

CBAC MISSION

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**”.

RESEARCH GOALS

Research projects at **CBAC** cover the entire spectrum from molecular and cellular processes to mechanisms, diagnosis and treatment of arrhythmias in patients. The cross-disciplinary structure of **CBAC** promotes collaborations between researchers and clinicians and fosters a multiple-approach strategy to the study, diagnosis and treatment of cardiac arrhythmias. Approaches include molecular, single-cell and whole-animal experiments, mathematical modeling and computer simulations, and patient studies during imaging, catheterization and open-heart surgery. Among the state-of-the-art techniques employed are genetics, biomolecular structural analysis, patch clamp recordings from single ion channels, ion-selective electrode measurements, high resolution electrical mapping, optical mapping of cardiac activation and cell-calcium, supercomputing and computer graphics, signal processing and image analysis.

Projects include:

- Molecular structure and electrophysiological function of cardiac ion channels
- Development of mathematical models of cardiac ion channels, cells and tissues
- Regulatory pathways in cardiac cells
- Mechanisms of hereditary cardiac arrhythmias
- Arrhythmias in myocardial ischemia and infarction
- Cell-to-cell communication and action potential propagation in the diseased heart
- Structure and function of the atrio-ventricular node
- Mechanisms of cardiac (ventricular and atrial) fibrillation and new



strategies for defibrillation

- Development and application of a novel imaging modality for cardiac arrhythmias
- Mechanisms of cardiac resynchronization therapy for heart failure

🌀 EDUCATION AND TRAINING GOALS

An important goal of **CBAC** is to enhance and promote education and training in biomedical engineering, life sciences, and clinical medicine. The cross-disciplinary structure of **CBAC** facilitates a synergistic relationship between training, research and clinical medicine. The educational component of **CBAC** builds on graduate programs in the Department of Biomedical Engineering and the Medical School. Through **CBAC**, graduate students and scientists in engineering and life sciences can participate in clinical lectures, seminars, case presentations and clinical procedures such as diagnosis and treatment of arrhythmias in the catheterization laboratory. Similarly, post-M.D. clinical fellows can participate in lectures and seminars in the basic science departments and in research projects in the basic science laboratories.

🌀 SUPPORT AND FACILITIES

Research is supported through grants to affiliated faculty. Funding agencies include: NIH, AHA, VA, Whitaker Foundation and NSF. A number of projects are funded through industrial support (pharmaceutical- and device-related studies). Facilities include state-of-the-art laboratories for genetics, molecular biology, cellular and subcellular electrophysiology, optical mapping of action potentials and cell-calcium, multi-electrode mapping of cardiac electrical activity, and theoretical and computer simulations using supercomputing. Studies can also be conducted in clinical facilities for MRI, CT and Ultrasound imaging, and for electrophysiology studies and arrhythmia treatment during cardiac catheterization and surgery.

Please visit our website located at <http://cbac.wustl.edu>.





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

(Case Western Reserve University, 1978); 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).

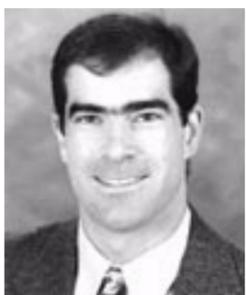
Research Interests: Our research aims at understanding the mechanisms that underlie normal and abnormal rhythms of the heart at various levels, from the molecular (ion channel) and cellular to the whole heart. We are also developing a novel noninvasive imaging modality (Electrocardiographic Imaging, ECGI) for the diagnosis and guided therapy of cardiac arrhythmias. Through the development of detailed mathematical models of cardiac cells and tissue, we are investigating the mechanisms and consequences of genetically-inherited cardiac arrhythmias, impaired cell-to-cell communication, and abnormal spread of the cardiac impulse in the diseased heart (e.g. myocardial infarction). ECGI imaging is currently being tested, evaluated and applied in patients with various heart conditions.



R. Martin Arthur, Ph.D.

(Univ. of Pennsylvania, 1968); Newton R. and Sarah Louisa Glasgow Wilson Professor of Engineering; Professor of Electrical and Systems Engineering; Professor of Biomedical Engineering.

