CENTER HEARTBEAT

FROM MOLECULE TO BEDSIDE TO STUDY & TREAT RHYTHM DISORDERS OF THE HEART

Newsletter of the Cardiac Bioelectricity and Arrhythmia Center (CBAC) Vol. 8 Fall 2014

Washington University in St. Louis

cbac.wustl.edu

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

Whitaker Hall home of BME and CBAC administration and research

Medical School Campus home of many CBAC members and research

Cardiac Bioelectricity & Arrhythmia Center

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 400,000 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.

From the Director's Desk....

The Need for a Balance Between Basic & Translational Research

We thank Huyen (Gwen) Nguyen for producing yet another issue of the CENTER HEARTBEAT. And many thanks to all who contributed to this issue.

The CBAC's stated mission is "to battle cardiac arrhythmias and sudden cardiac death through scientific discovery and its application in the development of mechanism-based therapy." In other words, we foster and conduct basic research and its translation to clinical application. In recent years, strong support has been voiced for the translational phase of research, often at the expense of basic discovery. In fact, history tells us that we need both, basic research and applied development, and that this should not be an either/or proposition. Untargetted basic research often leads to high-impact applied innovation, sometimes following many years (decades) of delay. I will try to illustrate this on 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 of 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 last 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."

So, the beat goes on, hopefully with a "balanced diet" of basic research and translational innovation.

Yoram Rudy

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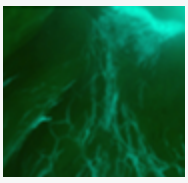
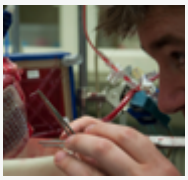
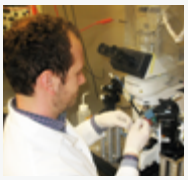
Director







Contents

A New Spin on Cardiac Conduction and Rhythm from Developmental Biology and Human Genetics

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Historically, key observations and technical advances have spurred scientific progress in the cardiac conduction system. Tawara performed painstaking histological reconstructions to delineate the anatomy of the central and peripheral conduction systems in 1906. Einthoven described the electrocardiogram in 1903. Subsequent advances in the 20th century, such as patch clamping and cloning methods, enabled discoveries that bring us to modern cardiac electrophysiology, a field that is mainly focused on the initiation and propagation of the action potential. In this review, we provide an overview of key discoveries from developmental biology and human genetics. They herald new avenues of investigation and could suggest targets for the next generation of anti-arrhythmic therapy.

Cardiac developmental genes regulate the programming of the conduction system.

Most cells and tissues in the body can be studied as isolated cells, in cell culture or in simple models like the fly, worm, or fish. Such methods and model organisms facilitate the molecular genetic dissection of pathways and phenotypes. The cardiac conduction system, however, is unlike most tissues. Due to its intricately complex nature, functional studies must be performed in situ in human or mammalian hearts, which impedes mechanistic studies. Furthermore, the function of components of the conduction system is usually experimentally inferred. For example, conduction from the atria to the ventricles is measured using electrodes, or voltage- and calcium-sensitive fluorescent dyes, while conduction through the AV node, His bundle and Purkinje system are not observed directly. Until relatively recently, the difficulties in studying this complex cellular network hampered mechanistic exploration of its developmental programming, until several key discoveries piqued the interest of the developmental biology community.

Developmental biologists seek to understand how cells and tissues arise and grow in an organism. To do so, they utilize molecular markers to trace the origin and fate of a cell. The markers can be antibodies or RNA probes for genes specifically expressed in the cell of interest. The markers can also be genetic. An old, yet elegant genetic method was the use of a retroviral vector that inserts into the genome of a progenitor cell. The cell in turn passes its transgenic reporter to its progeny. More recently, Cre-lox systems have largely replaced the use of retroviruses. Cre is a bacteriophage enzyme that recombines genomic DNA that is flanked or "flox'ed" by two 32-base pair sequences, known as loxP. The intervening sequence is excised. In a typical lineage analysis experiment, a transgenic mouse is engineered to express Cre in a specific cell-type and at a specific time. Induction of Cre activity removes the flox'ed sequence which had prevented the expression of a transgenic reporter gene. Thus, all the daughter cells of a Cre-positive progenitor inherit a genetic label. As no practical markers of the conduction system were available until just 15 years ago, the retroviral strategy was used to settle a longstanding controversy: Does the conduction system arise from a myocyte or neural lineage?

In a series of classic experiments, Gourdie and Mikawa infected chick embryos with a non-replicating retrovirus that encoded beta-galactosidase. Cells that express the enzyme turn blue in the presence of its substrate X-gal. The number of viral particles introduced was so low that only one or a few cells in the heart would be infected. Because it was improbable that two adjacent cells would be independently infected, one could conclude that a cluster of blue cells descended from a common progenitor. Blue cells in the central and peripheral conduction system were always associated with the adjacent contractile myocardium and no other cell type. Thus, a multipotent cardiac myocyte progenitor gives rise to the conduction and contractile myocardium (1,2). This conclusion was critical to interpreting a couple human genetic discoveries that soon followed.

Pediatric cardiologists have long recognized the association of conduction and rhythm abnormalities with congenital heart defects. Whether the electrophysiological abnormality is primary or a secondary complication can be hard to know. This is a practical concern because patients can suffer heart block, arrhythmia, or sudden death long after the surgical repair of a heart defect. Such a natural history had been observed among four families in which multiple members developed atrioventricular block often but not necessarily with an atrial septal defect. Genetic linkage analyses led to the discovery of heterozygous loss-of-function mutations of the cardiac transcription factor NKX2-5 (3). Likewise, Holt-Oram syndrome patients have varying degrees of atrioventricular block. The syndrome is characterized by malformations of the heart and radial aspect of the hand and forearm (4). Two groups independently discovered mutations of the transcription factor TBX5 as the cause of Holt-Oram syndrome. These discoveries provided a unifying explanation for the cardiac malformations and conduction defects.

NKX2-5 and the Drosophila homolog tinman were already known to be essential for normal morphologic development of the heart (5-7). Nevertheless, when the human mutations of TBX5 and NKX2-5 were reported in 1997 and 1998, it was far from obvious that either transcription factor would likewise regulate the embryonic development of the conduction system. No genes were known yet to regulate conduction system development in the mammalian heart, whereas many genes were known for the action potential. The electrophysiologic hypothesis, in which the expression of an ion channel or gap junction was abnormal in patients who had a transcription factor mutation, seemed more plausible. Furthermore, no markers were available to test the developmental hypothesis until Kupershmidt and Roden made a serendipitous observation. They had made a mouse knockout of the long QT gene, minK (Kcne1), replacing the coding sequence with lacZ. For reasons that are still not understood, the lacZ was specifically expressed in the conduction system (8). Similarly, the transgenic CCS-LacZ mouse line, which expresses lacZ under control of Engrailed-2 regulatory elements and integration-site regulatory elements, enabled the first visualization of the full extent of the murine Purkinje fiber network (9).

Crosses of the Nkx2-5 or Tbx5 knockout to the minK-lacZ mouse made it easy to see how either mutation affected the anatomy of the conduction system in 3-D. The Nkx2-5 null mutant embryos completely lacked the AV node primordium, whereas Nkx2-5 haploinsufficient mice had hypoplastic development of the AV node, His bundle and Purkinje system. Mere hypocellularity of the conduction system plausibly explains conduction abnormalities such as the low amplitude His electrogram and prolonged QRS. In fact, the conduction velocity through the Nkx2-5+/- His-Purkinje system is normal, as is the action potential in individual Purkinje cells (10,11). In the Tbx5 mutant, a visually striking proof of the developmental hypothesis is the congenital absence of the right bundle branch as the cause of a right bundle branch block pattern on the electrocardiogram (12).

These first descriptions of a developmental basis for defects of the conduction system spawned research on more than a dozen genes that encode transcription factors and signaling pathways ((13), Table 1). The genes play positive roles in patterning or programming multipotent cardiac myocyte progenitors to become components of the sinus node, central or peripheral conduction systems. Others genes play negative roles. PITX2, for instance, inhibits the development of a sinoatrial pacemaker in the left atrium (14). BMP and Notch signaling pathways have complex functions that depend upon the cellular context. For example, Notch signaling is critical for normal development of the AV node, but

it also inhibits the formation of atrioventricular accessory pathways (15).

In the course of dissecting genetic pathways, developmental biologists have created mouse strains that could be useful for studies of cardiac electrophysiology (Table 2). These include Cre lines in which a flox'ed gene can be deleted in a component of the conduction system. Reporter genes driven by an endogenous or transgenic regulatory element can illuminate the conduction system in hearts during or after an electrophysiologic experiment. For example, when inserted into the Connexin40 locus, green fluorescent protein (GFP) lights up the conduction system from the lower AV node to the Purkinje fibers (16).

Common polymorphisms of cardiac developmental genes influence conduction and arrhythmia phenotypes in humans.

Given how well understood the cardiac action potential is, one could reasonably have asked just a few years ago what fundamental discoveries remain to be made. By extension, it might have seemed less than worthwhile to perform expensive genome-wide association studies (GWAS) on cardiac intervals and arrhythmia phenotypes. In a GWAS, thousands to >100,000 individuals are phenotyped for a trait and genotyped at millions of single nucleotide polymorphisms (SNPs) across the genome. Statistical analyses identify SNP genotypes that are associated with the trait. A significant SNP flags a chromosomal region that affects the trait. The SNP is probably not causative, but it is physically linked to a regulatory or coding sequence for a gene that is. Because many SNPs are tested and the alleles of genes typically have a small effect on a complex trait, any detected SNP likely points to a common variant in the population.

The GWAS on conduction and rhythm traits have studied two general kinds of phenotypes. The first considers EKG intervals – RR, PR, QRS, QT – a quantitative trait. The second considers an arrhythmia in binary terms – i.e., affected or not; atrial fibrillation has received much attention. EKG intervals are appealing because their measurement is inexpensive and standardized. Some intervals are associated with clinically relevant traits, e.g., RR and risk of sudden death (17), or PR interval and risk of atrial fibrillation and pacemaker implantation (18). Thus, the identification of common variants for a cardiac interval or arrhythmia could offer novel insights into pathogenesis, prognosis or therapy. For example, allelic variants associated with a prolonged PR interval could help to identify individuals who are predisposed to atrial fibrillation, either alone or in response to a stressor like surgery or chronic hypertension. As a rule, quantitative traits and common diseases are not simply Mendelian, so GWAS can help to describe the genetic architecture of a phenotype, such as the number and types of genes involved and their effect.

As expected, the GWAS have identified ion channels, such as KCNE1, KCNQ1, KCNH2, KCNJ2, SCN5A and SCN10A. The surprising result was that developmental genes were discovered too (Table 3). In fact, the magnitudes of their effects are similar to those of the electrophysiologic genes. The causative variants are probably polymorphisms that regulate the expression of the genes. This has been the case for genes discovered by GWAS on many other complex traits. Polymorphisms that affect protein sequence are uncommonly found. How might common variants of developmental genes regulate cardiac conduction or affect the risk for an arrhythmia? Evidence exists for two general mechanisms.

Although completely speculative just a decade ago, a developmental basis is now well accepted. Abnormal embryonic development of the conduction system can manifest as an adult phenotype. For example, the Nkx2-5+/- mouse, which has half-normal levels of NKX2-5, has half as many Purkinje cells as the wild type (Fig. 1A). The QRS is wider because there are fewer Purkinje cells to depolarize the ventricular myocardium (10). Similarly, a regulatory polymorphism could cause a quantitative reduction of NKX2-5 gene expression and Purkinje cell number during development that is manifest on the postnatal EKG.

The second mechanism is electrophysiological. Although first studied in the context of cardiac development, transcription factors or signaling pathways could directly regulate the expression of electrophysiologic genes in the postnatal

heart. Genetic variation in the SCN5A/SCN10A enhancer affects the binding of TBX3 and TBX5 transcription factors, thereby reducing the expression of Nav1.5 (19,20). The results of GWAS and laboratory experiments support a gene regulatory network in which variants of TBX3, TBX5, and SCN5A have quantitative effects on the PR and QRS intervals and risk of atrial fibrillation (21-25).

Evolutionary pressure may have selected the same genes to regulate both the developmental programming and electrophysiologic maintenance of cardiac tissues. The dual regulation of His-Purkinje formation and SCN5A gene expression in the postnatal myocyte by TBX5 is a clear example. PITX2 offers another intriguing example. The transcription factor has plays a critical developmental function broadly related to left-right patterning, including suppression of sinus node development at the left sinoatrial junction and formation of the pulmonary venous myocardium (26-28). Abnormal development at either anatomic location could explain the GWAS association of PITX2 with atrial fibrillation (29,30). On the other hand, PITX2 is expressed in and regulates gene expression in the postnatal atrial myocardium. Conditional deletion of PITX2 in the adult mouse heart disrupts the expression of various ion channels and causes structural remodeling of the intercalated discs similar to that seen in human atrial fibrillation (31). Quantitative reduction in PITX2 expression in the atrial myocardium could explain a low threshold for inducible atrial tachyarrhythmia in the PITX2+/- mouse (14). PITX2 expression in the human left atrium does not correlate with SNP genotypes associated with atrial fibrillation (32), so whether the developmental or electrophysiologic mechanism is more relevant in humans is unclear.

