008 SEMINARS!

Date	Speaker, Affiliation, Talk Title
October 1, 2008 Thursday @ 4:00pm Whitaker Hall Auditorium	Neils F. Otani, Ph.D. Sr. Research Associate Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, "How Disturbances Propagate on Action Potential-What They Can Teach Us About Wave Break Up and Arrhythmia Control"
October 13, 2008	Robin Shaw, M.D., Ph.D. Assistant Professor of Medicine Department of Medicine, Division of Cardiology, Cardiovascular Research Institute, Biomedical Sciences Program, University of California, San Francisco "Directed Targeting of Connexons: Can the Model Be Generalized?"
October 20, 2008	Timothy W. Smith, M.D., Ph.D. Assistant Professor of Medicine Cardiovascular Division, Washington University School of Medicine, St. Louis, MO "Advances in the Treatment of Ventricular Tachycardia"
October 27, 2008	Jacques Billette, M.D., Ph.D. Professor, Department of Physiology, Faculty of Medicine University de Montreal, Quebec, CANADA "What Does Atrio-Ventricular Node Rate Dependence Mean?"
November 6, 2008 Thursday	Dario DiFrancesco, Ph.D. Professor of Physiology and Biochemistry, Department of Biomolecular Sciences and Biotechnology University of Milano, Italy "Pacemaker Mechanism: Control of Heart Rate in Health and Disease"
November 17, 2008	Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S. The Fred Saigh Distinguished Professor of Engineering, Professor of Biomedical Engineering, Medicine, Cell Biology & Physiology, Radiology and Pediatrics "Noninvasive Electrocardiographic Imaging (ECGI) of Electrophysiology and Arrhythmias"
November 24, 2008	Dorothy A. Hanck, Ph.D. Professor Department of Medicine, Section of Cardiology University of Chicago, Chicago, IL "How to Make an Antiarrhythmic Drug Out of a Local Anesthetic: Drug Interactions with Voltage-gated Na Channels"
December 1, 2008	R. Martin Arthur, Ph.D. The Newton R. and Sarah Louisa Glasgow Wilson Professor of Engineering, Department of Electrical and Systems Engineering Washington University, St. Louis, MO "Electrical Remodeling of the Diabetic Heart"
December 8, 2008	Joseph (Jody) A. O'Sullivan, Ph.D. Professor of Electrical and Systems Engineering, Associate Professor of Radiology, Professor of Biomedical Engineering, Director of Electronic Systems and Signals Research Laboratory, Associate Director, Center for Security Technologies Washington University in St. Louis, MO "Dual Energy Quantitative X-Ray CT Imaging"



"See the CBAC website for seminar video archive, www.cbac.edu"

An interdisciplinary approach to studying and treating rhythm disorders of the heart"

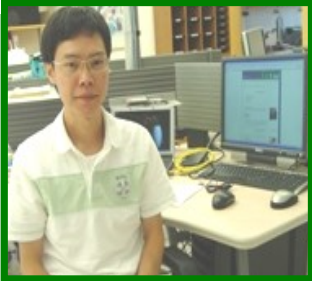
COLLABORATIONS WITH TAIWAN



Dr. Ching Hsing Luo

The CBAC travels across the seas to the city of Tainan, Taiwan where a collaborative relationship with National Cheng Kung University is flourishing. This collaborative activity was cultivated largely due to a relationship that was established some time ago when Dr. Ching Hsing Luo, Distinguished Professor of Electrical Engineering, was a student of Dr. Yoram Rudy's at Case Western Reserve University. Dr. Luo remains a protégé of Dr. Rudy's and is helping to cultivate a new generation of researchers who will continue to study cardiac electrophysiology. This summer, Dr. Luo and four of his students visited the CBAC. The students visited for the entire summer to observe and participate in research being done in Dr. Rudy and Dr. Jianmin Cui's labs. One of the students is **Hao-Kai Ken**, a Ph.D. student in Biological and Biomedical Sciences at National Cheng Kung University who came to work in Dr. Cui's lab on single cell biochip platform experiments using the patch clamp technique. We spoke to Hao-Kai about his interest in the biomedical sciences and what he hopes to accomplish with his

research and he had this to say, "During college I studied biomedical engineering because I was interested in the applications between medicine and materials. I also investigated bone repair materials. I imagined the fields that I would be interested in and one day, I saw a poster of the Institute of Nanotechnology and Microsystem Engineering and suddenly I thought about combining biomedicine with MEMS fabrication. I enrolled in the Institute of Nanotechnology and Microsystems for my Masters Degree where I studied protein microarray. As a child, I always wanted to be a scientist and I'm happy to be studying in this Ph.D. program. Personally, I feel that my most important achievement to date is my research in protein microarray because I published two papers for journals which is very important to me. In the future, I would like to study stem cell differentiation and I will focus on cardiac stem cells. The CBAC is famous for their research in cardiac electrophysiology and I'm interested in the patch clamp technique. I would like to combine the patch clamp with the single cell biochip platform. Moreover, I want to learn how to set up and operate the patch clamp and gene transfer and I believe that the CBAC is the best place to learn. The CBAC is great! The people are nice and friendly, the experiment instruments are all complete and perfect and every student works hard and owns their thoughts about their research. This is a good place to do research."

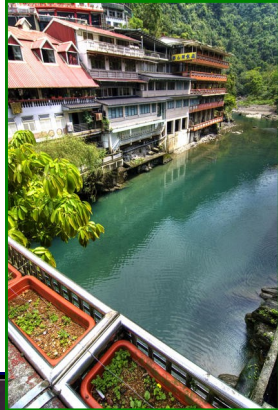


Fu-Chiang Young, Ph.D. Student

Fu-Chiang Young, also a Ph.D. student of Dr. Luo's shared his story with me. "As a child, I worked with my father who was an electrical engineer. I was interested in electrical circuitry particularly to design a program to apply microchip to an interface card and also data acquisition to data analysis. Following my graduation, I began to work with Dr. Luo researching electric physiology. I was introduced to the Luo-Rudy model of the cardiac cell which is famous in Taiwan, and I found the simulations of single cells amazing and exciting. The fact that a simple circuit could describe a cell membrane function was unbelievable to me. I gradually understood the subtleties of cell membrane behaviors as it relates to many conditions. At this time my major research is about the protein function of ion channels. Of the work that I have accomplished so far, my Master research is something that I am very proud of. My research (cont,d. on page 7)



Hao-Kai Ken, Ph.D. Student



Top to Bottom: Buildings along the river in Wulai, Taiwan; Tainan at Night; Chiang-Kai-Shek Memorial entry gate.

