An interdisciplinary approach to studying and treating rhythm disorders of the heart
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, multi-electrode body surface electrocardiographic mapping, imaging, 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

**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](http://cbac.wustl.edu).
**Director - Yoram Rudy, Ph.D., F.A.H.A.**
(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.

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**Amir A. Amini, Ph.D.**
(University of Michigan, Ann Arbor, 1990); Associate Professor; Director, Cardiovascular Image Analysis Lab

**Research Interests:** The efforts of our lab are focused on computational imaging and biomedical image processing and analysis: primarily the task of extracting information from medical images acquired from X-ray projection and CT devices, MR imagers, nuclear medicine scanners, and ultrasound in an automated and reproducible way. Areas of general interest include development of algorithms for intra- and inter-modality non-rigid registration of multi-dimensional images, automatic segmentation of anatomical structures, and estimation of object motion in biomedical images. Areas of particular interest include development of computational algorithms for analysis of cardiovascular MR images for automated morphometric determination of volumes, shapes, etc., as well as mechanical indices; e.g., myocardial strains, intravascular pressures, shear stress, etc.

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**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 ar-
chitectures 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.

Kyoungtae T. Bae, M.D., Ph.D.
(Ph.D.; University of Pennsylvania, 1988; M.D.; University of Chicago, 1992); Associate Professor of Radiology, Assistant Professor of Biomedical Engineering.

Research Interests: My research interest is quantitative and physiologic imaging and computer applications in diagnostic imaging. Radiology is a fast growing medical specialty. Rapid developments in computer and technology have provided an opportunity to explore for new radiology clinical applications and to use imaging as a quantification tool. I have been actively involved in image segmentation and quantification of the kidney and cyst structures and renal blood flow using MR and US to correlate with renal functional changes; (2) Development and evaluation of computer algorithms for automated detection of lung nodule, pulmonary embolism, and colonic polyp from CT images; (3) Development and evaluation of new technology to enhance or improve image-guided treatment of disease and injury, specifically image-guided hepatic tumor resection and 3D image-guided robotic treatment of atrial fibrillation; (4) Computer modeling and validation studies to improve our understanding of contrast medium pharmacokinetics and to optimize clinical application of contrast media; (5) Cardiovascular and coronary artery CT angiography imaging, coronary or cardiac calcium measurement, endoluminal aortic graft imaging, and coronary artery stent imaging; (6) Application of MR perfusion, diffusion and spectroscopy for imaging breast cancer, prostate cancer, liver, and muscle; and (7) High resolution CT imaging of the cochlea and bone structure, and reduction of artifacts caused by metallic prosthesis in CT images.

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.

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 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 electro-
cardiographic criteria for identifying “concealed” myocardial infarction in subjects with multiple infarctions.

Michael E. Cain, M.D.
Tobias and Hortense Lewin Professor of Medicine; Director, Cardiovascular Division.

Research Interests: Research is directed at determining the electrophysiologic, structural, and biochemical determinants of ventricular tachycardia (VT) and fibrillation (VF) in the setting of healed myocardial infarction, acute myocardial ischemia, or in response to injury leading to cardiomyopathy to improve pharmacologic and nonpharmacologic procedures for arrhythmia ablation by characterizing and localizing the tissue critical to arrhythmogenesis, and to provide the pathophysiologic foundation needed to refine methods of ECG analysis that will improve the identification of patients at risk for developing VT or VF. Using advanced signal-processing methods (signal averaging; Fourier analysis and autoregressive and other parametric methods of spectral estimation; and forward and inverse solutions in realistic torso and heart models) for the analysis of cardiac and body surface recordings acquired with a 190-channel computer-assisted ventricular and body surface mapping system in patients with healed infarction or cardiomyopathy who were undergoing arrhythmia surgery or cardiac transplantation, we have recently demonstrated the following: intramural reentry and focal mechanisms underlie VT in humans; tissue critical to VT activates before the terminal QRS complex/ST segment of the sinus beat; and signals detected during the terminal QRS complex and ST segment of ECGs are generated from myocardium adjacent to the site of infarction that is both spatially and temporally remote from the tissue containing the intramural reentrant circuit or encompassing the focal origin of VT. These data are being used to define the fundamental spectral, temporal, and spatial features in body surface ECGs that identify the unique alterations in ventricular activation and recovery characteristic of patients who suffer sustained VT or VF. This will allow refinement of methods of analysis of signal-averaged ECGs to incorporate the optimal passband, physiologically selected ECG lead systems tailored to each patient's torso, and the intervals during the cardiac cycle that will maximize detection of this deleterious electrophysiologic fingerprint, which will improve our ability to detect vulnerability to life-threatening ventricular arrhythmias.