Opportunities for research and novel therapeutic strategies

Once non-coding variants are identified by GWAS, the challenge is to provide a mechanistic link between the identified region (or region near the variant) and the associated phenotype, to better explain how genetic variation in these elements influences transcriptional regulation. DNA sequences conserved over greater evolutionary distances have long been thought to have a higher likelihood of being functional than those conserved over lesser evolutionary distances. Conserved non-coding sequences are frequently found in enhancers that are subject to a strong selective pressure to preserve critical developmental and postnatal homeostatic mechanisms. Traditionally, once an allelic variant is identified, subsequent functional analyses focus on the surrounding highly conserved sequences. These types of studies may include generating a mouse model to study the variant's function by knock-in of the variant allele using CRISPR/Cas technology to efficiently enable genome editing (33). Other mechanistic analyses include CHIP-sequencing (CHIP-seq), a technique that combines chromatin immunoprecipation with massively parallel DNA sequencing to identify the binding sites of transcription factors and/or other chromatin-associated factors (including DNA and histone modifying factors) in the region surrounding the variant allele.

The approaches described above produce linear maps of genomic information. More recently, it has been established that simply because a gene's expression pattern is preserved through evolution, it does not necessarily follow that the cis-regulatory elements controlling the expression have been evolutionarily conserved at the level of linear DNA sequence. For example, functional information can be conserved in vertebrate sequences at the level of 3D structures, while the genomic sequence alignment may not be similar. Therefore, zebrafish transgenesis has proven to be suitable for rapid screening of putative human enhancers on a large scale, even when the orthologous zebrafish sequence is not available (34). The relative ease of generating transgenic zebrafish, as well as their transparent external development, facilitates dynamic gene expression analysis throughout development.

The shape of the genome becomes even more fascinating when one begins to appreciate how it relates to genome functioning. The segregation of active and inactive chromatin inside the nucleus raises the possibility that nuclear positioning affects gene activity. This idea is supported by observations that certain genes loop out of their chromosome territory upon activation (35). This looping is likely driven by regulatory DNA sequences, such as enhancers and locus control regions (36). Again, evidence exists that this gene positioning can be controlled by transcription factors binding

to regulatory DNA sequences such as enhancer elements. Although we are still far from understanding the exact relationships, breakthrough technologies based on chromosome conformation capture (3C) technology are now available for the systematic analysis of DNA structure and nuclear organization. Ten years ago, Dekker et al. developed 3C technology, a biochemical strategy to analyze contact frequencies between selected genomic sites in cell populations (37). Since then, various 3C-derived genomics methods have been developed and utilized in this regard.

A better understanding of how gene expression is regulated may translate to novel therapeutics. For example, while an electronic pacemaker can perform many functions of the native sinus node, significant device limitations exist, including a limited battery life, failure of electrodes, potential for infection, and lack of autonomic responsiveness. One alternative to electronic devices might be to directly reprogram atrial cardiomyocytes in situ into induced-SAN (iSAN) cells. Important advantages of this type of approach are that once cellular reprogramming has occurred, regulation of the entire family of currents that regulate impulse initiation would be accomplished. Proof of concept for direct conversion of myocytes into conduction-like cells was demonstrated by Rentschler et al (38). Activation of Notch signaling, a developmental signaling pathway, converts murine ventricular cardiomyocytes into a subtype of specialized fast-conducting Purkinje cells (Fig 1B). Using a similar approach, Tbx18 was recently demonstrated to reprogram adult guinea pig ventricular myocytes into iSAN cells (39). These types of studies herald exciting research opportunities and, hopefully therapeutics, for the treatment of arrhythmias.

Members of the CBAC community collectively have tools and expertise that could illuminate mechanisms of arrhythmogenesis in genetic models. For example, what is the mechanism of atrial fibrillation in humans (or mice) who carry the deleterious PITX2 variants? Does loss of PITX2 predispose to increased automaticity in the pulmonary venous myocardium, or is the atrial myocardium prone to re-entrant circuits? Children who have congenital heart defects presumably related to genes like NKX2-5 and TBX5 typically do not develop symptomatic conduction disease or arrhythmia until they are adolescents or young adults. Are there factors in individuals with structurally normal hearts that interact with these genetic predispositions to cause disease? A more detailed understanding of the pathophysiology could enable better prognostic markers, to reduce risks associated with cardiovascular disease and design novel therapeutic strategies.

In summary, advances in genome sequencing technology coupled with better genetic tools are allowing us to delve deeper into mechanisms of disease-associated genetic variants. This may herald a new age of personalized care in the management of arrhythmias, based on genetic predisposition and development of drugs to more effectively treat arrhythmia disorders. For example, introduction of human disease-associated variants into zebrafish could provide a platform for rapid and inexpensive drug screening. Historically, anti-arrhythmic drug therapy has focused upon ion channels, but progress on this front has arguably slowed in recent years. After all, the last new molecular entity for the treatment of arrhythmias was dronedarone, approved in 2009. A better understanding of so-called “developmental” pathways could suggest novel means to reprogram cardiac myocytes, thus nudging the heart’s electrophysiologic phenotype toward a healthier state.

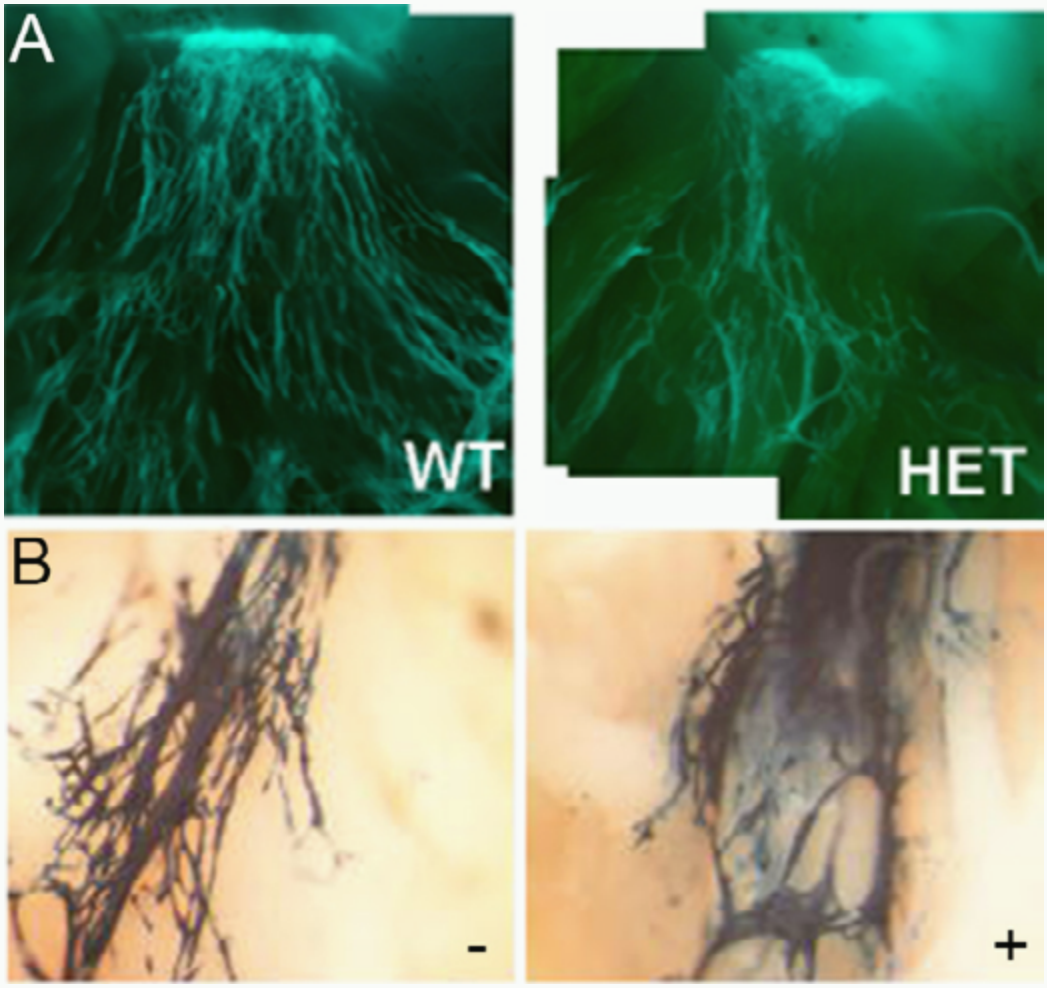

Fig. 1. Genetic manipulations in mice can reprogram the development of the conduction system. (A) There are more Purkinje cells in the left bundle branch of wild-type (WT) than Nkx2-5+/- (HET) mice, as depicted by a Cx40-GFP reporter. (B) The number of Purkinje cells in the right bundle branch of mice in which Notch signaling is activated (+) is greater than in the control (-).

Structure	Gene	Effect	Reference
Sinus node	Shox2	+	(14,40,41)
	Tbx3	+	(27)
	Tbx5	+	(42)
	Tbx18	+?	(43)
	Nkx2-5	-	(27)
	Pitx2	-	(14,27)
AV node	BMPR1A/BMP signaling	+/-	(44)
	Gata4	+	(45)
	Nkx2-5	+	(10,46)
	Notch1/Notch signaling	+	(15)
	Tbx2	+	
	Tbx3	+	(47)
	Tbx5	+	(45)
His bundle	Id2	+	(48)
	Nkx2-5	+	(10,48)
	Tbx3	+	(49)
	Tbx5	+	(48)
Bundle branches	Id2	+	(48)
	Nkx2-5	+	(10,48)
	Tbx3	+	(49)
	Tbx5	+	(48)
Purkinje system	Nkx2-5	+	(10,11,46)
Pulmonary venous myocardium	Nkx2-5	+	(28)
	Pitx2	+	(28)
AV accessory pathway	BMPR1A/BMP signaling	-	(44)
	Tbx2	-	(50)
	Notch1/Notch signaling	+	(15)

Table 1. Transcription factors and signaling pathways activate or suppress the development of components of the conduction system.

Transgene	Driver	Expression	Reference
Cre	cGATA6	AV node	(51)
	HCN4	Sinus node, central and peripheral conduction systems	(52)
	minK-BAC	AV node to Purkinje system	(53)
	Tbx2	AV canal, base of the ventricles, outflow tract, atrial septum and dorsal mesenchymal protrusion	(54)
GFP	Connexin 40	Atrium, lower AV node to Purkinje system	(16)
	Contactin 2	Sinus node, central and peripheral conduction systems	(55)
LacZ	Contactin 2	Sinus node, central and peripheral conduction systems	(55)
	Engrailed 2	Sinus node to Purkinje fibers including atrial pathways	(9)
	minK	Sinus node, central and peripheral conduction system	(8)

Table 2. Developmental biologists have created mouse strains that could be useful genetic tools to study the conduction system.

Gene	RR	PR	QRS	Repolarization	Atrial fibrillation	AV block
HAND1			(25)			
HEY2				(56)		
MEIS1		(21,23,24)				
NDRG4				(57-59)		
NKX2-5	(60)	(23,60)	(60)	(60)	(23,60)	
PITX2					(29,30)	
PRRX1					(29)	
SOX5	(61)	(23)			(23)	
TBX3		(23)	(25)			
TBX5		(21-24)	(22,25)		(22)	(22)
TBX20			(25)			
WNT11		(23)				

Table 3. GWAS have consistently found developmental genes to have an effect on cardiac intervals and rhythm phenotypes. References are given for each gene and trait.

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CBAC Faculty
Spotlight

"I want to utilize knowledge and expertise from across diverse fields and apply it to the treatment of human disease."

Stacey Rentschler

Assistant Professor of Medicine & Developmental Biology
Departments of Medicine & Developmental Biology
Washington University in St. Louis School of Medicine

Physician & Scientist

Dr. Stacey Rentschler M.D., Ph.D. joined the Department of Medicine, Division of Cardiology, in 2012. As a cardiology fellow at the University of Pennsylvania under the mentorship of Dr. Jonathan Epstein, she received the prestigious Burroughs Wellcome Fund Career Award for Medical Scientists, which is given to physicians working in basic biomedical or disease-oriented research. While a cardiology fellow, Dr. Rentschler developed a mouse model for preexcitation syndromes such as Wolff-Parkinson-White syndrome (WPW). In addition, she developed strategies for reprogramming cardiomyocytes into conduction system cells. Here, she gives us a better sense of who she is and what she does in her own words:

I arrived at Washington University in September 2012 from the University of Pennsylvania. I am a physician scientist with a research focus on the molecular and developmental basis of congenital and acquired arrhythmias. Much of my work centers around understanding the transcriptional and epigenetic programming of cellular electrophysiology as it relates to our understanding of arrhythmias, as well as to regenerative medicine approaches to treat conduction disorders.

