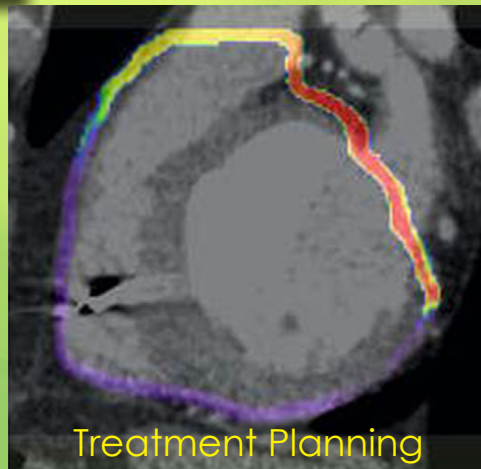
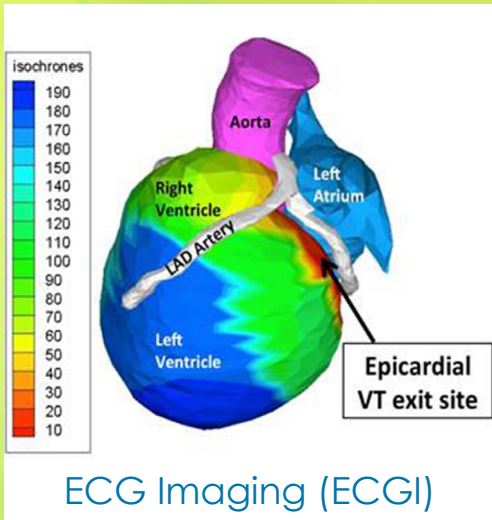


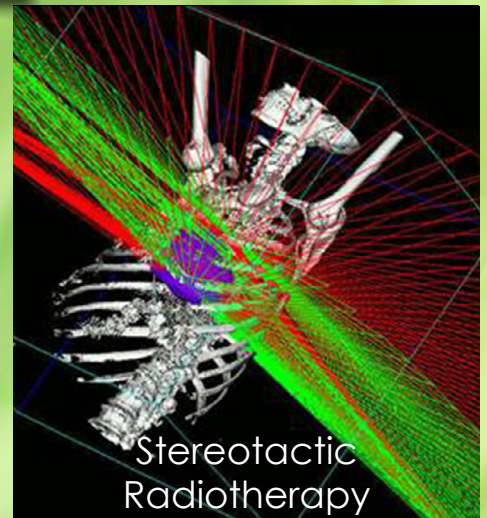
CENTER HEARTBEAT

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



Completely Noninvasive Arrhythmia Ablation

Using noninvasive arrhythmia imaging (ECGI, top left) to precisely guide (middle) entirely noninvasive cardiac radiotherapy (bottom right). Images courtesy of Clifford Robinson, MD, Yong Wang, PhD & Phillip S. Cuculich, MD



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.



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



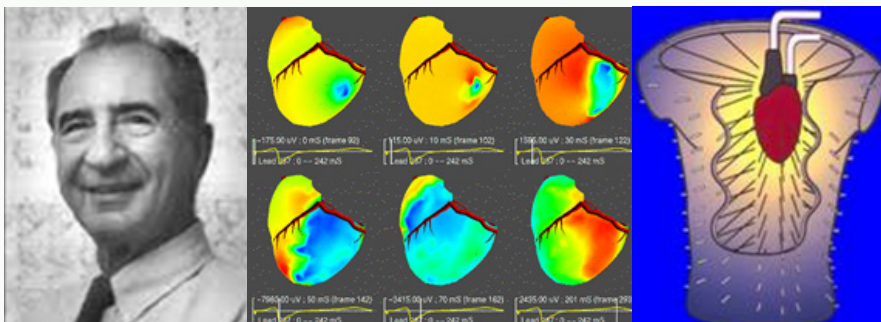
FROM THE DIRECTOR'S DESK....