"An interdisciplinary approach to studying and treating rhythm disorders of the heart"

FROM THE DIRECTOR'S DESK.....

BASIC SCIENCE AND TRANSLATIONAL RESEARCH: A VIEWPOINT

Recently, there has been much discussion of the relative importance (and hence funding priorities) of basic versus applied (translational) biomedical research. This debate has included the field of cardiac electrophysiology and arrhythmia. I believe that we are witnessing a “pendulum swing” towards translational research, at the expense of basic science. I do not think that we should treat this as an “either-or” issue; both basic and applied research are important and needed. However, I am concerned that by emphasizing short-term goals and outcomes, we are deemphasizing the critical and irreplaceable role of the long-term basic discovery process that is not driven by an application. Basic research is an essential part of our existence as thinking beings; it can often lead to an application, but the road is usually indirect and takes a long time, and the end point is not predictable. I will illustrate this at several levels: (1) Basic science in general, (2) life sciences and medical research, (3) cardiac electrophysiology and arrhythmias. (1) In general, basic research is driven by the natural curiosity of mankind and our need “to know.” Between 1599 and 1612 Johannes Kepler formulated the three laws of motion that describe the movement and trajectories of the planets. These laws paved the way for Newtonian Physics and the concept and understanding of gravity (1686). Needless to say, these scientific giants could not envision or imagine that based on their discoveries a man would walk on the moon in July 1969, nor were they aware of (or motivated by) the many other practical applications of their basic theories that were implemented two and three centuries later. (2) There are many examples of major contributions of basic biomedical and non-biomedical research to the practice of modern medicine. CT would not have been developed were it not for the discovery of x-rays many years earlier. MRI would not have existed were it not for basic studies of the physics of nuclear magnetic resonance (NMR), unmotivated by any medical application. Lewis Thomas in the Lives of a Cell says “Everyone forgets how long and hard the work must be before the really important applications become applicable. The great contemporary achievement of modern medicine is the technology for controlling and preventing bacterial infection, but this did not fall into our laps with the appearance of penicillin and the sulfonamides. It had its beginnings in the final quarter of the 19th century, and decades of the most painstaking and demanding research were required before the etiology of pneumonia, scarlet fever, meningitis, and the rest could be worked out. It overlooks a staggering amount of basic research to say that modern medicine began with the era of antibiotics.” Another major scientific discovery was the determination of the structure of DNA by Crick and Watson in 1951. This basic discovery is only now being translated into the practice of health care, with genotyping becoming an important tool for identifying individuals at risk of certain hereditary diseases and for developing a molecular-based approach to treatment. (3) Clinical cardiac electrophysiology (EP), as practiced today, provides numerous examples of basic research based diagnosis, prevention and treatment of cardiac arrhythmias and sudden death. The cardiac pacemaker and the ICD would not have been in existence without thorough understanding of the principles and mechanisms of electrical excitation of cardiac tissue and of the anatomy and function of the specialized conduction system of the heart. They would also not be practical without basic research in solid-state physics during the early 1900’s that led to the invention of the transistor and of miniature printed electronic circuitry. Basic knowledge of genetics provides new approaches for identifying patients at risk of fatal arrhythmias so that ICD can be implanted prophylactically. The entire practice of catheter ablation for management of arrhythmias is based on our understanding of arrhythmia mechanisms; there would be no ablation if we did not know about reentry, a basic phenomenon described and characterized initially by Mayer (1906). The most resounding point made in the monumental study of Comroe and Dripps (Science 1976; 192: 105-111) is that in the field of cardiovascular and pulmonary diseases “of 529 key articles, 41 percent of all work judged to be essential for later clinical advance was not clinically oriented at the time it was done; the scientists responsible for these key articles sought knowledge for the sake of knowledge. Of the 529 articles 61.7 percent described basic research.” There are many other examples, but to me it is clear that major breakthroughs require long-term and stable support of basic scientific research, not directed by predetermined specific applications. (cont’d. on page 8)



Yoram Rudy, Ph.D.,
F.A.H.A., F.H.R.S.

Awards & Honors

GRANTS & FUNDING

Ralph Damiano, Jr., MD; NIH R01 085113-01A1, “The Role of Inflammation in Post Operative Atrial Fibrillation. R. Damiano, Co-Inv, \$1,125,000, 09/30/2007-06/30/2012.

Igor Efimov , Ph.D.; NIH R01 HL085369, received 12.7% percentile for NIH R01 grant application HL085369 "Structure/ function of the Pacemaker and Conduction System of the Heart". Funding period 07/01/2008-06/30/2013.

Vadim Fedorov, Ph.D.; was awarded Beginning Grant-in-Aid from the Midwest Affiliate of the American Heart Association to study low-voltage atrial defibrillation. Funding period 07/01/2008-06/30/2010.

Richard W. Gross, MD, Ph.D.;

- * R01 HL041250, “Lipid Mediators of Signal Transduction in Smooth Muscle,” 20th year as PI.
- * R01, “Phospholipase Activation and Membrane Dysfunction in Diabetic Cardiomyopathy,” PI
- * SCCOR Grant, Project 1, CI

Yoram Rudy, Ph.D.:

- * *Inverse and Forward Problems in Electrocardiography*. Yoram Rudy, PI, \$1,362,285, 07/01/2008-6/30/2012 (years 24-27 of a Merit Award to Y. Rudy), NIH-National Heart, Lung and Blood Institute. Research under this grant will continue the development of Electrocardiographic Imaging (ECGI), a novel noninvasive imaging modality for Cardiac Electrophysiology and Arrhythmia. ECGI will be applied in patients with heart disease and cardiac rhythm abnormalities in order to study mechanisms and properties of cardiac arrhythmias in humans and to guide therapy.
- * *Cardiac Excitation and Arrhythmias*. Yoram Rudy, PI, \$380,000, 07/03/2008-6/30/2009 one year Bridge Award from the NIH-National Heart, Lung and Blood Institute.

HONORS

Ralph Damiano, Jr., MD., November, 2008; Was appointed as President of the Society of Clinical Surgery.

Igor Efimov , Ph.D., Optical mapping of the human heart is the first paper in history published in which arrhythmia in the human AV junction was mapped using fluorescence imaging. Hucker W.J., Federov V.V., Foyil K. V., Moazami N., Efimov I.R., “Optical Mapping of the Human Atrioventricular Junction, Circulation, 2008, 117(11): 1474-7.

Richard W. Gross, MD., Ph.D., is the first inventor on an issued patent entitled “Molecular Species Fingerprinting of Triglyceride Molecular Species by Electrospray Ionization Mass Spectrometry” (7,306,952).