I grew up in a very small town in the heart of Pennsylvania's coal region. My mom has told me that from the time I was a young girl she knew I would become a scientist because of my incessant questions. I was fortunate that much of my extended family lived in the same small town, including my grandparents. My grandmothers were important early role models for me. Though they lived modest lives, they were constantly looking for ways to better the lives of everyone around them in whatever way they could. Along with my mother, they taught me the importance of striving for the common good. I believe that the desire to better the world, coupled with an intense curiosity to understand mechanisms of disease, led to my career choice to become a physician-scientist. I feel very privileged to have a job where I can satisfy my desires to make new discoveries, to be involved in creative solutions to health-related problems, and to train and inspire future leaders in the field.

I attended Lehigh University in Pennsylvania and majored in Chemistry as an undergraduate. During my junior year, I took a course on the biomedical applications of chemistry, and this was when I first became interested in becoming a physician. I enrolled in the Medical Scientist Training Program at Mount Sinai School of Medicine in N.Y. During my medical school course work I became fascinated with cardiac physiology, which prompted me to pursue my Ph.D. training under the mentorship of Dr. Glenn Fishman studying the molecular basis of arrhythmias. Dr. Fishman is a wonderful mentor, and I will always be thankful that he supported my budding interest in the programming of the cardiac conduction system, even though it was not a focus in his laboratory at the time.

I first met Dr. Jonathan Epstein, who is also a physician-scientist, while I was in graduate school. I immediately told him that I wanted to pursue my post-doctoral training in his laboratory. Six years later, after completing graduate and medical school, I joined his laboratory. Dr. Epstein was instrumental in teaching me how to perform rigorous science. He provided me with a lot of freedom as a post-doctoral fellow to pursue my interest in the transcriptional regulation of cardiac conduction. I will always be thankful for the opportunity he gave me to explore my ideas at an early stage in my training, and I benefitted greatly from my exposure to the diversity and quality of science ongoing in his laboratory. Dr. Epstein nominated me for the Burroughs Wellcome Career Award for Medical Scientists. This award was the most significant research award I have received and has certainly played a large role in my career trajectory in two specific aspects. First, it launched me into a level of independence and confidence during my late post-doctoral period that would not otherwise have been possible. Second, the flexibility of this award has allowed me to make bold scientific choices.

I was attracted to come to Washington University because of its unique combination of strengths in all of the fields important to my research program, including cardiovascular research, developmental biology, arrhythmias, and genetics. I was fortunate to be able to do amazing science together with the people I met during my recruitment visits, and to have a lot of fun while doing it. Indeed, I have already benefited from scientific and career mentoring expertise from many senior faculty members across multiple disciplines. I have also had access to infrastructure to facilitate multidisciplinary endeavors, which I think is critical for success as a junior faculty member. I feel privileged to have wonderful new

colleagues and mentors here at Washington University who are working together toward common goals, and who are helping to guide me during the next phase of my career.

When I first saw the complex His-Purkine network within the heart, I immediately became fascinated. How is this network patterned and electrically programmed? Which diseases are associated with improper conduction system patterning or electrical programming? How can we utilize our current knowledge to better understand and treat patients suffering from conduction diseases? We are now beginning to understand that the same transcriptional networks that program the conduction system also regulate and maintain cellular electrophysiology broadly in the adult. I want to utilize knowledge and expertise from across diverse fields and apply it to the treatment of human disease. I hope that over my lifetime we can do more to bridge the gap between the discoveries in animal models and validation of novel therapies in clinical trials.

I believe my most important research achievement is yet to come, and will be discovered by talented individuals working in my laboratory.

Studying development has allowed me to see the amazing plasticity of cells, including terminally differentiated cells such as cardiomyocytes. A main focus of my research program is to decipher the transcriptional and epigenetic mechanisms that regulate cell lineage specification of the diverse subtypes of cardiomyocytes such as nodal, Purkinje, atrial, and ventricular in both mouse and human systems. Once we understand the critical regulatory networks involved in programming these diverse cell lineages, it may be possible to leverage these networks to allow interconversion of cell types in the adult heart for regenerative medicine approaches. In addition, since reactivation of many developmental signaling pathways occurs in adult injury responses, including the Notch and Wnt pathways, I hope to gain a better understanding for the role of Notch and Wnt in post-infarction remodeling, regeneration and arrhythmias.

I am most proud of the fact that I have a talented, supportive husband and that together we have two wonderful children who continually amaze us and keep our lives interesting.

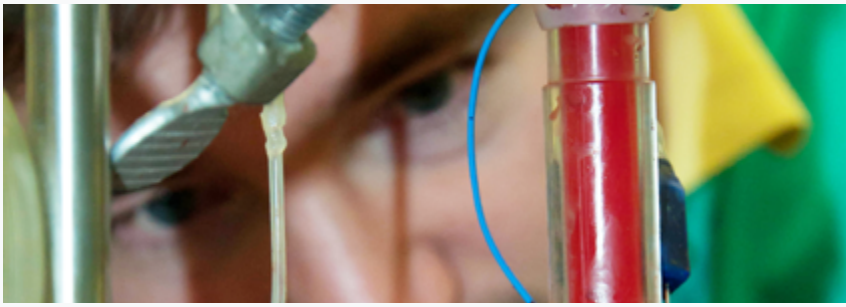
I enjoy spending time and sharing new experiences with my husband and two children, Cassie (10) and Noah (6). Having lived in the Northeast our entire lives, we have greatly enjoyed getting to know St. Louis over the past year. We have found St. Louis to be a nice balance of having enough fun things to do, but small enough that life is manageable for two physician-scientists with young children. We have also enjoyed getting to know the people here, both at home and at work. My other passions outside of work include playing basketball and traveling.

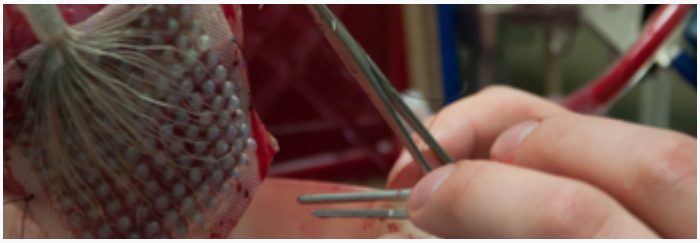
I have enjoyed interacting and collaborating with the outstanding members of CBAC, and have found the seminar series to be critically important for driving our collective science forward. I think the inclusive philosophy of CBAC, where experts in diverse areas of research are welcomed, has led to important discoveries and will continue to result in many more important discoveries by this community in the years to come.

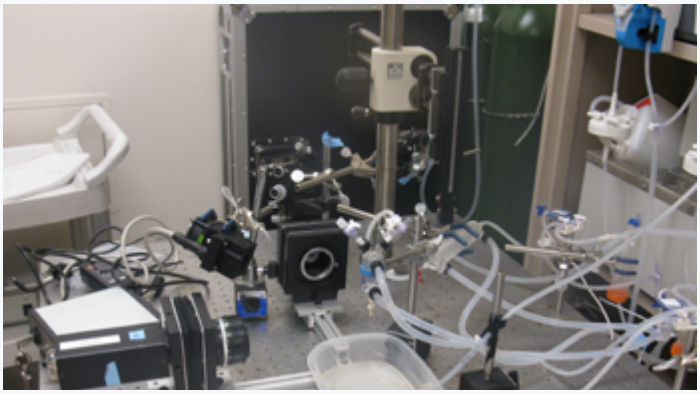
Stacey Rentschler and her laboratory members

CBAC Research Scientist

Spotlight







Bastiaan (Bas) J. Boukens

Research Scientist
Department of Biomedical Engineering
Igor Efimov Laboratory

Cardiac Electrophysiology

Bas Boukens' office is just a few doors down so it wasn't hard for me to find him. Peering into his office, one can see an easygoing young man comfortably dressed in jeans and a grey sweater. We chatted for a bit and he showed me the apparatus that he uses to conduct his research in the basement of Whitaker Hall.

CBAC: How long have you been in your current position? Can you give me an overview of what it is you do in your research?

I started to work at the Department of Biomedical Engineering in the lab of Dr. Efimov on the 1st of July 2013. My personal interest is the relation between cardiac molecular biology and electrophysiology. However, my core expertise is in experimental cardiac electrophysiology. Currently, I am trying to understand the repolarization patterns that give rise to the T wave and the mechanism underlying right ventricular outflow tract based arrhythmias. Furthermore, I am involved in several Ph.D. projects with a main focus on panoramic optical imaging of ventricular fibrillation and the optimization of forward and inverse calculations between local electrical events on the heart and the body surface electrocardiogram.

CBAC: How did you come about being part of Dr. Efimov's lab?

During my Ph.D. period, I presented my research on many conferences in the USA. There, I met Dr. Efimov several times. But before that I knew Dr. Efimov already from his work on the atrioventricular node and of his studies involving optical mapping. When a committee had to be selected for my thesis defense, I suggested to my mentors to invite Dr. Efimov to serve as an opponent. When Dr. Efimov was in Amsterdam, he asked me whether I wanted to come to St. Louis and work in his lab. I gladly accepted his invitation.

CBAC: While growing up, what kind of upbringing and experiences that may have inspired your career choice?

As a child, I did not have an idea of what I wanted to become, but I always asked questions and was highly reluctant to believe peoples' opinions for no reason. So maybe, in hindsight, I already was a small scientist. During high school, I really liked chemistry, physics, mathematics and biology. At that time, mathematics maybe suited me better but I found biology more interesting. Therefore, that is why I chose to study biomedical sciences at the University of Utrecht.

CBAC: How did you get into your area of specialization?

My university education was composed of 3 years bachelor and 2 years master. The master was composed of two internships of 9 and 6 months and three classes. I chose the master biology of disease in which I selected classes on physiology. I did my first internship (6 months) at the Department of Sports Medicine at the University Medical Center Utrecht (UMC). [I did] my second internship at the Department of Experimental Cardiology at the Academic Medical Center in Amsterdam. During that period, I learned how to measure the intact heart in a Langendorff set-up but also, and maybe more importantly, I was introduced into the philosophy of science. That inspired me and I strongly advise Ph.D. students to learn about Karl Popper. So it is after that internship that I knew that I wanted to become a philosophical doctor.

CBAC: Describe your doctoral and post-doctoral training experiences.

In the Netherlands, the Ph.D. period is not linked to a graduate school like here in the USA. It is composed of four years of research at a department at the university or academic medical center. This period can be prolonged when there is money. I worked during my Ph.D. period at the department of Experimental Cardiology and the department of Anatomy, Embryology & Physiology. After four years, my mentors and I decided to prolong my Ph.D. period so that I had the opportunity to finish several projects. After 5.5 years I received my Ph.D. certificate with Honors. After my Ph.D. period, I worked for seven months as a postdoctoral researcher at the department of Anatomy, Embryology & Physiology. In this same period, I visited the National Heart and Lung Institute, Imperial College London for one

month. There, I learned scanning ion conductance microscopy.

CBAC: What would you say most motivates you to do what you do? What are the goals you most want to accomplish in your work?

What drives me is that I want to contribute to the scientific field and help it move forward. Furthermore, I get really excited of thinking of hypotheses and designing experiments to reject or accept them. Also, I like to share knowledge either by writing or reviewing manuscripts or giving presentations. My goal is to eventually combine morphology, molecular biology and electrophysiology to understand cardiac physiology and pathology.

CBAC: What is your most important research achievement that you are most proud of? Why?

During the second year of my Ph.D., I had to analyze mouse electrocardiograms but I didn't have a clue how to interpret them. After a literature search, I realized that not much was known about the mouse electrocardiogram and that often, criteria were used that were based on the human electrocardiogram. Then, I decided that I first wanted to understand the normal electrocardiogram of mouse before I started to analyze the abnormal electrocardiogram of the mouse. So I set up a study to investigate this matter. After many experiments, I learned which deflection in the electrocardiogram was linked [to which] local electrical event on the heart. This study was later published in Cardiovascular Research. For me, this is my most important scientific achievement so far.

CBAC: What have been some of the things that you have learned in general since you have been in St. Louis?

The culture in the Netherlands is different from other countries in Europe and also from that of the United States. Therefore, I like to travel and visit countries and learn about other cultures and opinions. In the short period that I have lived in St. Louis, I already learned a lot about peoples' view on politics, law, life and other matters. This has broadened my view on life and makes me feel like I have grown as a person.