Research Interests: Studies carried out by Professor Arthur in collaboration with cardiologists at the Washington University School of Medicine are aimed at identifying adults who have had a heart attack and are at increased risk of having a subsequent attack. Even when these patients' hearts are beating normally, there are changes in their electrocardiograms that indicate they are at increased risk of developing a new life-threatening arrhythmia. Professor Arthur and his colleagues have identified subtle changes that occur in the spatial distribution, spectral characteristics, as well as in the waveforms of the electrocardiograms from patients at risk. Risk of arrhythmia occurrence is determined from the analysis of torso shape and from the nature and distribution of body-surface electrocardiograms. In another series of studies, one aimed at improving ultrasonic techniques for the detection and staging of cancer, Professor Arthur has devised synthetic-focus algorithms for medical ultrasonic imaging. In contrast to conventional imaging methods, these ellipsoidal-backprojection algorithms permit images produced by an array of transducers to be in focus at each picture element. Adaptive-focus techniques are being developed to improve image focus and simultaneously extract a velocity map of the tissue being imaged. In a joint effort, Professors Arthur and William D. Richard are developing special-purpose computer architectures to support real-time ellipsoidal backprojection imaging. This imaging system will use massive parallelism and will be based on custom CMOS VLSI circuits currently under development.



Philip V. Bayly, Ph.D.

(Duke University, 1993); Lilyan and E. Lisle Hughes Professor of Mechanical Engineering, Aerospace Engineering, and Biomedical Engineering.

Research Interests: Dynamics of nonlinear mechanical and biological systems, particularly systems exhibiting instability and complex behavior: Cardiac arrhythmias; brain biomechanics; signal and image processing of rapidly changing systems.



Sanjeev Bhalla, M.D.

(Columbia University College of Physicians and Surgeons); Assistant Professor of Radiology; Assistant Radiology Residency Program Director, Mallinckrodt Institute of Radiology

Research Interests: Dr. Bhalla is expert in computed tomography of the chest, and is actively investigating the use of multi-detector array CT with 3-D reconstruction as an alternative to pulmonary angiography in the diagnosis of pulmonary arteriovenous malformations in HHT.

John P. Boineau, M.D.

Professor of Surgery, Medicine, and Biomedical Engineering.

Research Interests: Dr. Boineau has broad interests in both basic and clinical cardiac electrophysiology. Since 1963, he has been involved in mapping to determine the mechanisms



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of abnormal and complex electrocardiograms in myocardial infarction, ischemic cardiomyopathy, hypertrophy, congenital heart disease, and various different cardiac arrhythmias. In the 1960s, he initiated arrhythmia ablation surgery with Dr. Will Sealy and worked out many of the basic substrates for a variety of arrhythmias, including those associated with myocardial infarction, preexcitation syndromes, atrial flutter and fibrillation. Later, with Drs. James Cox and Richard Schuessler and others, he developed procedures for ablating atrial fibrillation, including the Maze and Radial procedures, and postoperative atrial flutter in patients with congenital heart defects. Currently, he is developing new electrocardiographic criteria for identifying “concealed” myocardial infarction in subjects with multiple infarctions.



Jane Chen, M.D.

(Washington University School of Medicine, 1993); Assistant Professor of Medicine

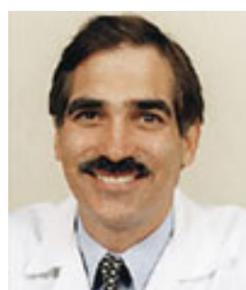
Research Interests: My clinical interests involve all aspects of interventional arrhythmia therapy, including implantation of pacemakers, defibrillators, and biventricular systems, as well as ablative therapy for supraventricular and ventricular arrhythmias, and management of atrial fibrillation. My research interests are mainly clinical, and I participate in multicenter trials involving devices and new technologies to assess risks for sudden cardiac death. I also am very involved in community education to raise awareness of heart disease and SCD and in women.



Jianmin Cui, Ph.D.

(State University of New York, 1992); Associate Professor of Biomedical Engineering on the Spencer T. Olin Endowment.

Research Interests: biophysics, molecular biology, ion channels in physiology and disease, channel structure-function relationship, ultrasound-mediated drug and gene delivery. Ion channels are the molecular units of electrical activity in all cell types. Bioelectricity is generated and modulated as different types of channels open and close in response to various stimuli, such as the binding of a neurotransmitter from outside the cell, a second messenger from inside the cell, or a change in the voltage across the membrane. My research interests focus on the mechanisms underlying conformational changes that occur as the channels open and close, and on the interaction of ion channels with other molecules during cellular electrical activity. The approach in our research is to use a combination of molecular biology, protein biochemistry, patch clamp techniques, and biophysical analysis and kinetic modeling. This approach allows us to manipulate channel protein structure, estimate the number of distinct conformational states of the channel protein, and determine the energy associated with the transitions among these states. Current projects involve two potassium channels: 1) The BK type calcium-activated potassium channels, which are important in, among other physiological processes, the control of blood vessel diameter and neurotransmitter release. They are implicated in hypertension and epilepsy; 2) The I_{Ks} potassium channels that play a key role in the rhythmic control of the heart rate. Defects in the channel protein have been shown to cause severe inherited cardiac arrhythmias that often lead to syncope and sudden death.