This issue of the Center Heartbeat is dedicated to the memory of Professor Bruno Taccardi, who passed away last year in Parma, Italy. Bruno was a gentleman-scientist in the truest sense of the word, and a dear friend and colleague of many years. He was a giant in the field of cardiac excitation and electrocardiography and will be sorely missed. Professor Taccardi was the Chairman of the Physiology Department at the University of Parma and later joined the Cardiovascular Research and Training Institute at the University of Utah. Among his many awards was the Medal of The Royal Academy of Medicine of Belgium.

Understanding cardiac electrophysiology and the properties and mechanisms of cardiac arrhythmias, requires investigation at all scales, from molecule and cell to the whole-heart and organism. Interactions across these scales result in emergent properties that determine the system-level behavior of the heart. Professor Bruno Taccardi focused his attention and scientific curiosity at the global scale of the cardiac system. Bruno has taught us much of what we know about the relationship between cardiac excitation and the electric fields that it generates in the myocardium and in the volume-conductor of the thorax. A clear understanding of this complex relationship is crucial to correct and insightful interpretation of cardiac electrograms and body surface electrocardiograms for both, experimental studies of basic mechanisms and clinical application in diagnosis and therapy. Bruno was a pioneer of cardiac mapping, considered by many to be a father of mapping as it is practiced today. He recognized early on that “a great deal of information on the topography and time-course of electrophysiological events in the heart can be obtained by mapping the instantaneous distribution of bioelectric potentials in two or three dimensions.”

Professor Taccardi was a master experimentalist, paying attention to the smallest of details not only during the experiment, but also during the preparation that preceded the experiment. He was meticulous about the quality of data and unbiased and rigorous in his interpretation of results. One of my fondest memories is working with Bruno on a paper for *Circulation* at Ruth's Diner outside Salt Lake City, with the magnificent mountain view as a backdrop. We sat there the entire day arguing, in the Talmudic sense, about every interpretation and every sentence of the manuscript. It was a stimulating and enjoyable experience that we both remembered fondly over the many years of our close friendship.

Bruno loved and appreciated the aesthetic side of things, be it art, music (he was an accomplished and very sensitive pianist), or science. A memorable summer at the Aspen Music Festival together with Bruno and his wife Irma revealed to me his deep love and understanding of music. As to science and passion for the process of scientific discovery, the words of Albert Einstein describe Bruno best: “The creative scientist studies nature with the rapt gaze of the lover, and is guided as often by aesthetics as by rational considerations in guessing how nature works” – Albert Einstein.



Yoram Rudy

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

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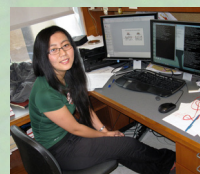
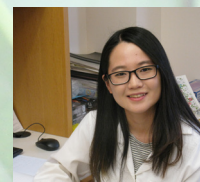
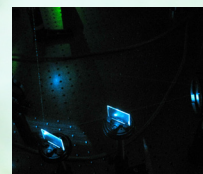
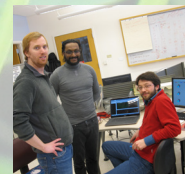
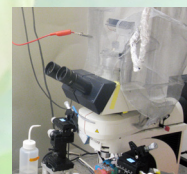
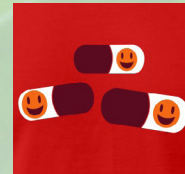
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PHARMACOLOGY OF KCNQ POTASSIUM CHANNELS: LIGANDS & DRUGS

BY MOAWIAH M. NAFFAA & JIANMIN CUI

Department of Biomedical Engineering
Center for the Investigation of Membrane Excitability Diseases
Cardiac Bioelectricity and Arrhythmia Center, Washington University in St. Louis, St. Louis, MO

Abstract

KCNQ potassium channels are diversely distributed in human tissues, associated with many physiological processes and pathophysiological conditions. These channels are increasingly used as drug targets for treating diseases. More selective and potent reagents on various types of KCNQ channels are desirable for appropriate therapies. The recent knowledge of structure and function of KCNQ channels makes it more feasible to achieve these goals. In this article, we review the structure and function of KCNQ potassium channels, and some existing compounds that either activate or inhibit KCNQ channels' functions. We focus on the effects of these compounds on KCNQ channels' functions, their selectivity on various KCNQ channels, their mechanism of interactions with the channels, and their use either as research tools or as therapeutic agents.