CBAC: What do you feel is your most important personal achievement?

During my time at the Academic Medical Center in Amsterdam, I supervised and helped many students to understand electrophysiology of the heart and more specifically mechanism of arrhythmias. I really enjoyed that. Several students, who already finished their internships and are now working in new locations, have contacted me to let me know that they have really benefited from my contribution in their education. I see that as one of my most important personal achievements.

CBAC: What are your future goals or what do you expect to accomplish in the next few years?

I think that nowadays the shortage of money, especially in Europe, makes science over-competitive, which does not always yield quality. Also, this can generate an environment for Ph.D. students in which producing papers is more important than solving scientific problems. My future goal is to build my own research group where I can put more emphasis on the "philosophical" in Ph.D. and thereby generate, to my opinion, a healthy balance between productivity and understanding physiology and pathology of the heart.

CBAC: What kind of hobbies and activities do you enjoy in your spare time?

At work, I spend a lot of time behind my computer analyzing data or writing manuscripts. Therefore, in my spare time, I play rugby to release my energy and empty my head. I also like to hike in the mountains, spend time with my family or drink a whiskey and smoke a cigar or pipe.

CBAC: What does the CBAC mean to you and how have you or will you benefit from being part of the CBAC?

I think the CBAC makes it easy for clinical and basic researchers to communicate, discuss science and set up collaborations. For my research, it helped me getting into touch with the department of Developmental Biology and the department of Thoracic Surgery. I also think the researchers that present at CBAC seminars bring excellent science to Washington University.

[*Boukens organized a symposium that broughttogether researchers from the Netherlands and the CBAC for a half day of presentations and discussions* *(see p. 24).*]

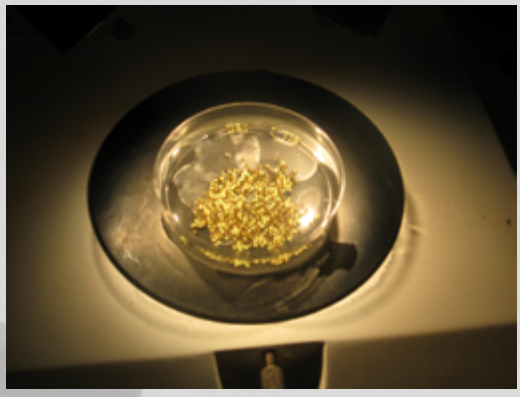
Bas J. Boukens was born in Hoorn, The Netherlands, on December 7, 1982. After studying Biomedical Engineering at the University of Utrecht, he started to work on his PhD-thesis at the Heart Failure Research Center, University of Amsterdam. He defended his thesis with honors in 2012. Then he worked as a postdoctoral researcher at the department of Anatomy, Embryology and Physiology, University of Amsterdam. The goal of his research is to understand the molecular mechanism underlying electrophysiological remodeling during heart disease.

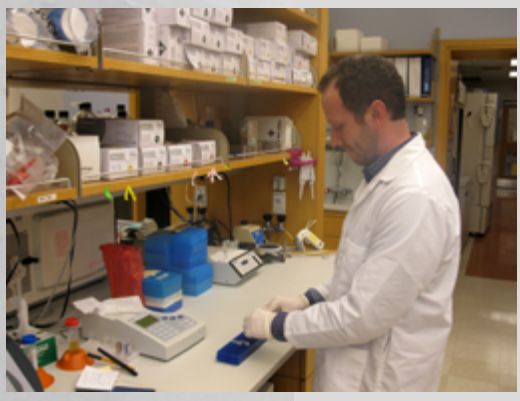
CBAC M.D.+Ph.D. Student Spotlight

Mark Zaydman

Department of Biomedical Engineering
Jianmin Cui Laboratory

Scientist





Top to bottom: Mark Zaydman; frog eggs (Xenopus oocytes) in a petri dish, Mark at his lab bench.

Mark is a MD/PhD student in Dr. Cui's lab in 150 Whitaker Hall. Most of his days are spent in a room with a customized fluorescent microscope that he retrofitted with probes and a scientific modeling clay [not silly puddy!] covered specimen tray hooked up to a computer that measures optical and electrical signals from ion channels expressed in frog eggs (Xenopus oocytes). With his thesis defense just around the corner, he found the time to answer some of our questions, giving us a better understanding of his work, life, and goals:

My parents immigrated to the US from the republic of Moldova. Growing up in an immigrant family, I was told that I could do anything I wanted when I grew up - as long as it was math or science. Luckily for my parents, I gravitated naturally toward science. From an early age, when asked what it was that I wished to be, I responded "a research scientist." To be honest, I had an unrealistic idea of what being a scientist would be like. I imagined that I would spend most of my time receiving indescribable gratitude from parents of children whose diseases I had cured. As an adult, I have a better understanding of the day-to-day, but the endless learning, constant challenges, and the excitement and gratification of discovery keep me dreaming of being a scientist.

During my undergraduate studies at Case Western Reserve University, I became fascinated by the idea that cells use electricity. In fact, presentations by our very own Drs. Igor Efimov and Jianmin Cui introduced me to cardiac bioelectricity and the molecular bases of these signals. Unfortunately for me, at the time, they left Case Western after my freshman year for Washington University. My confidence grew as I did well in the challenging BME program at Case, but I felt that my knowledge of human physiology was limiting my ability to contribute in the most impactful way. To fill in these gaps I pursued combined MD/PhD training, which brought me here to Wash U. I feel that having several years dedicated to studying physiology and pathophysiology, has given me a stronger perspective and breadth as a scientist, but it has really been my thesis work that has brought me the most joy and confidence in my career choice.

Dr. Cui and I have history going back to Case Western. In fact, he was my freshman academic advisor, and his presentations in my freshman year classes opened my eyes to the fascinating field of ion channel biophysics. I decided to come here because I knew several researchers that I was interested in working with and the MD/PhD is among the best in the country. During my admission interview, Dr. Cui asked me, "did you follow us here?" – Yes, I did.

I attended Case Western Reserve University in Cleveland Ohio where I received my Bachelors degree in Biomedical Engineering. While there, I was privileged to be a part of the lab of Dr. Kenneth Laurita at Metrohealth Hospitals. I am currently in the combined MD/PhD program here at Washington University. This spring I will defend my thesis and go back to finish the last two years of my medical training.

I started the M.D./Ph.D. program at Wash U in the summer of 2007 and I have been working on my Ph.D. in the lab of Dr. Jianmin Cui since

August 2009. In the Cui lab, we study the structure, function and regulation of voltage-gated ion channels. Voltage-gated ion channels generate the electrical signals that make muscle tissue contract, encode information in the nervous system, and trigger hormone release. A fundamental feature of their function is the ability to detect and react to changes in transmembrane voltage. This is achieved by the interaction between two distinct domains, the voltage-sensing domain, which detects changes in membrane voltage, and the pore domain, which opens and closes to modulate the membrane conductance. In my thesis work, I have been studying the fundamental mechanisms through which the functions of the voltage-sensing and pore domains are coupled. We have discovered that lipid molecules play a central role in communicating voltage-sensor activation to pore opening and the two domains couple through unique protein-protein and protein-lipid interactions at every stage in the gating pathway. This work has direct relevance to cardiac electrophysiology where, we have discovered, modulation of these coupling interactions is the major mechanism through which the accessory subunit KCNE1 modulates the function of the KCNQ1 voltage-gated potassium channel. In the heart, channels formed by KCNQ1 and KCNE1 generate the IKs current, which plays a critical role in regulating action potential duration. Patients with inherited mutations that decrease IKs are predisposed to sudden cardiac death. Our studies provide novel therapeutic strategies for targeting these abnormal channels.

The work itself is extremely motivating for me. It is both creative and challenging, and I feel that the work we have done is significant. I am thrilled that we have made fundamental contributions to the understanding of voltage-dependent gating, and we are extending this work to clinically relevant questions. I hope that this work provides a useful, conceptual framework for others studying voltage-dependent ion channels and their associated diseases.

I am very proud of the paper I published in PNAS in 2013 [See: "Kv7.1 ion channels require a lipid to couple voltage sensing to pore opening" at http://www.pnas.org/content/early/2013/07/16/1305167110.short]. It was a real journey, but in the end the story came together beautifully. Of course, I am now obsessed with my current work that is a direct continuation of that paper. I guess in research your new most important achievement may always be just around the corner.

Time goes by so quickly, I feel like I just moved here yesterday. I have learned that you can achieve a lot with good people and hard work, but I also learned that time and energy are limited resources. It does a lot of good to be realistic and focused, at least part of the time.

My most important significant personal achievement is meeting and marrying my wife Amanda. We have built a great life together, and her support has carried me through.

After completing medical school I plan to continue my scientific training in the form of a post-doctoral position. During my thesis work, I learned to work through a very basic problem. During my post-doc, I intend to expand my toolkit to problems at the tissue, organ or organism level so that I can ultimately run a lab of my own that works on the mechanistic underpinnings of human diseases.

As ion channel biophysicists in the biomedical engineering department we are a bit of an oddity. CBAC has provided me a sense of community and belonging on the Danforth Campus. Also, the CBAC invited seminar speakers have been amazing. This series of lectures has provided me first hand access to current experts in the field.

Papers that Mark has authored along with other CBAC members include:

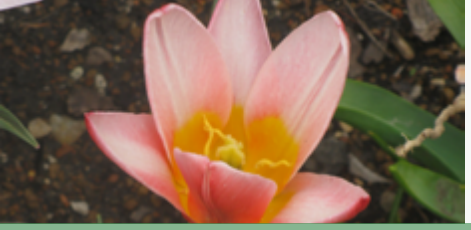
Zaydman MA, Silva JR, Delaloye K, Li Y, Liang H, Larsson HP, **Shi J, Cui J.** (2013) Kv7.1 ion channels require a lipid to couple voltage sensing to pore opening. Proc Natl Acad Sci USA. 2013 Aug 6;110(32):13180-5. doi: 10.1073/pnas.1305167110. Epub 2013 Jul 16.

Zaydman MA, Silva JR, Cui J. (2012) Ion channel associated diseases: overview of molecular mechanisms. Chem Rev. 2012 Dec 12; 112(12):6319-33. doi: 10.1021/cr300360k. Epub 2012 Nov 14.

Sun X, **Zaydman MA, Cui J.** (2012) Regulation of Voltage-Activated K(+) Channel Gating by Transmembrane β Subunits. Front Pharmacol. 2012 Apr 17; 3:63. doi: 10.3389/fphar.2012.00063. eCollection 2012

Li Y, **Zaydman MA,** Wu D, **Shi J,** Guan M, Virgin-Downey B, **Cui J.** (2011) KCNE1 enhances phosphatidylinositol 4, 5-bisphosphate (PIP2) sensitivity of IKs to modulate channel activity. Proc Natl Acad Sci USA. 2011 May 31; 108(22):9095-100. doi: 10.1073/pnas.1100872108. Epub 2011 May 16.

Wu D, Delaloye K, **Zaydman MA, Nekouzadeh A, Rudy Y, Cui J.** (2010) State-dependent electrostatic interactions of S4 arginines with E1 in S2 during Kv7.1 activation.
J Gen Physiol. 2010 Jun; 135(6):595-606. doi: 10.1085/jgp.201010408. Epub 2010 May 17. PMID: 20479111



News & Announcements

July 2013

Pamela Woodard - Director, Center for Clinical Imaging Research (CCIR) - and her collaborators were awarded the patent , "Natriuretic peptide-mediated imaging of artherosclerotic plaque," US Patent #8,436,140 issued on May 7, 2013. She also received a six-month, $137,000 grant from Astellas Pharma for research entitled, "Development of a PET-MR Myocardial Perfusion Examination Using Regadenoson."

August 2013

Philip Bayly was awarded a three-year $395,000 grant from the National Science Foundation (NSF) for the project, "Probing the Mechanics of the Axoneme in Genetically Modified Flagella."

Lihong Wang receives the 2014 IEEE Biomedical Engineering Award, the highest honor, conferred by the Institute of Electrical and Electronics Engineers (IEEE) in this field. Link: http://news.wustl.edu/news/Pages/25693.aspx

September 2013

Pamela Woodard, serving as co-chair, will be completing a twelve-month follow-up of the research entitled, "Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations (RESCUE) Trial" (PI: Stillman). The trial was extended to September 29, 2014 via the ACRIN fund. Amount awarded was $9,666,726 in total.

Lihong Wang was awarded the NIH Director's Transformative Research Award. He was one of only ten recipients of the award, given to scientists proposing highly innovative approaches to major contemporary challenges in biomedical research. Link: http://engineering.wustl.edu/newsstory.aspx?news=7473

Philip Bayly was awarded a $430,000 three-year grant from the National Science Foundation (NSF) for the project titled, "Measuring Anisotropy in Fibrous Soft Materials by MRI of Slow and Fast Shear Waves."