Ralph J. Damiano, Jr., M.D.

(Duke University School of Medicine, 1980); John M. Shoenberg Professor of Surgery; Chief of Cardiac Surgery.

Research Interests: Surgical treatment of arrhythmias; Pathophysiology of surgical ischemia; Hyperpolarizing cardioplegia; Cell volume regulation during cardioplegia; Transplant preservation (donor heart); Surgical robotics; Minimally invasive cardiac surgery.

Clinical Interests: Robotically assisted cardiac surgery; Endoscopic coronary artery bypass grafting; Beating heart surgery; Coronary artery revascularization; Valve repair and replacement; Arrhythmia surgery; Minimally invasive cardiac surgery; Transmyocardial laser revascularization (TMR).

Victor G. Davila-Roman, M.D.

(University of Puerto Rico, 1981); Associate Professor of Medicine, Anesthesiology, and Radi-





ology; Medical Director, Cardiovascular Imaging and Clinical Research Core Laboratory. **Research Interests:** Research interests are in the use of noninvasive cardiovascular imaging techniques to evaluate heart and blood vessel function. Specifically, I have been studying diseases of the heart, such as left ventricular hypertrophy that develops from high blood pressure. In the early stages of this disease, the heart function is normal and the walls of the myocardium become thickened. In the late stages of the disease, the walls become thin, the heart dilates, and the contractile function decreases. The reasons for this decrease have not been established, but animal data suggest that alterations in myocardial blood flow lead to changes in metabolic substrate utilization (i.e., glucose and fatty acids), and that these changes result in the heart becoming a less efficient pump. My research involves elucidation of some of the mechanisms that lead to this decompensated state in patients.



Igor R. Efimov, Ph.D.

(Moscow Institute of Physics and Technology); The Stanley and Lucy Lopata Associate Professor of Biomedical Engineering, Cell Biology & Physiology, and Radiology.

Research Interests: My lab is interested in developing better understanding of mechanisms of cardiac arrhythmias. We develop novel imaging modalities and mathematical models of the heart to investigate how electrical impulse propagates in the heart and when the propagation fails how a tornado-like arrhythmia develops, and how it can be terminated. We are also interested in bringing our scientific findings to clinical settings and work on technology transfer in the field of defibrillation.



Mitchell N. Faddis, M.D., Ph.D.

(M.D., Ph.D.; Washington University, 1993); Assistant Professor of Medicine, Radiology; Clinical Cardiac Electrophysiologist.

Research Interests: Catheter treatment of atrial fibrillation, pacemaker therapy for congestive heart failure, three dimensional imaging of the heart to guide catheter treatment of arrhythmias.



Richard Gross, M.D., Ph.D.

(New York University Medical School, 1976; Cardiology Fellow, Barnes Hospital, St. Louis, 1978-81; Washington University, St. Louis, Ph.D., 1982); Professor of Medicine, Chemistry, and Molecular Biology & Pharmacology; Director, Division of Bioorganic Chemistry and Molecular Pharmacology (Joint Appointment with the School of Medicine), Department of Internal Medicine, Department of Molecular Biology and Pharmacology and Department of Chemistry, Washington University School of Medicine.

Research Interests: Our research is focused on the chemical biology of membranes in health and disease. Biologic membranes are comprised of a structurally diverse array of thousands of distinct chemical entities in a bilayer configuration that are in constant motion providing a rich repertoire of chemical forces that can be used to modulate the conformation and function of transmembrane proteins such as ion channels and ion pumps. Our laboratory uses and develops many different chemical methods to study the structure and function of membrane systems to both advance our understanding of the fundamental processes underlying the chemistry of biologic membranes and to use this information to develop new strategies to have a favorable impact on the major disease processes of the 21st century. To identify the chemical mechanisms through which obesity predisposes to these disease processes, we have developed a novel technology, termed shotgun lipidomics, which allows the direct identification and quantitation of hundreds of lipid molecular species directly from organic extracts of tissue or biologic fluids. Currently we are using this technology to explore altered heart metabolism (metabolomics) through a systematic chemical biology approach. During the last decade, we have made substantial progress in understanding the chemical mechanisms regulating the intracellular phospholipases that release lipid second messengers. Through recombinant DNA techniques, we now express large quantities of these proteins to study their structure and regulatory mechanisms through a variety of chemical and molecular biologic methods. Of particular current interest are the