Jeanne Nerbonne, Ph.D., 2008 Distinguished Investigator Award, Washington University School of Medicine

Yoram Rudy, Ph.D. was appointed as the Hein J.J. Wellens Distinguished Professor in Cardiology, University of Maastricht, The Netherlands, 2008-2009.

Pamela K. Woodard, MD, Associate Professor, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology, Washington University School of Medicine was appointed Chair of the American College of Radiology (ACR) Imaging Network’s new Cardiovascular Imaging Research Committee in March 2008.



Announcements & News

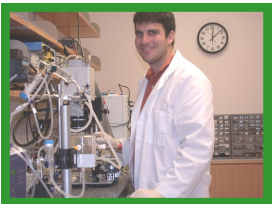


Igor Efimov, Ph.D., was promoted to full Professor of Biomedical Engineering. New appointment starts July 1, 2008.

Vadim Fedorov, Ph.D., was awarded the Beginning Grant-in-Aid from the Midwest Affiliate of the American Heart Association to study low-voltage atrial defibrillation. The Funding period is from July 1, 2008 to June 30, 2010.



William J. Hucker, Ph.D., On November 8, 2007 Dr. Hucker defended his Ph.D. thesis and was awarded the Doctor of Philosophy degree. Dr. Hucker is continuing his MD/Ph.D. training at the Washington University School of Medicine.



Leonid Livshitz, Ph.D., was promoted to Research Assistant Professor in the Department of Biomedical Engineering, Cardiac Bioelectricity and Arrhythmia Center in April 2008. Dr. Livshitz has been a member of Dr. Rudy's lab since 2004 where he started at Case Western Research University as a post-doctoral fellow and moved to Washington University when Dr. Rudy accepted the invitation to St. Louis. His research interests are focused on the mechanisms underlying arrhythmogenic effects of cell calcium and calcium dependent regulatory pathways.

Ali Nekouzadeh, Ph.D., was promoted to Research Assistant Professor in the Cardiac Bioelectricity and Arrhythmia Center under Dr. Rudy in April 2008. Dr. Nekouzadeh has been with the lab for 2.5 years and his area of specialization in research is modeling mechanical and electrical properties of tissues, cells and cell components. He is currently working on modeling the molecular mechanism of ion channel gating of voltage dependent channels, in particular I_{Ks} channels.



Thomas O'Hara, a Ph.D. student in the Rudy Lab received a two-year award from the Pre-doctoral Fellowship Program of the Midwest Affiliate Research Committee of the American Heart Association for his project on "Mathematical Model of Human Cardiac Ventricular Action Potential."



Crystal Ripplinger, Ph.D., February 1, 2008. Dr. Ripplinger defended her Ph.D. thesis and was awarded the Doctor of Philosophy degree. Dr. Ripplinger moved to Harvard as a postdoc.

Jonathan Silva, Ph.D., April 18, 2008. Dr. Silva defended his Ph.D. thesis and was awarded the Doctor of Philosophy degree. Dr. Silva has moved to Chicago where he is a post-doctoral fellow at the University of Chicago.



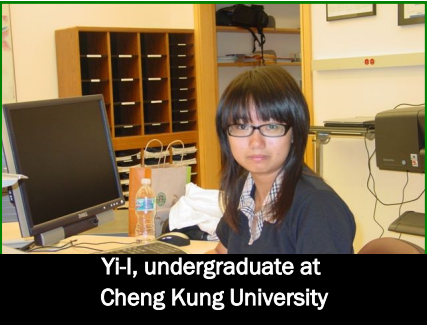
COLLABORATIONS WITH TAIWAN CONT'D. FROM PAGE 5



was to invent a machine for farmers to grade fruits according to the size and weight. I utilized a microchip and an 8255 interface card to connect with a PC by LabVIEW software to analyze the fruits physical properties and it immediately provided the best grading for the output of fruit. The machine was also suitable for different places of production because it was self-adjusting and unlimited by the variations of fruits. I became very interested in the CBAC as a result of the Luo-Rudy model published in 1994. Even now, it is a robust tool to simulate cardiac cell behaviors. Dr. Rudy is a legendary professor in the academic community in Taiwan. The CBAC has recently developed the ability to do research at a molecular level on single ion channels, and within the next decade it may lead the world in the development of molecular level theoretical research. Dr. Rudy's lab is a very special place to do research. The lab is a combination of robust and expert research groups and I am discovering more interesting and exciting information. In the future, I hope to model protein functions under different conditions such as ionic concentrations and the channel pore electrostatic forces and other forces to model ion-channel function."



The CBAC also hosted its youngest aspiring scientist to date, **Yi-I** (pronounced EE-EE) or interpreted in English as "Chill." Yi-I is in her third year of undergraduate studies in Electrical Engineering at National Cheng Kung University and Dr. Luo is her advisor. Yi-I celebrated her 18th birthday while visiting CBAC this summer. Yi-I's visit was much shorter than that of Fu-Chiang and Hao-Kai but, she was very focused on her objective to watch and learn as much as possible while visiting the Rudy Lab. Dr. Luo recognized the promise that Yi-I embodies and introduced her to ion channel modeling by having her read several papers published on the subject. Yi-I subsequently became very interested in the



subject and is now a member of Dr. Luo's team. Yi-I, like Fu-Chiang was introduced to channel modeling by way of the Luo-Rudy model which inspired her to want to visit the CBAC. "I think Dr. Rudy's lab is a great place for me to learn more about cell modeling. I've read papers about cell modeling written by members of the Rudy lab and I believe that this would be a great experience and will help tremendously in my future research endeavors." Although she is not able to conduct formal research at her current academic level, she continues to be a sponge, absorbing all that she can from the research of others and from Dr. Luo. On her experience so far, Yi-I states, "At this point, I do not have a lot of research experience but I am glad that the field I have chosen is one of the most advanced in current scientific research. The hard work that we do can result in a small but precious process affecting the health of humankind enabling them to not be tortured by illnesses." One of Yi-I's greatest achievements is her programming skill. "Last summer, myself along with two classmates made a cooperative effort to write a computer RPG game. Although the game was only partially finished after two months of hard work, we still thought it was a great experience. I am positive that my programming experience will be a big help when I am building models. I have to say that CBAC is really a wonderful place for research! I intend to complete my studies with Dr. Luo and hopefully come to Washington University to pursue a Ph.D."



CBAC SPECIAL SUMMER SEMINAR

This summer, the CBAC had the honor of hosting one of its' favorite collaborators, Dr. Livia Hool, NHMRC CDA Fellow, Head Cardiovascular Electrophysiology at The University of Western Australia, Crawley, WA Australia. Dr. Hool presented on the "Regulation of Cardiac L-type Calcium Channel Function by Changes in Cellular Redox State" on July 24th.