October 2013

Igor Efimov's paper with John Rogers entitled, "3D multifunctional integumentary membranes for spatiotemporal cardiac measurements and stimulation across the entire epicardium" is published in Nature Communications. Link: http://www.ncbi.nlm.nih.gov/pubmed/24569383. Complete media list at: http://efimov.wustl.edu/node/223

November 2013

Washington University School of Medicine in St. Louis offers genetic testing to help diagnose and treat patients with heart disorders that can lead to sudden death. **Phillip Cuculich** was involved in the development of the test - dubbed the Washington University CardioGene Set. Link: http://news.wustl.edu/news/Pages/26152.aspx

Members of the CBAC participated in the Amercian Heart Association Scientific Sessions 2013, Dallas, Texas. **Ralph Damiano** presented on: "Minimally Invasive Arrhythmia Surgery" and **Jean Schaffer** gave a presentation entitled, "Small Nucleolar RNAs and Metabolic Stress."

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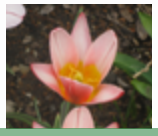


News & Announcements
Continued

November 2013 (cont.'d)

Poster Presentations by CBAC members included:

- "Pro-Arrhythmogenic Effects of the KCNQ1-V141M Mutation in Short QT Syndrome and Its Potential Therapeutic Targets - Insights From Modeling" by **Hsiang-Chun Lee** and **Jianmin Cui**
- "Diastolic Function in Normal Sinus Rhythm Vs. Chronic Atrial Fibrillation: Quantitative Comparison by Fractionation of E-wave Deceleration Time into Stiffness and Relaxation Components" by **Sándor Kovács**
- "Model-based Reexpression of Vortex Formation Time Differentiates Between Pseudonormal vs. Normal Left Ventricular Echocardiographic Filling Patterns" by graduate student **Erina Ghosh** and **Sándor Kovács**
- "Transgenic Expression of a Kir6.1 Gain-of-Function Mutation in the Mouse Heart Reults in Av Nodal Conduction Abnormalities" by Research Instructor **Haixia Zhang** and **Colin Nichols**
- "Voltage-Clamp Fluorometry Reveals a Unique Cardiac Phenotype for the hNaV1.5 DIII and DIV Voltage Sensors" by **Jonathan Silva**
- "Flourescence Tracking of Domain IV Voltage Sensor Motion Shows a Progressively Varying Molecular Phenotype in Long QT Syndrome Type 3 Mutants" by researcher **Angela Schubert** and **Jonathan Silva**
- "Distinct Mechanism of Lidocaine Interation with the DIII Voltage Sensor of the Cardiac Sodium Channel" by **Zoltan Varga** and **Jonathan Silva**
- "Thrombin-Inhibiting Nanoparticles Prevent Growth of Fibrin Clots by Inhibiting and Adhering to Clot-Bound Thrombin by graduate student **Jacob W. Myerson** and **Samuel Wickline**
- "Maturational Changes in Myocardial Mechanics During the First Month of Life in Healthy Full term Neonates" by Instructor **Philip Levy** and **Gautam Singh**

December 2013

Yoram Rudy, gave the keynote address entitled:"Mechanisms of Human Cardiac Arrhythmias: Noninvasive Studies with Electrocardiographic Imaging (ECGI)" at the University of Milano Department of Biotechnology and Biosciences, Department Day Celebration on December 5, 2013.

January 2014

Patrick Jay received the Established Investigator Award by the American Heart Association (AHA), a $400,000 five-year award, for the project titled, "Maternal Age: A Modifiable Risk Factor for Congenital Heart Disease"

February 2014

Igor Efimov and an international team of biomedical engineers and materials scientists have created a 3-D elastic membrane made of a soft, flexible, silicon material that is precisely shaped to match the heart's epicardium, or the outer layer of the wall of the heart. Link: http://engineering.wustl.edu/newsstory.aspx?news=7560

Philip Bayly received the Richard Skalak Award for outstanding paper in the Journal of Biomechanical Engineering.

March 2014

Yoram Rudy was awarded a $1,520,000 four-year grant (years 21-24 of the award) from the NIH – National Heart, Lung and Blood Institute for the project titled "Cardiac Excitation and Arrhythmias." The overall objective of this research is to provide mechanistic understanding of the relationships between the dynamic molecular structure of cardiac ion-channel proteins during their gating process and their function as charge carriers during the whole-cell action potential (AP).

April 2014

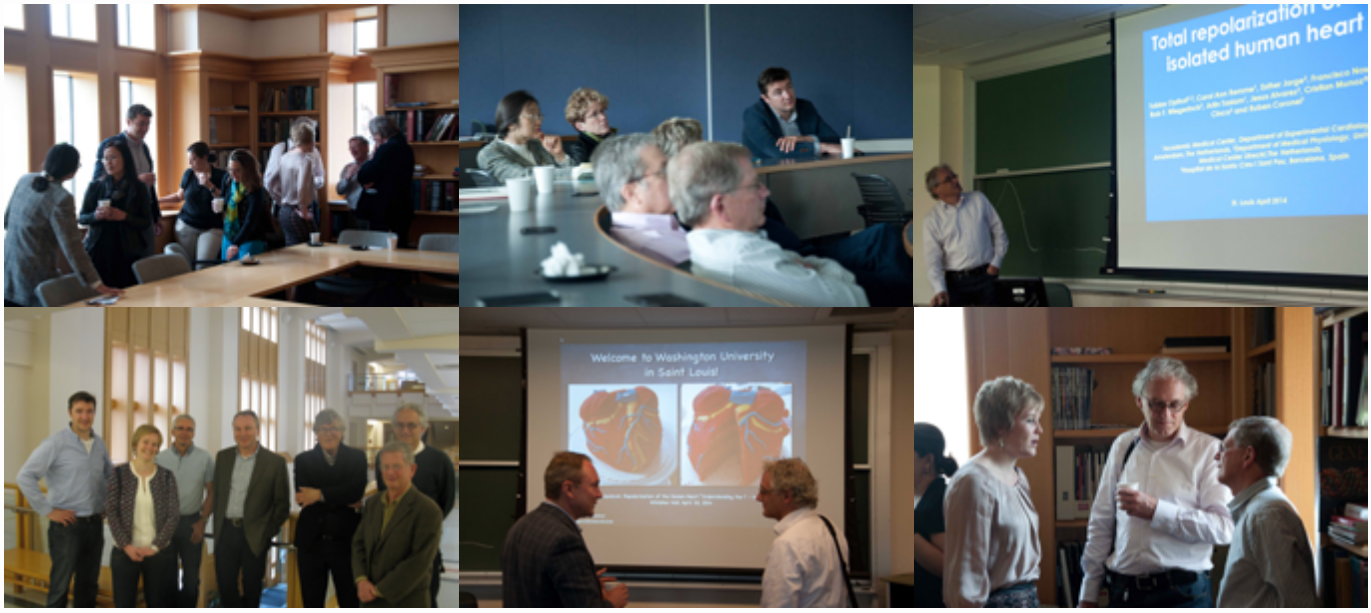
Jean Nerbonne led a team, which aslo includes CBAC members **Kathryn Yamada** and **Douglas Mann**, that found a link between human heart failure and sections of the genome once referred to as junk DNA. Link: https://news.wustl.edu/news/Pages/26848.aspx

Igor Efimov received the School of Engineering Dean's Faculty Award for Innovation in Research on April 16, 2014

Douglas Mann was elected to membership in the prestigious Association of American Physicians at its annual meeting on April 25 - 27 in Chicago. Each year, individuals having attained excellence in achieving pursuit of medical knowledge, and the advancement through experimentation and discovery of basic and clinical science and their application to clinical medicine, are recognized by nomination for membership by the Council of the Association.

Stacey Rentschler was awarded the American Society of Clinical Investigation (ASCI) Young Physcian-Scientist Award. Her work was recognized at the ASCI/AAP Joint Meeting Poster Session on April 26, 2014.

On April 30, 2014, Cardiac Bioelectricity and Arrhythmia Center (CBAC) brought together researchers from the Netherlands and the CBAC for a half day of presentations and discussions at the symposium: Repolarization of the Human Heart, "Understanding the T-Wave." Speakers included **Bas Boukens**, **Michiel J. Janse**, **Ruben Coronel**, **Yoram Rudy, Igor Efimov,** and **Veronique Meijborg**. Link: http://cbac.wustl.edu/pageEducationSymposium2014.asp



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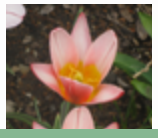


News & Announcements
Continued

May 2014

The CBAC was well represented at the 2014 Heart Rhythm 35th Annual Scientific Session in San Francisco, CA. Presentations by CBAC members included:

- "New Developments in Intracardiac Mapping and Noninvasive Mapping" by **Phillip Cuculich**
- "Simultaneous Endocardial and Epicardial Optical Mapping Explores the Conservation of Arrhythmia Dynamics Through the Transmural Depth in a Sheep Model of Acetylcholine-Induced Atrial Fibrillation" by graduate student **Sarah R. Gutbrod** and **Igor Efimov** among others
- "Transmural APD Gradient Synchronizes Repolarization in the Human Left Ventricle Wall" by research scientist **Bas Boukens**, graduate fellow **Matthew Sulkin**, research fellow **Fu Ng**, and **Igor Efimov**
- "The Role of Vagal Stimulation in HF Management" by **Douglas Mann**
- "Characterization of SEMA3A-Encoded Semaphorin as a Naturally Occurring Kv4.3 Protein Inhibitor and its Contribution to Brugada Syndrome" by **Jeanne Nerbonne**, among others
- **Timothy W. Smith** presented with others, "Performance and Safety of a New Automatic Antitachycardia Pacing Algorithm Based Upon Electrophysiologic First Principles"
- "Predictors of Myocardial Recovery in Pediatric Tachycardia-Induced Cardiomyopathy" by **Jennifer Silva**, among others
- "Cardiac Electrophysiology: present and future – the imprint of Silvio Weidmann" by **Yoram Rudy**

Poster presentations by CBAC members included:

- "Optical Imaging of Transmembrane and Mitochondrial Potential Unmask Different Spatiotemporal Responses to Targeted Metabolic Inhibition Versus Low-Flow Ischemia in Explanted Rabbit Hearts" by graduate fellow **Matt Sulkin,** student **Megan Tetlow**, research scientist **Bas Boukens**, and **Igor Efimov**
- "Delayed Activation and Low Expression of CX43 and SCN5A Underlie Fractionated Electrograms in the Human RVOT" by research scientist **Bas Boukens**, graduate student **Chris Gloschat,** graduate student **Austin Cocciolone**, and **Igor Efimov**
- "Dual Surgical Radiofrequency-Cryoablation Combinations Provide Different Lesion Depth and Size on Beating Human Tissue Preparations" by graduate fellow **Matthew Sulkin**, **Igor Efimov** and others
- "Electrophysiological Properties and 3-dimensional Structure of the Human Purkinje Fiber-Ventricular Muscle Junction" by graduate fellow **Katherine Holzem**, and **Igor Efimov**
- "Noninvasive Pre-Procedural Mapping for Differentiating Left Ventricular and Right Ventricular Outflow Tract Arrhythmias" by **Daniel Cooper**, **Phillip Cuculich**, **Mitchell Faddis**, **Yoram Rudy** and graduate students **Junjie Zhang**, **Christopher Andrews**
- "ECG Imaging of Electrophysiologic Substrate in Brugada Syndrome Patients" by graduate student **Junjie Zhang**, **Phillip Cuculich**, **Jennifer Silva**, **Daniel Cooper**, **Mitchell Faddis**,**Yoram Rudy** and collaborators
- "Pediatric Coronary Sinus Morphology Predicts Supraventricular Tachycardia Substrate" by **Jennifer Silva**, **George Van Hare** and others

June 2014

Pamela Woodard received the BJHF/ICTS Award worth $50,000 for research entitled, "Non-invasive Detection of Hypoxia in Atherosclerotic Plaque with 64Cu-ATSM PET-MRI."

July 2014

Steven George arrives as the new Professor and Chair of the Department of Biomedical Engineering, Washington University in St. Louis.

Lectures & Presentations

July 2013 - July 2014

DANIEL H. COOPER, M.D.

2013 Cooper DH. "Please "Clear" for Surgery: Preoperative Cardiac Risk Assessment." Cardiology Review for Primary Care Medicine, Jackson Hole, WY (August).

2013 Cooper DH. "Bradyarrhythmias: How SSSSSlow is too slow?" Cardiology Review for Primary Care Medicine, Jackson Hole, WY (August).

2013 Cooper DH. "Mitral Regurgitation: When do you fix the leak?" Cardiology Review for Primary Care Medicine, Jackson Hole, WY (August).