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mechanisms that regulate the recognition of membrane surfaces by signaling phospholipases and the resultant alterations in protein structure and function they engender. The recent identification of new signaling mechanisms mediated through phospholipase-calmodulin membrane-associated signaling platforms is rapidly expanding our understanding of the partnership of membranes and proteins in signaling functions. Through exploiting new advances in proteomics using both electrospray ionization (ESI) and matrix assisted laser desorption/ionization (MALDI) quadrupole time of flight spectrometer, high throughput analyses of the specific chemical mechanisms, and protein-target interactions regulating signaling phospholipases in multiple biologically relevant context can be made. Through this work, we seek to understand the mechanisms activating signaling proteins and identify new targets for pharmaceutical intervention.



Patrick Y. Jay, M.D., Ph.D.

(M.D., Ph.D.; Washington University, 1995); Assistant Professor of Pediatrics and Genetics.

Research Interests: Function of the cardiac transcription factor Nkx2-5 in the development of the cardiac conduction system and heart. Role of Nkx2-5 in the pathogenesis of postnatal conduction defects and cardiomyopathy. Genomic analysis of cardiac gene expression.

Clinical Activities: Pediatric cardiologist, St. Louis Children's Hospital.



R. Gilbert Jost, M.D.

(Yale Medical School, 1969); Elizabeth Mallinckrodt Professor of Radiology; Chairman, Department of Radiology; Director, Mallinckrodt Institute of Radiology.

Research and Clinical Interests: Radiology, medical imaging, new technologies, digital radiology, digital networking, x-rays, alternative screening.



Daniel Kelly, M.D.

(University of Illinois College of Medicine, 1982); Alumni Endowed Professor in Cardiovascular Diseases; Professor of Medicine, Pediatrics, and Molecular Biology & Pharmacology; Director, Center for Cardiovascular Research; Co-Director, Cardiovascular Division, Department of Medicine.

Research Interests: Our research focuses on gene transcriptional regulatory mechanisms and signaling events involved in the control of cardiac mitochondrial function. Evidence is emerging that perturbations in mitochondrial energy metabolism play a role in the development of inborn and acquired forms of cardiovascular disease. Previously, we found that the ligand-activated transcription factor, PPARalpha and its coactivator, PGC-1, play a pivotal role in the developmental and physiologic control of mitochondrial function and number in heart. The activity of the PPARalpha pathway is deactivated in the pathologically hypertrophied or hypoxic heart. PPARalpha-null mice, which model the hypertrophied and hypoxic heart, exhibit a stress-induced phenotype in which cardiac lipid and energy balance is deranged. In contrast, mice with cardiac-specific overexpression of PPARalpha exhibit a phenotype similar to the diabetic heart. The transcriptional coactivator, PGC-1, is an inducible regulator of mitochondrial biogenesis during cardiac development. Conditional PGC-1 gain-of-function and loss-of-function studies are currently being performed with cardiac myocytes in culture and in genetically engineered mice to further characterize the biologic and physiologic role of PGC-1 as a master regulator of cardiac energy metabolism. We are exploring the role of PPARalpha/PGC-1 in cellular growth versus death decisions in cell culture and in vivo. Gene expression array studies combined with candidate gene analyses are also being performed to identify new PGC-1 interacting proteins and to identify candidate genetic modifiers of the cardiac disease phenotype in humans. The long-term goal of our studies is to define the role of derangements in mitochondrial function in the pathogenesis of heart failure, diabetes mellitus, and obesity. PPAR/PGC-1, as a ligand-activated complex, is a target for the development of novel therapeutic strategies.

Sándor J. Kovács, M.D., Ph.D.

(Ph.D., Caltech, 1977; M.D., University of Miami, 1979); Associate Professor of Medicine, Physi-





ology, Physics, and Biomedical Engineering.