Introduction

KCNQ potassium channels control the electrical excitability of neuronal, cardiac muscle, and smooth muscle cells, as well as ion transport in epithelia (1-3). There are five genes encoding the KCNQ subunits (KCNQ1-5) that are identified by molecular cloning and recombinant expression (4-8). KCNQ subunits form homotetramer and heterotetramer channels that are expressed in various tissues. KCNQ1 homomeric channels are mainly expressed in the heart, smooth muscle, and epithelia, where auxiliary subunits from the KCNE family associate with the channel to modify the channel properties (9). KCNQ 2-5 channels are mainly expressed in the nervous system (2,6,7,10-13). KCNQ channels have slowly activating and slowly deactivating kinetics, and open at voltages close to the resting membrane potential, and the K⁺ currents persist with prolonged membrane depolarization. These special characteristics of potassium channels enable them to take part in regulating cardiac and neuronal excitabilities, which are responsible for action potential termination in the heart and enhancing the threshold for action potential firing in the nervous system. They have roles in hippocampal theta oscillation by facilitate neuronal resonance and network oscillations in cortical neuron (14,15). M-channels also regulate release of transmitters, and control spike generation and

afterdepolarization in hippocampal neurons (14-20). KCNQ channels are involved in a wide spectrum of physiological functions, such as rate adaptation of the heart during adrenergic stimulation (21), hearing (22), pain sensing (23,24), learning, memory, and synaptic plasticity (15,25-27).

The KCNQ subunit contains six transmembrane segments, S1-S6. S1-S4 serve as the voltage sensor domain (VSD), and S5-S6 are the pore-gate domain (PGD) (Fig.1). The N- and the long C-terminal intracellular domains contain sites that are regulated by intracellular signaling molecules (28-30). The KCNQ1-5 genes share between 30-65% amino acid identities, with the highest similarity in the transmembrane regions (7,31). The S4 transmembrane segment, like in other voltage gated channels, contains positively charged residues that sense changes of the membrane voltage and move across the membrane to activate the channel. The loop between S5 and S6 contains the K⁺ selectivity filter with the signature sequence TxxTxGYG. Generally, all KCNQ subunits are homologous in their intracellular N- and C-terminus regions (32,33). However, their C-terminus is variable in length, with KCNQ5 being the longest, and KCNQ1 being the shortest. The number of amino acids in different subunits varies from 676 in

KCNQ1 being the shortest. The number of amino acids in different subunits varies from 676 in KCNQ1 to 900 in KCNQ5 (7,31). The length variability of the C-terminus may have implications for modulations of these channels. The five KCNQ genes were found on different chromosomal loci, with all but KCNQ5 mapping to human diseases (2).

In the heart, KCNQ1 co-assembles with KCNE1 to form the IKs channel. The IKs current, a slow delayed rectifier K⁺ current, plays a key role in repolarization of the cardiac action potential (34,35). The evidence comes from the similar kinetics and voltage dependence of the IKs current in the heart and the current of KCNQ1 and KCNE1 expressed heterologously in cell lines or *Xenopus* oocytes. The evidence also comes from the pharmacological profile of ligands that are classified as type III antiarrhythmic drugs, such as clofilium, which similarly blocks IKs currents and KCNQ1+KCNE1 heteromultimeric currents.