2013 Cooper DH. "Aortic Valve Disease – What's New in the Management of Aortic Stenosis?" Cardiology Review for Primary Care Medicine, Jackson Hole, WY (August).

2013 Cooper DH. "Achy, Breaky Heart: Heart Failure Overview" Cardiology Review for Primary Care Medicine, Jackson Hole, WY (August).

2013 Cooper DH. "Sorting Through the Headlines...The Brave New World of Anticoagulation". Cardiology Review for Primary Care Medicine, Jackson Hole, WY (August).

2013 Cooper DH. "EP Emergencies: Management of Electrical Storm" Cardiology Core Conference, Washington University School of Medicine, St. Louis, MO (August).

2013 Cooper DH. " Ablation of Ventricular Arrhythmias: WU Approach" EP Grand Rounds, Washington University School of Medicine, St. Louis, MO (September).

2013 Cooper DH. "Decisions about Atrial Fibrillation in the Inpatient Cardiology and EP Consult Services" Nonvalvular Atrial Fibrillation Preceptorship: A Hands-On, Patient-Based Didactic Workshop, Washington University School of Medicine, (November).

2013 Cooper DH ""Battling Ventricular Tachycardia: Predicting, Drugging, Burning, Cutting...and everything but the Kitchen Sink!" Internal Medicine Grand Rounds, Washington University School of Medicine, St. Louis, MO, (November).

PHILLIP S. CUCULICH, M.D.

2013 Top 10 in Cardiology International Meeting, University Hospital of Lausanne, Switzerland "New Visions on AF and VF Triggers" (October)

2013 Cardiology for Primary Care, Jackson Hole, WY

2013 American Heart Association Scientific Sessions, Dallas, TX "Left Atrial Appendage Occluders: An Electrophysiologist's Perspective" (November)

2014 Boston Atrial Fibrillation Symposium, Orlando, FL "Advances in & Limitations of Noninvasive Mapping of AF" (January)

2014 American College of Cardiology Scientific Sessions, Washington DC (March)

2014 Cardiology for Primary Care, Orlando, FL

2014: Stanford BioDesign in Electrophysiology Symposium, Palo Alto, CA (May)

2014 Heart Rhythm Society Scientific Sessions, San Francisco, CA (May)

2014 Cardiostim 20th World Congress Cardiac Electrophysiology, Nice, France (June)

JIANMIN CUI, PH.D.

2013 Graduate Program in Cellular and Molecular Biology, University of Wisconsin-Madison "Voltage Dependent Activation of IKs Channels-Requirement of PIP2 and ATP" (November)

Lectures & Presentations

July 2013-July 2014 Continued

RALPH J. DAMIANO JR., M.D.

2013 Moderator: EACTS Lunch Symposium on the Surgical Management of AF. AtriCure Satellite Symposium. Vienna, Austria (October)

2013 Top Advances in the Treatment of Structural Heart Disease. Moderator. Barnes-Jewish Hospital/Washington University School of Medicine Heart & Vascular Center Satellite Course. Dallas, Texas (November)

2013 Minimally Invasive Arrhythmia Surgery. Cardiovascular Seminar, American Heart Association, Annual Scientific Sessions. Dallas, Texas (November)

IGOR R. EFIMOV, Ph.D., F.A.H.A., F.H.R.S.

2013 "Arrhythmogenic and autonomic remodeling of failing human heart", University of Bonn, Germany, (July).

2013 "Low Energy Atrial and Ventricular Defibrillation", Sorin Group, Paris, France, (July)

2013 "Optical Imaging of the Human Heart", University of Pennsylvania, Philadelphia (September)

2013 "Arrhythmogenic and autonomic remodeling of failing human heart", University of Wisconsin at Madison, School of Medicine and Public Health, Madison, WI (September)

2013 "Human heart physiology in health and disease", Cardiac Physiome Society, 2013 Annual Meeting. Bar Harbor, ME (October)

2013 "Two centuries of electrotherapy: from VF to AF", L'Institut de Rythmologie et Modélisation Cardiaque (LIRYC) Workshop, Château Pape Clément, Bordeaux (October)

2013 "Optocardiography of Failing Human Heart", Saint Petersburg State University, Russia (November)

2013 "Pathogenesis: Basic Mechanisms of Atrial Flutter and Fibrillation", Contemporary Approach to Diagnose and to Treat Atrial Flutter in CAD Patients, International congress and teaching program, Moscow, Russia (November)

2013 "Pro-fibrillatory remodeling of failing human heart: excitation-contraction coupling, metabolism, signaling", Seventh TRM Forum on Computer Simulation and Experimental Assessment of Cardiac Function. Lugano, Switzerland (December)

2014 "Computational mapping inside the black box", 13th Atrial Fibrillation Symposium, Prague, Czech Republic (March)

RICHARD R. GROSS, M.D., Ph.D.

2013 Gordon Conference on Lipids, Molecular & Cellular Biology, "The Pleiotropic Roles of the Patatin-like Family of Phospholipases in Cellular Signaling and Bioenergetics Revealed through Lipidomics" Waterville Valley, NH (July)

2013 Society for Heart and Vascular Metabolism Conference (SHVM), "Insights into Cardiac Physiology from Lipidomic Analysis" Cambridge, MD (October)

2014 Cardiovascular Research Seminar, "Mitokines, Metabolic Channeling, and Quantum Tunneling in Myocardium" (April)

SÁNDOR J. KOVÁCS, M.D., Ph.D.

2013: "Diastolic Function in Normal Sinus Rhythm Vs. Chronic Atrial Fibrillation: Quantitative Comparison by Fractionation of E-wave Deceleration Time into Stiffness and Relaxation Components" Amercian Heart Association Scientific Sessions, Dallas , Texas (November)

2013: "Model-based Reexpression of Vortex Formation Time Differentiates Between Pseudonormal vs.Normal Left Ventricular Echocardiographic Filling Patterns" Amercian Heart Association Scientific Sessions, Dallas , Texas (November)

DOUGLAS L. MANN, M.D.

2013 "Impact of Diabetes and Metabolic Syndrome on Ventricular and Arterial Function in Heart Failure and "Cardiac Remodeling as a Therapeutic Target in Heart Failure [Keynote Address]," Mayo Clinic Symposium on "Success with Failure," Lake Tahoe, CA (August)

2013 "Recovery of Left Ventricular Recovery: Miracle, Myth, Magic or Molecular Target?," University of Kansas Medical Center Cardiovascular Grand Rounds, Kansas City, KS (August)

2013 "Role of Innate Immunity in Cardiac Injury and Repair," James T. Willerson Basic Science Seminar, Texas Heart Institute, Houston, TX (September)

2013 "Circulating microRNA as a Heart Failure Biomarker," Session on Novel Biomarkers for Heart Failure - Eventual Targets for Therapy Session, 17th Annual Meeting of he Heart Failure Society of America, Orlando, FL (September)

2013 "The Cardiac Autonomic Nervous System: A Primer," Session on Device-Based Autonomic Modulation for Heart Failure: The Next Frontier, 17th Annual Meeting of he Heart Failure Society of America, Orlando, FL (September)

2013 "Recovery of Left Ventricular Recovery: Miracle, Myth, Magic or Molecular Target?," William Beaumont Hospital, Royal Oak, MI (October)

2013 "Role of Innate Immunity in Cardiac Injury and Repair," MCBP External Seminar, Medical University of South Carolina, Charleston, SC (October)

2013 "Recovery of Left Ventricular Recovery: Miracle, Myth, Magic or Molecular Target?," Cardiology Grand Rounds, Texas Heart Institute, Houston, TX (November)

2013 "Role of Innate Immunity in Cardiac Injury and Repair," [John Forester Distinguished Lecturer]Institute of Cardiovascular Sciences, University of Manitoba,Winnipeg, Canada (November)

2013 "Recovery of Left Ventricular Recovery: Miracle, Myth, Magic or Molecular Target?," Comprehensive CV Center Research Conference Distinguished Speaker Series, University of Alabama, Birmingham, AL (November)

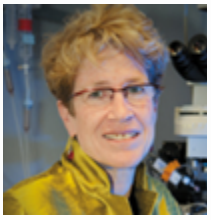
2013 "Autonomic Modulation of the Failing Heart," State of the Heart Lecture, Loyola University Medical Center, Chicago, IL (November)

2014 Blount Lectureship, Division of Cardiology, Department of Medicine, University of Colorado Health Sciences Center, Aurora, CO (February)

2014 Neil Stone Lectureship, Northwestern University, Division of Cardiology, Chicago, IL (April)

Lectures & Presentations

July 2013-July 2014 Continued



JEANNE M. NERBONNE, Ph.D.

2013 Dutch Heart Foundation Lecturer, Dutch Physiological Society 29th Annual Symposium, Adaptive Physiology, Keynote Speaker, Utrecht, Netherlands

2014 Department of Physiology, Feinberg School of Medicine at Northwestern University, Chicago, IL (March)

2014 Department of Pharmacology, Emory University, Atlanta, GA (March)

COLIN G. NICHOLS, Ph.D.

2014 "K channels: From structure to disease" Membrane Protein Group Research day, University of Montreal, Canada (May)

2014 Chair, Abstract Session, Gordon Research Conference, "Ion Channels: The Molecular Basis of Excitability and Disease" Mount Holyoke College in South Hadley, MA (July)

YORAM RUDY, Ph.D., F.A.H.A., F.H.R.S.

2013 Fondation Leducq Transatlantic CaMKII Alliance Meeting: "Relating Molecular Dynamics of an Ion-Channel Protein to the Action Potential" University of Iowa (July)

2013 FDA Cardiotoxicity Working Group Meeting, Development and Use of Computer Models: "Constructing and Validating Models of the Human Cardiac Myocyte" FDA Research Campus – Silver Spring, MD (July)

2013 40th International Congress on Electrocardiology: "Noninvasive Mapping of Human Cardiac Arrhythmias with ECGI", University of Glasgow, Scotland (August)

2013 Oxford University, Department of Computer Science, "Electrocardiographic Imaging of Cardiac Electrophysiology and Arrhythmia", Oxford, UK (August)

2013 Oxford University, Institute of Mathematics, "Multiscale Modeling of Cardiac Repolarization", Oxford, UK (August)

2013 Denis Escande Symposium on Cardiac Arrhythmias, "Integrated Arrhythmia Research", University of Amsterdam Academic Medical Center, Amsterdam, The Netherlands(August)

2013 Computing in Cardiology Conference, "Multiscale Modeling of Cell Electrophysiology: From Ion-Channel Molecular Structure to the Action Potential", Zaragoza, Spain (September)

2013 Cardiac Electrophysiology Society Meeting on Ventricular Tachycardia: Mechanisms and Substrate, "Noninvasive Mapping of VT Substrate Electrophysiology in the Clinic", Dallas, Texas, (November)

2013 7th TRM (Theo-Rossi-di-Montelera Foundation) Forum on Computer Simulation and Experimental assessment of Cardiac function, "Electrophysiologic Substrate and Cardiac Resynchronization Therapy (CRT) in Heart Failure Patients: Insights from Noninvasive ECG Imaging [ECGI]", Lugano, Switzerland (December)

2013 First European Conference for Standardization of Advanced ECG Analysis In Arrhythmia Diagnostics. 2013 Focus: Quantification of the Atrial Fibrillation Substrate Complexity, "AF Complexity Assessed by Noninvasive ECG Imaging (ECGI)", Lugano, Switzerland (December)

2013 University of Milano Department of Biotechnology and Biosciences, Keynote in Department Day Celebration, "Mechanisms of Human Cardiac Arrhythmias: Noninvasive Studies with Electrocardiographic Imaging (ECGI)", Milan, Italy (December)

2013 University of Milano Department of Biotechnology and Biosciences, Department Seminar "Multiscale Modeling of Cell Electrophysiology: From Ion-channel Molecular Structure to the Action Potential", Milan, Italy (December)

2014 Heart Rhythm Society 35th Scientific Sessions: “Cardiac Electrophysiology: present and future – the imprint of Silvio Weidmann”, San Francisco (May).
2014 University of California, Davis, Department of Pharmacology, “Noninvasive mapping of cardiac electrophysiology and arrhythmias in the intact human heart”, Davis, CA (May)
2014 Technion – Israel Institute of Technology, School of Medicine, “Cardiac Repolarization: From Molecule to the Human Heart”, Haifa, Israel (June)
2014 Technion – Israel Institute of Technology, Department of Biomedical Engineering, “Noninvasive Electrocardiographic Imaging of Cardiac Electrophysiology and Arrhythmias in the Intact Human Heart”, Haifa, Israel (June)
2014 Cardiostim 2014 -12th World Congress on Cardiac Arrhythmias, “Iks Structure – Function and Noninvasive Mapping of LQTS Substrate in Patients”, Nice, France (June)
2014 6th International Workshop on Computational Methods in Pharmaceutical Sciences, “Multi-scale Modeling of Cardiac Cell Electrophysiology: From Ion-channel Molecular Structure to the Action Potential”, Krakow, Poland (July)
2014 6th International Workshop on Computational Methods in Pharmaceutical Sciences , “Noninvasive Mapping of Cardiac Electrophysiology and Arrhythmias in the Intact Human Heart”, Krakow, Poland (July)

STACEY L. RENTSCHLER, M.D., Ph.D.