Research Interests: The Cardiovascular Biophysics Research Group (CBRG) pursues a multi-disciplinary (theory + experiment) program encompassing selected aspects of physiology, engineering, physics and the clinical medicine. The overall goal is to solve basic and applied problems in cardiovascular physiology and medicine using a multidisciplinary approach, to discover “new” physiology, and to advance the frontiers of diagnosis and therapy. Areas of interest include: characterization of the kinematic and material properties of cardiovascular tissue and its relation to matrix biology, 4-chamber heart function, diastolic function, ventriculo-arterial impedance, maximization of information extraction from physiologic signals, mathematical modeling of cardiovascular function and its in-vivo verification, and development of new technology for imaging and physiologic signal acquisition and processing.



Bruce D. Lindsay, M.D.

Associate Professor of Medicine; Director, Clinical Electrophysiology Laboratory.

Research Interests: Areas of interest include radiofrequency ablation techniques for supraventricular and ventricular arrhythmias, investigational anti-arrhythmic drugs, advanced technology for implantable defibrillators and pacemakers, and prospective identification of patients who are at increased risk of sudden death from arrhythmias. The Clinical Electrophysiology Service also participates in several clinical trials sponsored by the National Institutes of Health and industry. An ongoing investigation is evaluating a computer controlled system that uses magnetic fields for precise guidance of catheters in the heart.



Achi Ludomirsky, M.D.

(Sackler School of Medicine, Tel-Aviv University, Israel, 1975); The Louis Larrick Ward Professor of Pediatrics and Biomedical Engineering; Director, Pediatric Cardiology.

Research Interests: Therapeutic ultrasound; Clinical application of high intensity focal ultrasound; Micro electronic mechanical sensors (MEMS) for the study of cardiac physiology; Tissue characterization by Doppler ultrasound.

Clinical Activities: Diagnosis, treatment and prevention of congenital heart disease; Fetal cardiology; Development of cardiac devices for the treatment of fetuses, children and adults with congenital heart disease.



Arye Nehorai, Ph.D.

(Stanford University, 1983); Chairman and Professor of the Department of Electrical & Systems Engineering.

Research Interests: Our research deals with analysis of space-time data. Typically, we obtain such data from sensors distributed in space and take temporal measurements from each of them. The goal is extract information of interest, depending on the application. The desired information is called signal, hence this area is called signal processing. Our processing is statistical, since there is noise in the measurements. However, unlike most researchers in our field, we also compute physical models for the measurements. A common example of the problems we solve is finding the positions of sources emitting energy. Such problems appear in defense, communications, biomedicine, and environmental monitoring. In defense, we develop methods for locating targets using novel sensors that provide full information in time and space. These are used in radar and sonar applications. In communications, our methods can be used to locate a 911 caller, using an array of antennas or GPS and triangulation. In biomedicine, we develop methods for locating electrical sources in the brain using arrays of electrodes (EEG) or magnetometers (MEG) placed around the head. Our solutions are important for clinical applications such as finding origins of seizures, or in neuroscience for mapping the brain functions. We are developing procedures that find the stiffness of the heart wall using MRI. We also estimate the electrical current density in the heart with ECG and MCG sensor arrays. In environmental monitoring, we introduced techniques for detecting and locating sources emitting chemical substances. We apply our methods to biochemical defense and finding landmines. Our models can predict the space-time dispersion of a biochemical agent after it is



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released. In summary, our research is interdisciplinary, encompassing physical and statistical modeling, algorithm development, performance analysis, and simulations. We solve diverse problems arising in engineering and sciences.



Jeanne M. Nerbonne, Ph.D.

(Georgetown University, 1978); Alumni Endowed Professor of Molecular Biology and Pharmacology.

Research Interests: A primary focus of the research in this laboratory is to define the molecular mechanisms controlling the properties and cell surface expression of the voltage-gated K^+ (Kv) channels that underlie action potential repolarization in a normal and diseased heart. Investigators in this laboratory use a sophisticated combination of biochemical, electrophysiological, and

molecular techniques to define the molecular correlates of myocardial Kv channels. Transgenic and targeted deletion strategies are used to define the Kv pore-forming and accessory (b) subunits that underlie the various repolarizing Kv currents in (mouse) ventricular and atrial myocytes. These approaches, which allow one to manipulate functional Kv channel expression in vivo, are also being used to explore the molecular mechanisms underlying electrical remodeling in the hypertrophied (mouse) myocardium. Other investigators in this laboratory are exploring the properties of the Kv channels expressed in different neuronal cell types, the roles of different types of Kv channels in mediating neuronal firing properties and the molecular basis of functional neuronal Kv channel diversity. Trainees in this laboratory can opt to pursue an independent project in any of these areas or can choose to work on human tissue in studies aimed at exploring the molecular mechanisms underlying remodeling in the damaged/diseased myocardium.