Although KCNE1 is a peptide of 129 amino acids with a single transmembrane helix (36-39), its association with KCNQ1 drastically alters every aspect of channel function. Comparing to the channels formed by KCNQ1 alone, the KCNQ1+ KCNE1 channels show an increased total current amplitude, a shift in the voltage-dependence of activation toward more depolarized potentials, a prolonged activation and deactivation time course (40), a different ion permeability (41-43), altered effects of drugs on channel activity (44-46), and increased effects of protein kinase A (PKA) phosphorylation on channel function (47,48).

The KCNQ1 gene was identified in a study of long QT (LQT) syndrome, a condition that leads to cardiac arrhythmia (8). It is found that more than 300 mutations in KCNQ1 and KCNE1 are associated with long QT syndrome (LQTS) (8,49-56). The mutations of KCNQ1 have also been associated with atrial fibrillation and short QT syndrome (57,58). Some mutations in the KCNQ1 gene also causes deafness in addition to LQTS syndrome (2,8,59,60).

KCNQ1 + KCNE2 form constitutively active channels at physiological membrane potentials, however, the total conductance of the expressed channels is low (61). The ability of these channels to remain open may be essential for their function in particular nonexcitable polarized epithelial cells (62-64), such as the gastric, thyroid, and choroid plexus epithelium (62-66). In parietal cells, apical KCNQ1 + KCNE2 channels control the potassium recycling pathway to counterbalance any K⁺ influx through the apical gastric H⁺/K⁺-ATPase (62,65,66). The KCNQ1-KCNE2 channels expressed in

the basolateral membrane of thyrocytes are needed for normal production of thyroid hormone by the thyroid gland (64). In an in vitro study, KCNQ1-KCNE2 channels in FRTL-5 of rat thyroid cell lines were inhibited by a general KCNQ antagonist, chromanol 293B (67).

KCNQ1 is also detected in crypt cells of the small intestine and the colon (32). KCNQ1 is thought to assemble with KCNE3, as shown by mRNA detected in intestinal tissues. The channels of KCNQ1+KCNE3 have been observed to have similar characteristics to a cAMP-activated K⁺ conductance present in the colon of a rabbit, suggesting that they may be involved in regulating cyclic AMP-regulated K⁺ currents in the colonic crypt cells (10,68). These channels carry currents that may play a role in intestinal Cl⁻ homeostasis, which is disrupted in some disorders, such as cystic fibrosis and cholera (68).

There is evidence for roles of KCNQ1 in the functioning of the inner ear. mRNA of KCNQ1 and KCNE1 was detected on the apical surface of marginal cells of the stria vascularis of the cochlea (60). It is believed that KCNQ1 and KCNE1 form functional heteromeric channels, however, these channels are believed to be tonically active (partially or slowly activated over the time). Unlike in the heart, KCNQ1 in the cochlea has a role in the recycling of K⁺ ions. Imbalance in the concentration gradient of K⁺ reduces the endolymph potential, leading to decreased sensitivity to auditory stimuli. Lange-Nielsen syndrome (JLNS), the patients of which show severe long QT syndrome and bilateral deafness, is associated with mutations in either KCNQ1 (JLNS1) or KCNE1 (JLNS2).

KCNQ2-5 potassium channels are expressed in the nervous system to form M-current or M-current-like channels. These channels are affected by muscarinic receptor signaling and are responsible for regulating neuronal excitability (69,70). M-current channels open near the resting membrane potential, close to the firing threshold of the action potential, providing a powerful brake on neuronal excitability. All M-current channels can be inhibited by M1 muscarinic activation (71) and by linopirdine (12,72). M-current was discovered early in the 1980s by Brown and Adam, who first noticed currents of slowly voltage-gated potassium channels that are blocked by muscarinic G-protein-coupled receptors within sympathetic neurons, therefore they called it the M-current (73).