2013 Washington University, Department of Biomedical Engineering, St. Louis, MO (December)
2014 Washington University, Cardiac Bioelectricity & Arrhythmia Center, St. Louis, MO (February)
2014 University of Missouri, 2014 Cardiovascular Research Day, Columbia, MO (February)
2014 “Canonical Wnt Signaling Regulates Atrioventricular Junction and Nodal Myocyte Programming and is Dysregulated in a Murine Model of Ventricular Preexcitation” Weinstein Cardiovascular Development Conference, Madrid, Spain (May)
2014 Gordon Conference on Notch Signaling in Development, Regeneration & Disease, Bates College, Maine (July)

JEAN E. SCHAFFER, M.D.

2013 “Small Nucleolar RNAs and Metabolic Stress” American Heart Association Scientific Sessions, Dallas, TX (November)
2014 Co-Chair, Session, The Deuel Conference on Lipids “Triglycerides/ Droplets/Regeneration” Coronado, CA (March)

GAUTAM K. SINGH, M.D., D.C.H., M.R.C.P., F.A.C.C.

2013 The Univentricular vs. Biventricular Heart: Embryology of the Lesions and Prenatal Predictors. 41st Annual Scientific Meeting of North American Society for Cardiac Imaging, Atlanta, GA (September 28 - October 1)
2013 Childhood Obesity: A Systemic Malady. WEIGHING IN: The Public Health Impact and Promise of Science in Addressing Obesity Conference, Washington University Institute of Public Health, (October)
2014 Alterations in Cardiovascular Structure and Function in Children with Obesity. The 5th Congress of Asia Pacific Pediatric Cardiology Society Meeting, New Delhi, India (March)

GEORGE F. VAN HARE, M.D.

2014 Landmark Advances in Pediatric Cardiology: Ablations for Arrhythmias in Congenital Heart Disease: The Early Years. American College of Cardiology Annual Scientific Session. Washington DC (March)
2014 16th Annual Dr. Martha Carpenter Lecture, Univeristy of Virginia Department of Pediatrics, Charlottesville VA. “Cardiac Arrhythmia Ablation in Children: Learning how the heart works by destroying stuff.”

Lectures & Presentations

July 2013-July 2014 Continued

LIHONG WANG, Ph.D.

2013 Photoacoustic tomography: Breaking through the optical diffusion and diffraction limits. SIAM Annual Meeting, San Diego, CA. Plenary (July)

2013 Synergy between light and sound: Photoacoustic tomography and ultrasonically encoded optical focusing, Workshop on Biomedical Optics and Ultrasonics, Shenzhen Institutes of Advanced Technology, Shenzhen, China (August)

2013 Photoacoustic tomography: Breaking through the optical diffusion and diffraction limits. Institute for Neuroscience and Cognition, University Paris Descartes, Paris, France (October)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. State Key Lab of Modern Optical Instrumentation, Zhejiang University, Hangzhou, China (October)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. Joint Research Center of Photonics of the Royal Institute of Technology (Sweden), Zhejiang University and Lund University, Hangzhou, China (October)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. 17th International Conference on Photoacoustic and Photothermal Phenomena (ICPPP), Suzhou, China. Keynote (October)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. Advanced Molecular Imaging and its Clinical Translation, Harvard Medical School, Boston, MA. (October)

2013 Synergy between light and sound: Photoacoustic tomography and TRUE optical focusing. Engineering Optical Wavefront for Biomedical Imaging, Janelia Farm Research Campus, HHMI, Ashburn, VA (November)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. Department of Bioengineering, UCSD, San Diego, CA (December)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. Saint Louis Section of IEEE Winter Social, Engineer's Club, St. Louis, MO. Keynote (December)

2013 Photoacoustic tomography: Beat optical diffusion and diffraction. The Forty-Second Annual Wendell G. Scott Memorial Lecture, Mallinckrodt Institute of Radiology, WUSTL, St. Louis, MO (December)

2014 Photoacoustic tomography: Ultrasonically beating optical diffusion and diffraction. Air Force Office of Scientific Research, Southern Office of Aerospace Research and Development (AFOSR/SOARD), Santiago, Chile. Talk given via video conferencing (January)

2014 Photoacoustic tomography: Ultrasonically beating optical diffusion and diffraction. Hot Topics (Plenary), BIOS, SPIE Photonics West, San Francisco, CA (February)

2014 Photoacoustic tomography: Ultrasonically beating optical diffusion and diffraction. Stereotaxis, Inc., St. Louis, MO (February)

2014 Photoacoustic tomography: Ultrasonically beating optical diffusion and diffraction. Eli Lilly, Indianapolis, IN (March)

2014 Photoacoustic tomography: Breaking through the optical diffusion limit. American Institute of Ultrasound in Medicine (AIUM) Annual Convention, Las Vegas, NV (April)

2014 Photoacoustic tomography: Ultrasonically beating optical diffusion and diffraction. Annual Research Retreat, Department of Pediatrics, WUSTL, St. Louis, MO. Keynote Speaker (April)

Publications
July 2013 - July 2014

DANIEL H. COOPER, M.D.

Zhang, J, Cooper, DH, Rudy, Y, "Electrophysiologic mechanism of deteriorating cardiacfunction in a patient with inappropriate CRT indication and frequent ventricular ectopy" Pacing and Clinical Electrophysiology, 2013; 36; 1024-1026

Cuculich PS, Cooper DH. Pericardial Invasion: Lessons learned from SAVR and TAVR. J Am Coll Cardiol. 2014 Apr 22;63(15):1520-1. Epub 2014 Jan 30; PMID: 24486274

JANE CHEN, M.D., F.A.C.C., F.H.R.S.

Chen J, Pan H, Lanza GM, Wickline SA. Perfluorocarbon Nanoparticles for Physiological and Molecular Imaging and Therapy. Adv Chronic Kidney Dis. 2013 Nov;20(6):466-78. PMID: 2420659

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Hu L, Chen J, Yang X, Senpan A, Allen JS, Yanaba N, Caruthers SD, Lanza GM, Hammerman MR, Wickline SA. Assessing intrarenal nonperfusion and vascular leakage in acute kidney injury with multinuclear 1 H/19 F MRI and perfluorocarbon nanoparticles. Magn Reson Med. 2014 Jun;71(6):2186-96. PMID: 23929727

PHILLIP S. CUCULICH, M.D.

Zhang J, Desouza KA, Cuculich PS, Cooper DH, Chen J, Rudy Y. Continuous ECGI mapping of spontaneous VT initiation, continuation, and termination with antitachycardia pacing. Heart Rhythm. 2013; 10:1244-5. PMID: 22222277

Saint LL, Damiano RJ Jr, Cuculich PS, Guthrie TJ, Moon MR, Munfakh NA, Maniar HS. Incremental risk of the Cox-maze IV procedure for patients with atrial fibrillation undergoing mitral valve surgery. J Thorac Cardiovasc Surg 2013; 146:1072 PMID: 23998785

Robertson JO, Cuculich PS, Saint LL, Schuessler RB, Moon MR, Lawton J, Damiano RJ, Maniar HS. Predictors and Risk of Pacemaker Implantation After the Cox-Maze IV Procedure. Ann Thorac Surg 2013; 95:2015-21. PMID: 23642681

Desouza KA, Joseph SM, Cuculich PS, Ewald GA, Rudy Y. Noninvasive mapping of ventricular activation in patients with transplanted hearts. Journal of Electrocardiology. 2013; 46: 698-701. PMID: 23773656

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JIANMIN CUI, Ph.D.

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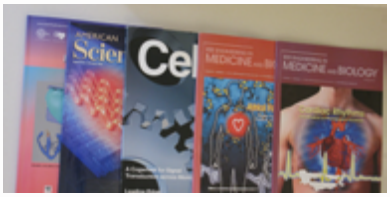
Sun X, Shi J, Delaloye K, Yang X, Yang H, Zhang G, and Cui J (2013) The interface between membrane-spanning and cytosolic domains in BK channels is involved in β subunits modulation of gating. J Neurosci.33:11253-11261. PMCID: 3718382

Zaydman MA, Silva JR, Delaloye K, Li Y, Liang H, Larsson HP, Shi J, and Cui J (2013) Kv7.1 ion channels require PIP2 to couple voltage sensing to pore opening. Proc. Natl. Acad. Sci., U.S.A. 110:13180-13185. PMCID: 3740903



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Li M, Chang S, Yang L, Shi J, McFarland K, Yang X, Moller A, Wang C, Zou X, Chi C and Cui J (2014) Conopeptide Vt3.1 preferentially inhibits BK channels containing β4 subunits via electrostatic interactions. J Biol Chem. 289:4735-4742. PMCID 3931035

RALPH J. DAMIANO JR., M.D.

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Melby SJ, Schuessler RB, Damiano RJ Jr: Ablation technology for the surgical treatment of atrial fibrillation. ASAIO Journal 2013; 59:461-468 PMID: 23995989

Saint LL, Lawrance CP, Schuessler RB, Damiano RJ Jr: Performance of a novel bipolar/monopolar radiofrequency ablation device on the beating heart in an acute porcine model. Innovations 2013;8:276-283. PMID:24145972

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Maniar HS, Bell JM, Moon MR, Meyers BF, Marsala J, Lawton JS, Damiano RJ Jr: Prospective evaluation of patients readmitted after cardiac surgery: Analysis of outcomes and identification of risk factors. J Thorac Cardiovasc Surg 2014;147:1013-1020. PMID:24365269

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Robertson JO, Saint LL, Leidenfrost J, Damiano RJ Jr: Illustrated techniques for performing the Cox-Maze IV procedure through a right mini-thoracotomy. Ann Cardiothorac Surg 2014;3:105-116

Saint LL, Lawrance CP, Leidenfrost JE, Robertson JO, Damiano RJ Jr: How I do it: minimally invasive Cox-Maze IV procedure. Ann Cardiothorac Surg 2014;3:117-119

Watanabe Y, Weimar T, Kazui T, Lee U, Schuessler RB, Damiano RJ Jr: Epicardial ablation performance of a novel radiofrequency device on the beating heart in pigs. Ann Thorac Surg 2014;97:673-678.

Montecalvo A, Damiano RJ Jr: Managing of the left atrial appendage in the era of minimally invasive surgery. Intervent Cardiol Clin 2014; 3:229-238

VICTOR DÁVILA-ROMÁN, M.D.

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Cade WT, Overton ET, Mondy K, de las Fuentes L, Dávila-Román VG, Waggoner AD, Reeds DN, Lassa-Claxton S, Krauss MJ, Peterson LR, Yarasheski KE: Relationships among HIV infection, metabolic risk factors, and left ventricular structure and function. AIDS Res Hum Retroviruses. 2013 Aug;29(8):1151-60. Epub 2013 May 6; PMID: 23574474

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IGOR R. EFIMOV, Ph.D.

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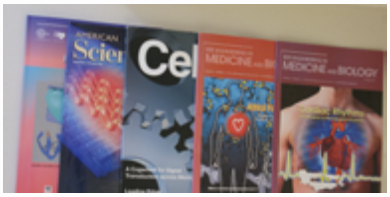

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Janardhan AH, Gutbrod SR, Li W, Lang D, Schuessler RB, Efimov IR, Multi-Stage Electrotherapy Delivered Through Chronically Implanted Leads Terminates Persistent Atrial Fibrillation with Lower Energy than a Single Biphasic Shock. JACC, 2014 Jan 7-14; 63(1): 40-8. PMID: 24076284.

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RICHARD W. GROSS, M.D., Ph.D.

Sharma, J., Eickhoff, C.S., Hoft, D.F., Ford, D.A., Gross, R.W., and McHowat, J. Absence of myocardial calcium-independent phospholipase $A_{2\gamma}$ results in impaired PGE2 production and decreased survival in mice with acute Trypanosoma cruzi infection. Infect. Immun. 2013, 81:2278-2287. PMCID: 3697611.

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Liu, X., Moon, SH., Mancuso, D.J., Jenkins, C.M., Guan, S., Sims, H.F., and Gross, R.W. Oxidized fatty acid analysis by charge-switch derivatization, selected reaction monitoring, and accurate mass quantitation. Anal. Biochem. 2013, 442:40-50. PMCID: 3823533.

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PATRICK Y. JAY, M.D., Ph.D.

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SÁNDOR J. KOVÁCS, M.D., Ph.D.

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DOUGLAS L. MANN, M.D.