Colin G. Nichols, Ph.D.

(Leeds University, 1985); Professor of Cell Biology and Physiology.

Research Interests: My research group is focused on the molecular and cellular regulation of potassium channels, and their role in linking cellular metabolism to electrical activity in cardiac and other tissues. We have developed a detailed biophysical understanding of inwardly rectifying channels and the structural basis of channel activity, as well as clinically relevant understanding of the mechanistic basis of inherited potassium channel diseases. Our latest efforts are directed towards a more complete understanding of the molecular basis, the physiological role, and clinical relevance, of potassium channel activity, using combinations of biochemical, genetic, physiological and biophysical approaches.



Joseph A. O'Sullivan, Ph.D.

(University of Notre Dame, Notre Dame, IN, 1986); The Samuel C. Sachs Professor of Electrical Engineering; Professor of Radiology and Biomedical Engineering; Director, Electronic Systems and Signals Research Laboratory; Associate Director, Center for Security Technologies.

Research Interests: Information theory, estimation theory, and imaging science, with applications in object recognition, tomographic imaging, magnetic recording, radar, and formal languages.



Edward K. Rhee, M.D.

(University of Pittsburgh School of Medicine, 1993); Assistant Professor of Pediatrics; Director, Arrhythmia Services.

Research Interests: Interests include catheter ablation of arrhythmias in children and adults with congenital heart disease, pediatric pacing and defibrillation, and cardiac resynchronization therapy (biventricular pacing) in pediatric heart failure.



Jean E. Schaffer, M.D.

(Harvard Medical School, 1986); Associate Professor of Medicine, Molecular Biology & Pharmacology.

Research Interests: While fatty acids are critical for many cellular functions, accumulation of excess fatty acids in non-adipose tissues leads to cell dys-



function and/or cell death. This lipotoxicity plays an important role in the pathogenesis of diabetes and heart failure. We are using genetic approaches to identify molecules that are important for channeling imported long chain fatty acids to specific cell fates, and to identify lipid metabolic and signaling pathways critical for fatty acid-induced apoptosis. Specifically, we have used a promoter trapping strategy to isolate mutant cell lines resistant to fatty acid-induced apoptosis. We are presently characterizing the disrupted gene that confers resistance in each mutant. We have also created transgenic mouse lines with tissue-restricted overexpression of proteins that facilitate fatty acid transport to understand the physiology of lipotoxicity. Our studies may provide insight to the pathogenesis of human disorders such as obesity, diabetes, and heart failure, in which fatty acid homeostasis is perturbed.



Richard B. Schuessler, Ph.D.

Associate Research Professor of Surgery; Associate Research Professor of Biomedical Engineering; Director, Cardiothoracic Surgery Research Laboratory.

Research Interests: Surgical treatment of atrial fibrillation; Mechanisms of atrial fibrillation; Inflammatory mechanisms in postoperative atrial fibrillation; Basic cardiac electrophysiology; Normal and abnormal sinus node electrophysiology; Mapping of cardiac electrophysiology; Animal models of cardiac arrhythmias.



Jinyi Shi, Ph.D.

Research Faculty, Biomedical Engineering.

Research Interests: biophysics, molecular biology, ion channels in physiology and disease, channel structure-function relationship, ultrasound-mediated drug and gene delivery. Ion channels are the molecular units of electrical activity in all cell types. Bioelectricity is generated and modulated as different types of channels open and close in response to various stimuli, such as the binding of a neurotransmitter from outside the cell, a second messenger from

inside the cell, or a change in the voltage across the membrane. The Cui lab research interests focus on the mechanisms underlying conformational changes that occur as the channels open and close and on the interaction of ion channels with other molecules during cellular electrical activity. The approach in our research is to use a combination of molecular biology, protein biochemistry, patch clamp techniques, and biophysical analysis and kinetic modeling. This approach allows us to manipulate channel protein structure, estimate the number of distinct conformational states of the channel protein, and determine the energy associated with the transitions among these states. Current projects involve two potassium channels: 1) The BK type calcium-activated potassium channels, which are important in, among other physiological processes, the control of blood vessel diameter and neurotransmitter release. They are implicated in hypertension and epilepsy; 2) The I_{Ks} potassium channels that play a key role in the rhythmic control of the heart rate. Defects in the channel protein have been shown to cause severe inherited cardiac arrhythmias that often lead to syncope and sudden death.