Western Australia

Dr. Hool shares with the group photos of the lush Australian landscape and diverse culture

(U-C) Dr. Rudy introduces Dr. Hool to seminar attendees; (L-R) CBAC group enjoys the pre-seminar reception; (L-L) CBAC members attend seminar.

FROM THE DIRECTOR'S DESK CONT'D....

FROM PAGE 6

AN NIH – NHLBI WORKSHOP ON SYSTEMS APPROACH TO CARDIAC RESEARCH

On August 20-21, 2007, I chaired a workshop, "Systems Approach to Understanding Electromechanical Activity in the Human Heart" convened by The National Heart, Lung and Blood Institute (NHLBI) in Washington, D.C. The 13 workshop participants were expert cardiac electrophysiologists, cell biophysicists, and computational modelers. The objective of the workshop was to advise NHLBI on new research directions for developing integrative approaches to the study of human cardiac function and its alteration by disease. "Systems approach" can be defined as an integrative approach that, in contrast to the traditional reductionism approach of science, assembles the system (the heart) from its molecular, cellular and tissue components. The last decade has generated a wealth of information at the genetic, molecular and cellular scales of the cardiac system. It is timely and important to begin integrating this information within and between scales, to the level of the whole heart, as electromechanical cardiac function and its alteration by disease (e.g., heart failure, arrhythmias) occur at the organ level.

The Workshop resulted in specific recommendations to the NHLBI; details can be found on the NHLBI website at <http://www.nhlbi.nih.gov/meetings/workshops/electro.htm> ; a paper summarizing the Workshop has been published in the September 9, 2008 issue of Circulation. 2008; 118:1202-1211.

"An interdisciplinary approach to studying and treating rhythm disorders of the heart"

CBAC Faculty Members

- Samuel A. Wickline, M.D., saw@wustl.edu
Professor of Medicine; Adjunct Professor of Physics and Biomedical Engineering; Co-Director of Cardiology
- Pamela K. Woodard, M.D., woodardp@wustl.edu
Associate Professor, Diagnostic Radiology, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology
- Kathryn A. Yamada, Ph.D., F.A.H.A., kyamada@wustl.edu
Research Professor of Medicine; Director, Mouse Cardiovascular Phenotyping Core, Center for Cardiovascular Research, Cardiovascular Division

CBAC Faculty Alumni:

- * Amir A. Amini, Ph.D.
- * Kyongtae T. Bae , M.D., Ph.D.
- * Michael Cain, M.D.
- * Daniel P. Kelly, M.D.
- * Bruce Lindsay, Ph.D.
- * Achi Ludomirsky, M.D.
- * Vladimir P. Nikolski, Ph.D.
- * Edward Rhee, Ph.D.

Learn more information about the CBAC Faculty members at the
CBAC website located at
<http://cbac.wustl.edu/pageFaculty.asp>.
Also visit Dr. Rudy's lab website at
<http://rudylab.wustl.edu/>



An interdisciplinary approach to studying and treating rhythm disorders of the heart"

CBAC Faculty Members



Director - Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S. The Fred Saigh Distinguished Professor of Engineering; Professor of Biomedical Engineering, Cell Biology & Physiology, Medicine, Radiology, and Pediatrics; Director of the Cardiac Bioelectricity and Arrhythmia Center (CBAC), rudy@wustl.edu	Patrick Y. Jay, M.D., Ph.D., jay_p@wustl.edu Assistant Professor of Pediatrics and Genetics
R. Martin Arthur, Ph.D. , rma@wustl.edu Newton R. and Sarah Louisa Glasgow Wilson Professor of Engineering; Professor of Electrical and Systems Engineering; Professor of Biomedical Engineering	R. Gilbert Jost, M.D., jostg@wustl.edu Elizabeth Mallinckrodt Professor of Radiology; Chairman, Department of Radiology; Director, Mallinckrodt Institute of Radiology
Philip V. Bayly, Ph.D. , pvb@wustl.edu Professor of Mechanical Engineering, and Chair of the Department of Mechanical, Aerospace, and Structural Engineering.	Sándor J Kovács, Ph.D., M.D., sjk@wustl.edu Professor of Medicine and Physiology, Adjunct Professor of Physics and Biomedical Engineering, Director, Cardiovascular Biophysics Laboratory
Sanjeev Bhalla, M.D., bhallas@wustl.edu Associate Professor of Radiology; Assistant Radiology Residence Program Director, Mallinckrodt Institute of Radiology	Tony J. Muslin, M.D., F.A.H.A., amuslin@wustl.edu Oliver M. Langenberg Distinguished Professor of the Science and Practice of Medicine; Professor of Cell Biology and Physiology; Director, Center for Cardiovascular Research (CCR); Director, Cardiology Research Fellowship Program
John P. Boineau, M.D., schuesslerd@wustl.edu Professor of Surgery, Medicine, and Biomedical Engineering	Arye Nehorai, Ph.D., nehorai@wustl.edu Chairman and Professor of the Department of Electrical & Systems Engineering
Jane Chen, M.D., janechen@wustl.edu Assistant Professor of Medicine	Jeanne M. Nerbonne, Ph.D., jnerbonne@wustl.edu Alumni Endowed Professor of Molecular Biology and Pharmacology
Jonas Cooper, M.D., M.P.H., JCOOP-ER987623610@wustl.edu (Washington University School of Medicine, 2001, MD; Harvard University, 2008, MPH)	Colin G. Nichols, Ph.D., cnichols@wustl.edu Professor of Cell Biology and Physiology
Jianmin Cui, Ph.D., jcui@wustl.edu Associate Professor of Biomedical Engineering on the Spencer T. Olin Endowment	Joseph A. O’Sullivan, Ph.D., jao@wustl.edu Professor of Electrical and Systems Engineering, Associate Professor of Radiology, Professor of Biomedical Engineering, Director of Electronic Systems and Signals Research Laboratory, Associate Director, Center for Security Technologies
Ralph J. Damiano, Jr., M.D., damianor@wustl.edu John M. Shoenberg Professor of Surgery; Chief of Cardiac Surgery	Jean E. Schaffer, M.D., jschaff@wustl.edu Professor Internal Medicine, Developmental Biology
Victor G. Davila-Roman, M.D., vdavila@wustl.edu Associate Professor of Medicine, Anesthesiology, and Radiology; Medical Director, Cardiovascular Imaging and Clinical Research Core Laboratory	Richard B. Schuessler, Ph.D., schuesslerr@wustl.edu Associate Research Professor of Surgery; Associate Research Professor of Biomedical Engineering; Director, Cardiothoracic Surgery Research Laboratory
Igor R. Efimov, Ph.D., igor@wustl.edu Professor of Biomedical Engineering	Jingyi Shi, Ph.D., jshi22@wustl.edu Research Faculty, Biomedical Engineering
Mitchell N. Faddis, M.D., Ph.D., mfaddis@wustl.edu Assistant Professor of Medicine, Radiology; Clinical Cardiac Electrophysiologist, Barnes Hospital	Gautam K. Singh, M.D., M.R.C.P., singh_g@wustl.edu Associate Professor, Department of Pediatrics, Director of Non-invasive Cardiac Imaging Research; Co-Director, Echocardiography Laboratory
Richard W. Gross, M.D., Ph.D., rgross@wustl.edu (Joint Appointment with the School of Medicine), Professor of Biological, Biophysical and Bioorganic Chemistry, Departments of Medicine, Molecular Biology and Pharmacology and Chemistry, Washington University School of Medicine	Timothy W. Smith, D.Phil., M.D., tsmith@wustl.edu Assistant Professor of Medicine
	Jason W. Trobaugh, D.Sc., jasont@wustl.edu Research Instructor in Medicine, Electrical and Systems Engineering
	Lihong Wang, Ph.D., lhwang@wustl.edu Gene K. Beare Distinguished Professor; Department of Biomedical Engineering; Director, Optical Imaging Laboratory