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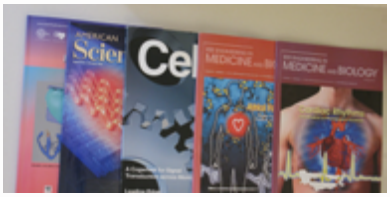

Publications
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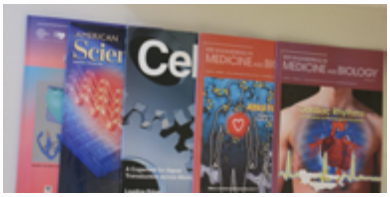

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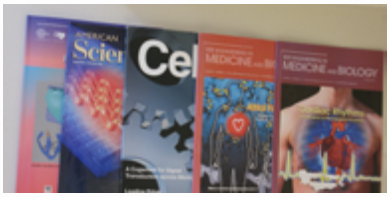

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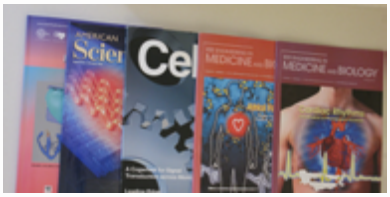

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KATHRYN A. YAMADA, Ph.D., F.A.H.A.

Yamada KA, Patel AY, Ewald GA, Whitehead DS, Pasque MK, Silvestry SC, Janks DL, Mann DL, Nerbonne JM. How to build an integrated biobank: the Washington University Translational Cardiovascular Biobank & Repository experience, Clin Transl Sci, 2013;6:226-231. PMCID: PMC3682669

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Yang K-C, Yamada KA, Patel AY, Topkara VK, George I, Cheema FH, Ewald GA, Mann DL, Nerbonne JM. Deep RNA sequencing reveals dynamic regulation of myocardial noncoding RNA in failing human heart and remodeling with mechanical circulatory support. Circulation, 2014;129:1009-1021. PMCID: PMC3967509

New CBAC Members

C. William (Bill) Balke M.D., F.A.C.P., F.A.H.A.

Professor of Internal Medicine
Cardiovascular Division
Chief of Cardiology, John Cochran VA Medical Center
Washington University
School of Medicine in St. Louis

Biography:

Dr. Bill Balke joined the faculty on June 1, 2014. He serves as the new chief of cardiology at the John Cochran VA Medical Center. Dr. Balke is internationally recognized for his cardiovascular research, specifically on calcium handling in hypertrophy and heart failure. He most recently served as a Professor in the Department of Medicine at the University of California, San Francisco School of Medicine. He also was a member of the university's Board of Directors for the Clinical and Translational Science Institute (CTSI). Since 1998, he has served as the Associate Editor of the *Journal of Investigative Medicine* and sits on multiple editorial boards.

Research Interests:

Dr. Balke's research interests focus on the role of individual ions (especially calcium) as second messengers in the regulation of a variety of cellular processes relevant to cardiovascular function.

Education and Training:

1981 M.D. Temple University School of Medicine - Philadelphia, PA
1977 B.A. University of Pennsylvania - Philadelphia, PA
1975 B.S. Haverford College - Haverford, PA

Steven C. George, M.D., Ph.D.

Elvera and William Stuckenburg Professor & Chair
Department of
Biomedical Engineering
Washington University in St. Louis

Biography:

Dr. Steve George was named the Elvera and William Stuckenburg Professor and Chair of the Department of Biomedical Engineering starting in July 2014. Previously he was a professor of biomedical engineering and of chemical engineering & materials science at the University of California, Irvine. In addition, he was the Edwards Lifesciences Professor and director of the Edwards Lifesciences Center for Advanced Cardiovascular Technology and founding William J. Link Professor and Chair of the Department of Biomedical Engineering at UC - Irvine from 2002-09.

Research Interests:

- Pre-vascularization of implantable thick tissues;
- 3-D microphysiological systems to simulate cardiac and tumor tissue.

Education and Training:

1995 Ph.D. University of Washington - Seattle, WA
1991 M.D. University of Missouri - Columbia, MO
1987 B.S. Northwestern University - Evanston, IL

CBAC Member Listing

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Chief of Cardiothoracic Surgery
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Medical Director, Cardiovascular Imaging and Clinical Research Core Laboratory
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Cardiovascular Division
Chief of Cardiology, John Cochrane VA Medical Center
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The Lucy and Stanley Lopata Distinguished Professor of Biomedical Engineering
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CBAC Member Listing
Continued

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Email: saw@wustl.edu

Pamela K. Woodard, M.D., F.A.C.R., F.A.H.A., F.C.C.P.
Director, Center for Clinical Imaging; Research (CCIR); Professor of Radiology & Biomedical Engineering
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Kathryn A. Yamada, Ph.D.
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Director, Mouse Cardiovascular Phenotyping Core
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CBAC Faculty Alumni:

Jane Chen, M.D.
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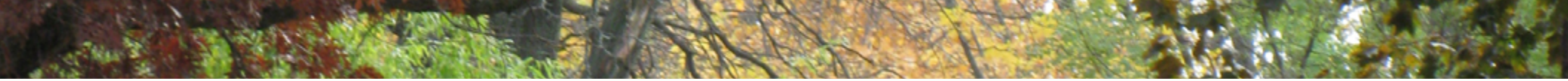
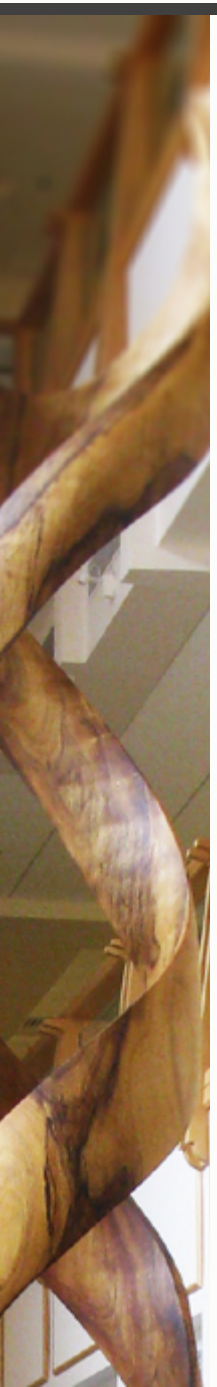
Amir A. Amini, Ph.D.
Kyongtae T. Bae, M.D., Ph.D.
John P. Boineau, M.D.
Michael Cain, M.D.
Jonas A. Cooper, M.D., M.P.H.
Vadim V. Fedorov, Ph.D.
Daniel P. Kelly, M.D.
Bruce Lindsay, Ph.D.
Leonid Livshitz, Ph.D.
Ali Nekouzadeh, Ph.D.
Achi Ludomirsky, M.D.
Tony J. Muslin, M.D.
Vladimir P. Nikolski, Ph.D.
Edward Rhee, Ph.D.

Learn more about CBAC Faculty members at this CBAC website: http://cbac.wustl.edu/pageFaculty.asp



The **C**ardiac **B**ioelectricity & **A**rrhythmia **C**enter (CBAC) presents:

CBAC 2014-15 Seminar Schedule



Fall

10/6

Understanding the Mitochondrial Dynamism-Mitophagy-Apoptosis Interactome

Gerald W. Dorn, M.D. - Philip & Sima K. Needleman Professor
Director, Center for Pharmacogenomics
Washington University School of Medicine

10/13

Mechanisms Contributing to Myocardial Potassium Channel Diversity, Regulation and Remodeling

Jeanne Nerbonne, Ph.D., F.A.H.A. - Alumni Endowed Professor of Molecular Biology & Pharmacology in Developmental Biology & Internal Medicine; Director, Center for Cardiovascular Research (CCR) Co-Director, Center for the Investigation of Membrane Excitability Diseases (CIMED); Washington University School of Medicine

10/27

Late Sodium Current, a Mechanism for Angina, Heart Failure, and Arrhythmia, is Controlled by Nitrosylation Mechanisms Within the Cardiac Sodium Channel Complex

Jonathan C. Makielski, M.D. - Professor of Cardiovascular Medicine, University of Wisconsin-Madison School of Medicine & Public Health

11/3

Tissue Engineering a 3D *In Vitro* Model of Perfused Human Cardiac Muscle

Steven C. George, M.D., Ph.D. - Elvera and William Stuckenberg Professor & Chair, Department of Biomedical Engineering
Washington University in St. Louis

Spring

1/26

Mark E. Anderson M.D., Ph.D.
William Osler Professor of Medicine
Director of the Department of Medicine
Johns Hopkins University School of Medicine
Physician-in-chief of The Johns Hopkins Hospital

2/16

Colin Nichols, Ph.D.

Carl F. Cori Professor of Cell Biology & Physiology
Department of Cell Biology and Physiology
Director, Center for the Investigation of Membrane Excitability Diseases (CIMED)
Washington University School of Medicine

2/23

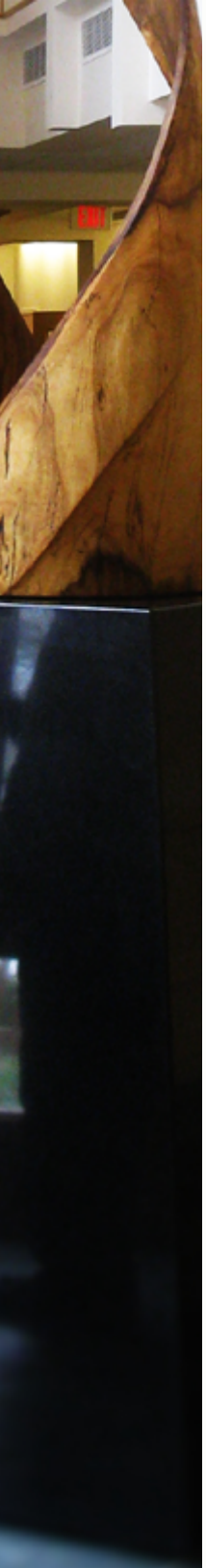
Sandor Gyorke, Ph.D.

Professor, Department of Cell Biology and Physiology
Associate Director, The Dorothy M. Davis Heart & Lung Research Institute
Director, Multiphoton/Confocal Microscopy Core Facility
The Ohio State University College of Medicine

3/9

C.William Balke, M.D., F.A.C.P., F.A.H.A.

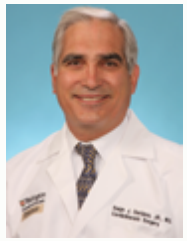
Professor of Internal Medicine
Cardiovascular Division
Chief of Cardiology, John Cochrane VA Medical Center
Washington University School of Medicine



11/10

Atrial-Selective Drug Targets: Hope or Hype for Antiarrhythmic Treatment of Atrial Fibrillation?

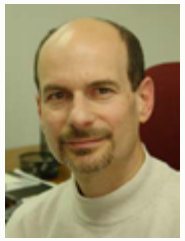
Ursula Ravens, M.D., Ph.D., F.E.S.C., F.A.H.A. - Senior Research Professor Department of Pharmacology & Toxicology
Technical University of Dresden, Germany



12/1

Surgical Treatment of Atrial Fibrillation: Present State-of-the-Art

Ralph J. Damiano Jr., M.D. - Everts A. Graham Professor of Surgery, Chief of Cardiac Surgery
Washington University in St. Louis School of Medicine



12/15

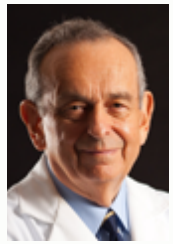
Rotational Waves in Atrial Fibrillation: Role, Mechanisms and Mapping

Omer Berenfeld, Ph.D. - Associate Professor of Internal Medicine & Biomedical Engineering
Center for Arrhythmia Research
University of Michigan Health System, Ann Arbor, MI

4/13

Arthur Moss, M.D.

Professor of Medicine (Cardiology)
Founding Director, Heart Research Follow-up Program
University of Rochester Medical Center



4/27

Ye Chen-Izu, M.S., Ph.D.

Associate Professor
Pharmacology, Bioengineering, Cardiology
University of California, Davis

5/11

David Paterson, D.Phil., D.Sc.

Professor & Associate Head of Division
Division of Medical Sciences, University of Oxford
Department of Physiology, Anatomy & Genetics
University of Oxford, UK
Editor-in-Chief *The Journal of Physiology*

Mondays, 4:30 pm - 5:30 pm
Whitaker Hall Room 218 | Danforth Campus

Hors d'oeuvres reception after the seminar
5:30 pm, Whitaker Hall, Room 319

CBAC

Washington University in St. Louis

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"Rowing to a Better Heart"

If you would like to be added to the CBAC email list to receive information on upcoming seminars, events, news, or to be added to the newsletter mailing list to receive future newsletters, contact Huyen (Gwen) Nguyen at nguyeng@wustl.edu.