Gautam K. Singh, M.D., M.R.C.P.

(M.D., Patna Medical College, India, 1982; M.R.C.P., Royal College of Physicians, London, U.K., 1988); Associate Professor, Department of Pediatrics, Director of Non-invasive Cardiac Imaging Research; Co-Director, Echocardiography Laboratory

Research Interests: Cardiac mechanics in congenital heart disease particularly with single ventricular physiology by non-invasive cardiac imaging; non-invasive cardiac tissue characterization and cardiac kinematic in fetuses and children affected by cardiac disease, metabolic abnormalities and obesity; tissue characterization and cardiac mechanics in developing fetus in animal model.

Clinical Interests: Diagnosis, treatment and prevention of congenital heart disease, preventive pediatric cardiology, fetal cardiology, non-invasive cardiac imaging.

Timothy W. Smith, D.Phil., M.D.

(D.Phil.; University of Oxford, 1989; M.D.; Duke University, 1993); Assistant Professor of Medicine.

Research Interests: 1) My clinical research interests span all areas of clinical arrhythmia, in-



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cluding ways to optimize diagnosis and therapy of both bradyarrhythmias and tachyarrhythmias. This includes the use of implantable device therapy (pacemakers and implantable cardioverter-defibrillators) and implantable ECG monitors, as well as catheter techniques for mapping and ablation. 2) My basic science interest concerns the cellular mechanisms of arrhythmias, specifically the role of membrane ion transport systems (ion channels and active transporters). Calcium homeostasis (or failure to maintain homeostasis) is often implicated in arrhythmogenesis, but myocyte calcium transport and sequestration is a complicated interaction of multiple mechanisms. Further understanding may help assess the possibility of improved pharmacologic arrhythmia control.

Clinical Interests: My clinical interests encompass all aspects of care of the arrhythmia patient. I perform diagnostic electrophysiology studies, catheter ablation, and pacemaker and cardioverter-defibrillator implants. I attend on the clinical arrhythmia consultation service and on the cardiology inpatient service. In the ambulatory clinic I participate in follow-up and evaluation of patients with pacemakers and defibrillators. I evaluate and treat ambulatory patients for the gamut of arrhythmia problems, including atrial fibrillation, paroxysmal supraventricular tachycardias, ventricular arrhythmias, bradycardia, risk assessment for sudden death, syncope (fainting), and palpitations.



Jason W. Trobaugh, D.Sc.

(Washington University in St. Louis, 2000); Research Instructor in Medicine, Electrical and Systems Engineering.

Research Interests: Ultrasonic imaging, stochastic image models, and image analysis; medical image registration; temperature imaging with ultrasound; inverse ECG for detection of arrhythmia risk.



Lihong Wang, Ph.D.

(Rice University, 1992); Gene K. Beare Distinguished Professor; Department of Biomedical Engineering; Director, Optical Imaging Laboratory

Research Interests: Dr. Lihong Wang's group focuses on the research on non-ionizing biophotonic imaging. His group has made seminal contributions to ultrasound-modulated optical tomography, photoacoustic tomography, thermoacoustic tomography, modeling of light transport in biological tissue, and polarization-sensitive optical coherence tomography. In particular, his laboratory invented frequency-swept ultrasound-modulated optical tomography, dark-field confocal photoacoustic microscopy, exact reconstruction algorithms for thermoacoustic tomography, Mueller-matrix optical coherence tomography, and spectroscopic oblique-incidence reflectometry. His Monte Carlo model of photon transport in scattering media has been used worldwide.



Samuel A. Wickline, M.D.

(University of Hawaii School of Medicine, 1980); Professor of Medicine; Adjunct Professor of Physics and Biomedical Engineering; Co-Director of Cardiology.