FOCUS ON.....DR. CHARLES ANTZELEVITCH

CBAC Seminar Topic: “Atrial Selective Sodium Channel Blockers as a Novel Strategy for the Management of Atrial Fibrillation”

Delivered on January 28, 2008

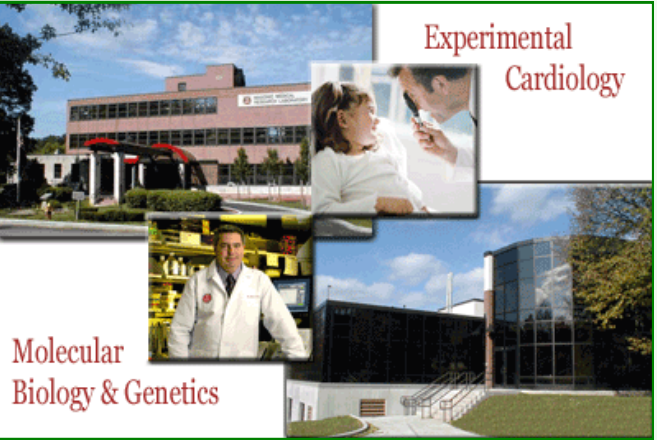


Dr. Charles Antzelevitch

Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., F.H.R.S. is the Executive Director and Director of Research of the [Masonic Medical Research Laboratory](#) (MMRL), an internationally prominent biomedical research institute located in Utica, NY. He also holds an academic appointment as Professor of Pharmacology at the SUNY Health Science Center at Syracuse and an endowed chair in Experimental Cardiology (Gordon K. Moe Scholar) at the MMRL.

Dr. Antzelevitch was the guest speaker for the CBAC Spring 2008 Seminar on January 28th where he addressed “Atrial Selective Sodium Channel Blockers as a Novel Strategy for the Management of Atrial Fibrillation.” A synopsis of Dr. Antzelevitch’s talk to the CBAC group follows: “Current pharmacologic strategies for the management of atrial fibrillation (AF) include use of 1) sodium channel blockers, which are contraindicated in patients with coronary artery or structural heart disease because of their potent effect to slow conduction in the ventricles, 2) potassium channel blockers, which predispose to acquired long QT and Torsade de Pointes arrhythmias because of their potent effect to prolong ventricular repolarization, and 3) mixed ion channel blockers such as amiodarone, which are associated with multi-organ toxicity. The risk of developing severe ventricular arrhythmias and/or organ toxicity by currently available drugs has prompted the development of atrial-selective antiarrhythmic agents. Until recently the principal focus has been on development of agents that selectively inhibit the ultra-rapid delayed rectifier outward potassium channels (I_{Kur}), taking advantage of the presence of these channels in atria, but not ventricles. Recent experimental studies have demonstrated important atrioventricular differences in biophysical properties of the sodium channel and have identified sodium channel blockers such as ranolazine and chronic amiodarone that appear to take advantage of these electrophysiological distinctions and act to specifically or predominantly depress sodium channel current (I_{Na})-mediated parameters in canine atria vs. ventricles. Atrial-selective sodium channel blockers such as ranolazine effectively suppress AF in experimental models of AF involving canine isolated coronary-perfused right atrial preparations at concentrations that produce little to no effect on ventricular electrophysiological parameters. The effectiveness of these agents to depress I_{Na}-mediated parameters and to suppress AF appears to be potentiated by their ability to prolong the atrial action potential duration, secondary to I_{Kr} block. These findings point to atrial-selective sodium channel block as a new strategy for the management of AF.”

You can read more about Dr. Antzelevitch’s work at www.mmrl.edu.



“SPOTLIGHT ON DR. JEANNE SCHAFFER”



Jean E. Schaffer, M.D.

The CBAC has the honor of having some of the world’s foremost researchers and practitioners in the field of cardiology and cardiovascular research as part of its membership. Dr. Jeanne Schaffer is one of those extraordinary members whose love for science has translated into a dynamic career in cardiovascular research.

Dr. Schaffer is an Associate Professor, Department of Medicine, Department of Molecular Biology and Pharmacology in the Washington University School of Medicine. Among her many accomplishments Dr. Schaffer received the honor of being appointed as the [Virginia Minnich Distinguished Professor of Medicine](#) in February, 2008. Dr. Schaffer’s work is focused on the serious cardiovascular complications associated with diabetes and obesity. The risk factors for someone with diabetes or who is obese are very high for coronary artery disease which tends to manifest itself in a much more aggressive form in these individuals than in those who are not challenged with these dis-

eases. The goals of the studies in the [Schaffer lab](#) are to characterize the fundamental cellular mechanisms of lipotoxicity, and to understand how these processes contribute to organ dysfunction in rodent models of metabolic disease.