Clinical Interests: As an attending physician in the clinical electrophysiology laboratory and on the cardiac arrhythmia service, I evaluate and manage the care of both in- and outpatients with cardiac arrhythmias, including those with VT, VF, paroxysmal supraventricular tachycardias, and atrial fibrillation/flutter.

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:** Robotic 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 Radiology; 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.

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, Physiology, 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 antiarrhythmic 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.

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 (β) 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 inves-
tigators 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.

Vladimir P. Nikolski, Ph.D.
(Moscow Institute of Physics and Technology, 1987); Research Assistant Professor of Biomedical Engineering.
Research Interests: Basic studies of cardiac electrophysiology and defibrillation therapy in animal models; Fluorescent optical mapping of action potentials and calcium transients in the whole heart and cell culture; Immunohistochemistry of gap junction and ion channel proteins.

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.

Jeffrey E. Saffitz, M.D., Ph.D.
Paul E. Lacy and Ellen Lacy Professor of Pathology and Medicine; Professor, Internal Medicine.
Research Interests: The goals of our research are to elucidate mechanisms of sudden cardiac death and ultimately, to develop novel therapies to prevent lethal arrhythmias. Our research is focused on characterization of structural and molecular determinants of intercellular coupling in the normal and diseased heart and elucidation of the role of deranged intercellular coupling at gap
junctons in the pathogenesis of sudden cardiac death. We have shown that gap junc-
tions interconnecting mammalian cardiac myocytes contain channels made of three dis-
tinct proteins (connexins) that have unique functional properties. Diverse structural and
molecular features of intercellular coupling appear to determine the special electrophysi-
ological properties of atrial and ventricular myocardium. Our current research efforts
involve the use of genetically altered mice to understand the functional roles of specific
connexin gene products and to elucidate cellular and molecular mechanisms underly-
ing remodeling of intercellular connections in the diseased heart that may predispose
to the development of lethal ventricular arrhythmias. We take advantage of multiple ex-
perimental techniques including the production of new genetically altered mouse mod-
els, cellular and tissue electrophysiology, general molecular biological analyses of gene
expression, and quantitative morphometric methods involving confocal immunofluores-
cence microscopy, electron microscopy, and three-dimensional reconstructions of the
microscopic structure of myocardium as it pertains to impulse propagation.
**Clinical Interests**: Cardiovascular pathology.

**Richard B. Schuessler, Ph.D.**
Associate Research Professor of Surgery; Associate Research Profes-
sor of Biomedical Engineering; Director, Cardiothoracic Surgery Research
Laboratory.

**Research Interests**: Surgical treatment of atrial fibrillation; Mechanisms
of atrial fibrillation; Inflammatory mechanisms in postoperative atrial fibril-
lacion; Basic cardiac electrophysiology; Normal and abnormal sinus node
electrophysiology; Mapping of cardiac electrophysiology; Animal models of cardiac ar-
rrhythmias.

**Jinyi Shi, Ph.D.**
Research Faculty, Biomedical Engineering.

**Research Interests**: biophysics, molecular biology, ion channels in physi-
ology 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 modu-
lated 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 mes-
senger 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-acti-
vated potassium channels, which are important in, among other physiological process-
es, the control of blood vessel diameter and neurotransmitter release. They are impli-
cated 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.
**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, including 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.

**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 angio-
genesis in early cancer and atherosclerosis by targeting vascular avb3 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.
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