Research Interests: The next generation of pharmaceutical agents will be targeted against specific molecular pathways and/or locales within the body. Our laboratory is engaged in a multidisciplinary effort (physics, engineering, chemistry, cell physiology, pharmacology) to develop systemically deliverable ligand-targeted nanoparticles for noninvasive in vivo image-based detection of picomolar quantities of pathological epitopes that are the sources of cancer and cardiovascular disease. We also have devised strategies for delivering drugs or genes to those sites with the use of these targeted nanoparticle carriers. We have invented 150-250 nm perfluorocarbon emulsions that can incorporate various classes of ligands (e.g., antibodies, small molecules) and selected drugs active against cancer and atherosclerosis and thrombosis. These particles also can be imaged in vivo with MRI, nuclear, CT, or ultrasound methods based on incorporation of payloads of gadolinium chelates, radionuclides, iodinated compounds, or perfluorocarbon content, respectively. We developed the tools for sensitive imaging and quantification of picomolar levels of molecular epitopes such as fibrin in silent unstable plaque,



tissue factor induction in vascular smooth muscle cells after vascular injury that leads to restenosis, and angiogenesis in early cancer and atherosclerosis by targeting vascular $\alpha_v\beta_3$ integrins in experimental cancer and after cholesterol feeding in animals. We also have incorporated drugs such as doxorubicin, taxol, and fumagillan that can be delivered selectively to individual cells of choice through a patent-pending process of "contact facilitated drug delivery" which are proving to dramatically enhance tumor lysis and plaque regression. These methods set the stage for the next generation of imaging agents capable of multispectral in vivo immunocytochemistry and targeted drug/gene delivery with direct assessment of the doses delivered to the specified cells at a highly localized anatomic site.



Pamela K. Woodard, M.D.

(Duke University School of Medicine, 1990); Associate Professor, Diagnostic Radiology, Cardiovascular Imaging Laboratory.

Research Interests: Dr. Woodard's expertise is in cardiovascular MR and CT imaging. Her research includes coronary MR angiography with novel MR contrast agents, multi-detector coronary CT angiography, assessment of cardiac perfusion and viability using contrast-enhanced and BOLD MR techniques, and MR assessment of carotid atherosclerotic plaque. She is PI at Washington University on an R01-entitled "MRI-Based Computational Modeling for Carotid Plaque Rupture and Stroke" (NIBIB), in collaboration with Dalin Tang, Ph.D. (PI), at Worcester Polytechnic Institute, and is principal investigator at Washington University on a multi-center R01 entitled, "Prospective Investigation of Pulmonary Embolism Diagnosis-II" (NHLBI), a grant designed to assess the utility of the multidetector contrast enhanced spiral CT for the assessment of pulmonary embolism and deep venous thrombosis. Dr. Woodard is also principal investigator on numerous FDA phase II and III trials and is a consultant to the pharmaceutical industry.



Kathryn A. Yamada, Ph.D., F.A.H.A.

(Georgetown University, 1982); Research Associate Professor of Medicine.

Research Interests: Mechanisms of arrhythmogenesis in the diseased heart; Cardiac connexin biology with emphasis on the role of connexin45 in normal and diseased hearts; Electrical remodeling induced by heart failure and myocardial infarction; Cardiac electrophysiology of transgenic mice expressing mutant or deficient gap junction and/or ion channel proteins.

CBAC Alumni:

Amir A. Amini, Ph.D.

Kyongtae T. Bae , M.D., Ph.D.

Michael Cain, M.D.

Vladimir P. Nikolski, Ph.D.

Jeffrey E. Saffitz , M.D., Ph.D.



CBAC CENTER

The **Cardiac Bioelectricity & Arrhythmia Center (CBAC)** is an interdisciplinary center set up to foster intellectual interactions and collaborations between researchers and clinicians from the Washington University Danforth and Medical School campuses in an effort to understand the heart's irregular rhythms and to prevent their fatal consequences.

The **CBAC** center includes 33 faculty members from various departments in the Danforth and Medical School campuses.

CBAC holds a seminar series which is split into two sessions during the academic year (September through May) and consists of a Fall session and a Spring session. The seminars are held most Monday afternoons at 5:30 pm in Whitaker Hall, room 218 on the Danforth campus at Washington University in St. Louis and have proven to be an important educational and informational vehicle. With talks from experts in various fields relating to rhythm disorders of the heart, the seminars offer advancement of knowledge in the research and clinical fields supported by the center. The **CBAC** seminars are videotaped with permission from the speakers, and MPEG and DIVX formats of the video files can be downloaded and viewed from the **CBAC** website.

CBAC publishes information about the center's faculty members and their research through the CBAC website located at <http://cbac.wustl.edu>. The center also publishes educational dissemination materials that currently include the CBAC Video Archives and the CBAC Newsletter which is also distributed both in print and available online in PDF format.

Want to Be Added to the CBAC Email List?

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.



Cardiac Bioelectricity & Arrhythmia Center (CBAC)

Washington University in St. Louis



Providing an "arch" in cardiology and cardiovascular research between the School of Engineering & Applied Science and the School of Medicine