Dr. Schaffer’s journey to the world of science and subsequently health care, began with a determination to prove that she was a formidable opponent to anyone who would think that women could not be good scientists. “My initial interest in science began as a purely “I’ll show you” response to a sexist high school chemistry teacher. However, I quickly found enjoyment in learning about the intricacies of living cells. As part of my biochemistry major in college, I had an outstanding research experience in Matthew Meselson’s lab that sealed my decision to become a scientist. I chose a medical school program that focused on the training of physician scientists, so that I could both continue my scientific training and learn about human disease. Beyond my general biochemistry studies I initially had little idea of what I might pursue, either as a scientist or as a physician. However, during internal medicine training at the Brigham & Women’s Hospital, I enjoyed my time on the cardiology service, which helped me to decide on specialty training in that area. As a cardiology fellow I chose to work in Harvey Lodish’s laboratory at the Whitehead Institute for Biomedical Research, because Harvey had an outstanding track record of mentoring physician scientists. In his laboratory, I received training in molecular and cellular biology that has served as a foundation for my subsequent work. As a college and medical student at Harvard, I participated in research at each stage of my education. Clinical training in medicine and cardiology left little time for science, but I returned to the lab for a concentrated period of full-time training during fellowship. I spent five years as a visiting scientist at the Whitehead Institute. I left Boston in 1995 to take my first faculty position at Washington University where I have remained since.”

When asked what she is most proud of accomplishing in her career, Dr. Schaffer stated, “I am proud of my accomplishment in establishing a robust, independent scientific program, that is recognized internationally. My near term goals are to identify the mechanisms through which abnormalities in lipid metabolism lead to cell dysfunction and cell death in non-adipose tissues such as the heart. My group is also working to translate findings from our basic work to clinical studies. The overall long-term goal of my group is to advance our approaches to the diagnosis, treatment and prevention of cardiovascular complications of diabetes.”

And finally, of the CBAC, Dr. Schaffer states, “CBAC provides a terrific platform for interactions among scientists with a shared interest in cardiac bioelectricity and cardiovascular pathophysiology from both Washington University campuses.”

The CBAC congratulates Dr. Schaffer on her appointment to the Virginia Minnich Distinguished Professor of Medicine and we know that this will be a banner year of further growth and success for Dr. Schaffer.



Lectures & Presentations, Cont'd.

Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S., cont’d.:

- * Technion – Israel Institute of Technology School of Medicine, Grand Rounds in Cardiovascular Science, Haifa, Israel, June 2, 2008. Noninvasive Electrocardiographic Imaging (ECGI) of Cardiac Electrophysiology and Arrhythmia.
- * Cardiostim – World Congress in Cardiac Electrophysiology and Cardiac Techniques, Nice, France, June 19, 2008. Noninvasive ECG Imaging.
- * “Cardiac Arrhythmias and Sudden Death: From Genes to Prevention” symposium at the Hatter Cardiovascular Research Institute of Cape Town University in South Africa, August, 2008. He presented two invited talks about the molecular basis of cardiac repolarization, and about Electrocardiographic Imaging (ECGI) of cardiac arrhythmias.
- * Hein J. J. Wellens Distinguished Professor, Maastricht University, The Netherlands. September 15, 2008. Installation speech on “Computational Biology and ECG Imaging in the Study of Cardiac Electrophysiology and Arrhythmias.”
- * "Frontiers in Computational Electrocardiology" invited speaker, Maastricht University, The Netherlands, September 17, 2008. Two presentations: “How to Understand and Model Structure-Function Relations of Cardiac Ion Channels” and “Basic Principles of ECG Imaging From the Viewpoint of Computational Modeling.”

Welcome New CBAC Members



Jonas Cooper, MD, MPH., Washington University School of Medicine, 2001, MD; Harvard University, 2008, MPH), JCOOPER987623610@wustl.edu

My career is predominantly a clinical one, treating patients with all manner of heart rhythm disorders. This includes medical management, device implantation (pacemakers, defibrillators, cardiac resynchronization devices), and mapping & ablation for arrhythmias.



Tony J. Muslin, MD, F.A.H.A., <http://dbbs.wustl.edu/rib/muslinANTJ>

Harvard Medical School, 1984, Oliver M. Langenberg Distinguished Professor of the Science and Practice of Medicine; Professor of Cell Biology and Physiology; Director, Center for Cardiovascular Research (CCR); Director, Cardiology Research Fellowship Program.



Kimberly M. Smith, CBAC Administrator, ksmith32@wustl.edu

I am so excited and pleased to be a new member of the CBAC family. I knew from the beginning that this department would be a great fit for both myself and the Center and I was right. I have spent over twenty years working with a variety of non-profits ranging from Project Upward Bound to the Saint Louis Symphony Orchestra and for profit organizations like Nestlé Purina PetCare and a biotechnology company all in capacities that afforded me the opportunity to help improve the quality of life for others and for me, the CBAC is no different. Whether an individual works in an administrative, research or patient treatment capacity, each one plays an integral role in making life better for those living with illnesses, students or coworkers and at the end of the day, that is what is important to me. My secret to being able to find success and fulfillment wherever I go is to respect everyone and treat everyone the way that I would like to be treated, do unto others as you would have them do unto you, even when it is a challenge. The rewards of showing respect are much greater than the sacrifices of pride and self-importance that one might make. The BME is rich with diversity, culture and learning opportunities that make it a lively and exuberant environment to work in. I look forward to being a part of breakthrough cardiology research and working with everyone from the Danforth campus to the Medical School. “Thank you” to everyone for being so welcoming!

Lectures & Presentations, Cont'd.



Richard W. Gross, M.D., Ph.D., Professor of Medicine, Chemistry, Molecular Biology & Pharmacology, Washington University, <http://www.chemistry.wustl.edu/faculty/rgross>

- * *Mass Spectrometry Heartland Workshop*, presenter, organized by the American Chemical Society.
- * “Shotgun Lipidomics and Multidimensional Mass Spectrometry” at the American Society of Nephrology, presenter, *Renal Week 2007 – “A System Wide View of Lipid Alterations in Disease”*.
- * Cardiac Bioelectricity and Arrhythmia (CBAC) seminar, presenter, “*Biologic Membranes and Cardiac Bioelectricity*”.
- * “*Biologic Membranes as Signaling Platforms in Health and Disease*” speaker, *Functional Genomics Consortium Symposium* at Kansas State University.



Jeanne Nerbonne, Ph.D., Alumni Endowed Professor of Developmental Biology, Neurosciences Program, Molecular Cell Biology Program, Washington University School of Medicine, <http://dbbs.wustl.edu/rib/nerbonneJeaM>

Invited Conferences and Symposia:

- * “Multiple Mechanisms Involved in Myocardial Potassium Channel Regulation, Remodeling and Arrhythmogenesis.” The Cardiac Arrhythmias Symposium: Troubles with Rhythm: Molecular and Genetic Basis for Cardiac Arrhythmias. GEPRON, Montreal, Quebec, Canada, May, 2008.
- * “Atrial Fibrillation.” Cardiostim 2008: 9th Biennial World Congress on Cardiac Arrhythmias and 16th World Congress on Cardiac Electrophysiology and Cardiac Techniques. Symposium entitled: Atrial Fibrillation, Nice, France, June, 2008.
- * “Molecular and Functional Diversity of Repolarizing Myocardial K⁺ Channels.” Division of Cardiovascular Medicine, University of Iowa, Cedar Rapids, IA, November, 2007.
- * “Molecular Basis of Functional Voltage-Gated Potassium (Kv) Channel Diversity...Focus on Kv4 Channels.” Department of Biology, University of Richmond, April, 2008.
- * “Voltage-gated K⁺ channels and the fine tuning of neuronal membrane excitability.” Neurosciences Program Distinguished Lecture Series Invited Speaker. University of California at Davis, Davis, CA, September, 2008.



Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S., The Fred Saigh Distinguished Professor of Engineering, Biomedical Engineering, Medicine, Cell Biology and Physiology, Radiology and Pediatrics, Director of the CBAC, www.rudylab.wustl.edu

- * New York University, Cardiology Grand Rounds, New York, January 4, 2008
- * Cornell University, Weill Medical College, Department of Physiology and Biophysics, New York, January 7, 2008
- * University of California, San Francisco, Department of Medicine Grand Rounds, March 13, 2008.
- * University of California, San Francisco, Cardiology Seminar, March 13, 2008
- * Ventricular Arrhythmia and Sudden Death Symposium, San Francisco, March 14-16, 2008
- * Heart Rhythm Society 29th Annual Scientific Sessions, May 16, 2008, San Francisco, California. The Molecular Basis for the Clinical Electrocardiogram – Electrocardiographic Imaging (ECGI): Solving the Electrocardiographic Inverse Problem.
- * Heart Rhythm Society 29th Annual Scientific Sessions, May 16, 2008, San Francisco, California. Why do T-waves Change? – Fundamental Basis of the T Wave.
- * Technion – Israel Institute of Technology, Department of Biomedical Engineering, Special Lecture in memory of Professor Samuel Sideman, Haifa, Israel, June 1, 2008. Computational Biology and Noninvasive Imaging of Cardiac Arrhythmia.

“An interdisciplinary approach to studying and treating rhythm disorders of the heart”



University of Nantes

PhD's on Point

Celine Marionneau, Ph.D.



In each issue of the “*Center Heartbeat*” we will feature not only the accomplishments and challenges of the faculty and staff members of the CBAC but, we will also shine the spotlight on students and fellows who are completing graduate or post doctoral work in CBAC affiliate laboratories.

In this issue, we are featuring **Celine Marionneau, Ph.D.** Dr. Marionneau is a Postdoctoral Research Associate in the department of Developmental Biology where she is a member of Dr. Jeanne Nerbonne’s lab. Dr. Marionneau is a native of France born in a small city in the region of La Vendée which is West of France. She then moved to Nantes, one of the biggest cities in France, where she began her studies at the University of Nantes. The University of Nantes is well known for its research in chemistry, food science, cancer and cardiac physiology. She received her undergraduate degree in biochemistry, MS in cell biology and PhD in biology. Dr. Marionneau talked about how her interest in science developed and how that subsequently resulted in her becoming a postdoctoral fellow at Washington University. “My decision to pursue science began very early on, while I was in high school. I wanted to be a medical researcher although I did not really know at the time what this entailed. I was initially discouraged by a high school work experience in a veterinary analysis lab where the work was repetitive and boring. This experience actually led me to consider medicine as a possible alternate. However, once I was introduced to a university research lab, I realized that I really wanted to be a scientist. I became interested in cardiac electrophysiology while attending classes given by Dr. Denis Escande at the University of Nantes. Denis was a tremendous and passionate teacher who had a remarkable career in cardiac electrophysiology research. I went on to do my Ph.D. in his lab. Tragically, Denis died in November 2006, at the young age of 53. I am proud that I had the privilege of entering the field of cardiac electrophysiology as a result of his teaching and mentoring. I will be grateful to him forever. “ Dr. Marionneau’s work in Dr. Nerbonne’s lab focuses on the molecular characterization of the voltage-gated K⁺ (Kv) channel Kv4.2 complexes in the heart and in neurons. When asked what she is most proud of in her research experience she stated, “The development of my postdoctoral project in Jeanne’s lab has been my most important research achievement. Indeed, I developed a proteomics project aimed at identifying the components of cardiac (and neuronal) Kv4.2 channel complexes, as well as, the posttranslational modifications of these components. Biochemistry and mass spectrometry analyses were new to me as well as to anyone in the lab. This was thus challenging, but I finally got it to work. I hope I will be able to tell more about this story in my next paper!” On a personal level, her pride stems from a different source, “My most important personal achievement is my postdoctoral experience in St. Louis. When I moved to St. Louis, I had to start fresh in a new country with a new culture and a new language living far away from my family. Fortunately, I have developed close friendships with both Americans and Europeans who have made my life enjoyable. I am also very grateful to my boss Jeanne Nerbonne, who has always been very supportive to me both scientifically and personally.” Celine’s testament is proof that one cannot live by work alone and experience fulfillment, the interpersonal relationships are very important to help maintain balance in one’s life. As for the CBAC seminars, Dr. Marionneau sees great value in their content, “Attending the seminars organized by the CBAC and listening to talks given by the most prestigious scientists in the cardiac electrophysiology field has been a great experience. It is a chance, as a young investigator, to have the possibility to listen and to meet renowned specialists. Being exposed to the CBAC seminars and discussions also allowed me to put my scientific project in the broader context of cardiac arrhythmias. The partnership with the CBAC researchers has also open doors to collaborations on very interesting and promising projects.”

Dr. Marionneau intends to return to France where she hopes to obtain a faculty position and continue her research that will focus on understanding the regulation of the functional expression of cardiac ion channels. In parallel with science, she looks forward to reuniting with the love of her life who has been waiting for her to return to France.



Nantes

“An interdisciplinary approach to studying and treating rhythm disorders of the heart”

Outside the Walls of the CBAC



The Computer Science Faculty Building in the present day Technion

Dr. Rudy journeyed to The Technion Israel Institute of Technology, located in Haifa in May, 2008 as the liaison on behalf of the McDonnell International Scholars Academy. The purpose of this trip was to assist in building student and faculty exchange and research collaborations between Washington University and The Technion.

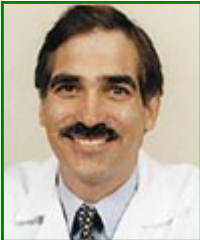


The Israel National Museum of Science, Technology and Space.
A historic building from the first Technion campus

Tom O'Hara, a Ph.D. student of Dr. Rudy, traveled to Hungary and Ohio to do collaborative research. During the Fall 2007 semester, Tom spent a month with Professor András Varró in the Department of Pharmacology and Pharmacotherapy at the University of Szeged in Hungary. Tom participated in an experiment in which they measured various aspects of electrical behavior in human ventricular heart cells. Tom also spent several months in the Spring of 2008 with Dr. David Van Wagoner at the Department of Molecular Cardiology at the Cleveland Clinic in Ohio where they performed additional studies on human ventricular heart cells, looking at calcium currents in particular. Currently, Tom is working to combine results from the Hungary and Cleveland experiments into a study investigating basic ventricular calcium current behaviors. The study is special because the results have never before been measured in non-failing human ventricular heart cells. They provide a critical missing piece in the collection of available data Tom is using to construct a mathematical model for all major aspects of human ventricular heart cell electrical behavior.



Lectures & Presentations



Ralph J. Damiano, Jr., MD, John M. Schoenberg Professor; Chief of Cardiac Surgery, Cardiothoracic Surgery, Washington University School of Medicine, damianor@wustl.edu

- * Atrial Fibrillation: Where Are We Going? Surgical Ablation. American Heart Association. Orlando, Florida. November 5, 2007.
- * The Surgical Treatment of Atrial Fibrillation Combined with Coronary Artery Disease. Twenty Years of Innovation in Atrial Fibrillation Conference. Falls Church, Virginia. November 16, 2007.
- * The HRS Expert Consensus Statement: Cardiac Surgery. Twenty Years of Innovation in Atrial Fibrillation Conference. Falls Church, Virginia. November 16, 2007.
- * Surgery for Atrial Fibrillation. Invited Surgeon. Latest Techniques in Cardiac Surgery. Leipzig, Germany. December 7, 2007.
- * Atrial Fibrillation and Sole Surgical Therapy. 5th Annual Cleveland Clinic Atrial Fibrillation Summit. New York, New York. December 15, 2007.
- * Atrial Anatomy: A Surgeons Perspective. Invited Lecturer. Surgical Management of Atrial Fibrillation (Moderator). Boston Atrial Fibrillation Symposium. Boston, Massachusetts. January 17, 2008.
- * Ablation Devices for the Treatment of Lone Atrial Fibrillation. Invited Lecture. STS/AATS Tech Con 2008. January 27, 2008.
- * The Cox-Maze IV Procedure. Invited Guest Lecture. Cardiovascular Center, University Hospital Maastricht. February 15, 2008.
- * Current Techniques and Outcomes in Atrial Fibrillation Surgery. Annual Turina Lecture. University of Zurich. Zurich, Switzerland. February 19, 2008.

Lectures & Presentations, Cont'd.

Ralph J. Damiano, Jr., MD, cont'd.

- * Current Surgical Techniques for Ventricular Tachycardia. Second Annual Ventricular Arrhythmia and Sudden Death Symposium. San Francisco, California. March 15, 2008.
- * Can We Make the Atria Fibrillation-Proof? Future Directions in Atrial Fibrillation Ablation. CRISTI Lecture Series. Medical City of Dallas. Dallas, Texas. April 22, 2008.
- * Catheter versus Surgical Ablation of Atrial Fibrillation. 10th Annual Cardiac Symposium. Inland Empire Heart & Vascular Institute. San Bernardino, California. April 26, 2008.
- * Current Outcomes for Surgery for Atrial Fibrillation. Visiting Professor. University of Zurich. Zurich, Switzerland. February 18-19, 2008.
- * Atricure Cox-Maze Symposium Moderator and Lecturer. Fort Lauderdale, Florida. January 26, 2008.
- * Bipolar Radiofrequency Cox Maze IV Procedure. The Great Ablate Debate 08. Fort Lauderdale, Florida. January 27, 2008.
- * The Growing Role of Surgery for Atrial Fibrillation. Atricure AF Lunch Symposium. 5th Annual Meeting of German, Swiss, Austrian Cardiac Surgeons. Innsbruck, Austria. February 18, 2008.
- * The Science of Bipolar Pen Ablation. The Epicardial Frontier. Atricure Symposium. American Association of Thoracic Surgeons Annual Meeting. San Diego, California. May 12, 2008.
- * Why Use Irrigation for Cardiac Ablation? Meet the Experts Presentation. Medtronic Booth. American Association of Thoracic Surgeons Annual Meeting. San Diego, California. May 12, 2008.
- * Surgery for Atrial Fibrillation: Recent Advances and Expanding Indications. Advances in Treatment for Atrial Fibrillation. Barnes Jewish Hospital Community Event. Holiday Inn South County Center. St. Louis, Missouri. October 25, 2007.
- * Aortic Valve Replacement in the Elderly: What Are the Options? BJC Continuing Medical Education Event. Ritz Carlton. St. Louis, Missouri. November 20, 2007.
- * Recent Advances in Aortic Valve Replacement. Cardiology Advances for the Primary Care Physician 2008. St. Louis University. Crowne Plaza Hotel. St. Louis, Missouri. April 5, 2008.
- * Surgical Treatment of Hypertrophic Cardiomyopathy. Hypertrophic Cardiomyopathy Conference. Barnes-Jewish Hospital. St. Louis, Missouri. April 11, 2008.



Igor R. Efimov, Ph.D., F.A.H.A., F.H.R.S., Professor of Biomedical Engineering, Washington University, <http://efimov.wustl.edu/>

- * "Basic Electrophysiological Mechanisms of Initiation of Supraventricular Tachyarrhythmia," keynote speaker, VIII Pan Slavic International Congress on Cardiac Pacing and Electrophysiology, "CARDIOSTIM," St. Petersburg, Russia, February 14, 2008.
- * "New approaches for the low energy cardioversion and defibrillation," VIII Pan Slavic International Congress on Cardiac Pacing and Electrophysiology "CARDIOSTIM", Saint Petersburg, Russia, February 15, 2008.
- * "Mechanisms of ventricular fibrillation and a new approach to cardioversion-defibrillation," VIII Pan Slavic International Congress on Cardiac Pacing and Electrophysiology "CARDIOSTIM", Saint Petersburg, Russia, February 15, 2008.
- * "Electroporation in the intact heart: implications for defibrillation, arrhythmia and stunning," Medtronic, Inc., Minneapolis, MN. January 28, 2008.
- * "Biophotonic Imaging of Atrial Pacemaker Complex," Cardiovascular Research Seminar, Washington University School of Medicine, St. Louis, MO, January 24, 2008..
- * "Heterogeneous protein expression in the cardiac pacemaker and conduction system," Department of Biochemistry and Molecular Biology, Saint Louis University, St. Louis, MO, December 12, 2007.