The M-current has been identified in both the central and peripheral nervous systems. A decade after its discovery, members of KCNQ potassium channel family

were found to carry the M-current (2). KCNQ2/3 heteromeric channels were mainly named the classical M-current (7,12,74). KCNQ2 and 3 are chiefly expressed in the nervous system, where they colocalize in some neuronal populations (75,76). This finding may suggest that these channels are assembled in a subset of neurons and are expressed as heteromeric channels (75-77). However, they are not always colocalized in brain tissues (75). There is also evidence that KCNQ2 homomeric channels are expressed in vivo (78-80). Additionally, KCNQ5 may also be expressed heteromeric channels with KCNQ3 (7).

It was found that all KCNQ channels need PIP2 (phosphatidylinositol 4,5-bisphosphate), a phospholipid in the inner leaflet of the plasma membrane, for activation (81). PIP2 is required for the movements in the voltage sensor domain to trigger the pore gate domain to open (82,83). Thus, KCNQ channels are both voltage-gating and ligand-regulating potassium channels. M1 muscarinic activation activates phospholipase C by G-protein (Gq), which hydrolyzes PIP2, thereby inhibiting KCNQ channels (84). M-current channels can control the rate of neuron firing because of their special biophysical properties and subcellular localization (76,85), and they can further potentiate membrane excitability, due to downregulation as a result of G protein-coupled cell signaling. This is an important balancing regulatory pathway of M-current physiology (2,3,86).

Inhibition of M-current in a mouse model leads to disorder in hippocampus-dependent spatial memory (15). In rodent models, acute stress can cause impaired retrieval of the hippocampus-dependent spatial memory (87,88). Acute stress has been shown to raise the output of 5-hydroxytryptamine (5-HT) in the hippocampus (89,90). 5-HT was reported as an inhibitor of M-current channels in mammalian neurons (91). Therefore, M-current channels might be involved with the acute stress that causes disruption of spatial memory retrieval and synaptic plasticity. In addition, a study has reported a decrease in KCNQ with aging in brain tissues of drosophila (25), and KCNQ3 channels were reduced in the mice hippocampus after object recognition training (26).

KCNQ2/3 channels maintain neuronal excitability at a normal level. Any decreases in M-current activity because of genetic or other factors are directly linked to neuronal hyperexcitability-associated disorders, such as epilepsy. This disease is characterized by recurrent seizures due to synchronized electrical hyperexcitability in the central nervous system. For instance, benign

familial neonatal convulsions in an infant were found to be associated with mutations in KCNQ2 and KCNQ3 channels (4,92). Reduction of M-current is also associated with tinnitus, autism, and bipolar disorders (4,92-96), and with types of progressive hearing loss linked to mutations in KCNQ4 (6).

The M-current was first identified in bullfrog sympathetic ganglia (73). The equivalent mammalian channels were identified in the superior cervical ganglion (SCG) of rats (97). Studying M-current was difficult until selective agents acting on these channels were discovered such as linopirdine and XE991, allowing researchers to screen known K⁺ channel genes (10). Such selective ligands help to screen various channels pharmacologically, to compare their distinctive biophysical properties, and to study the expression of many subunits of both homomeric and heteromeric channels. Thereafter, KCNQ2/3 heteromeric channels were explored as M-current channels in the SCG of rats (12,75). This history highlights the importance of pharmacological agents as tools in the study of KCNQ channels.

KCNQ subunits are diverse in their assembly, forming both homomeric and heteromeric channels. The assembled channels have various phenotypes, differing in their expression level, cellular targeting, biophysical characteristics, and pharmacological profiling. The composition of expressed channels in vivo is difficult to know for certain, however, studying their characteristics and comparing them with channels that express in vitro offer insights in to the subunits' composition in various human tissues (13). Information about KCNQ subunits and tissue-specific localization, combined with drug discovery approaches using potent selective ligands, would improve our knowledge and advance treatment therapeutics. In this article, we review the compounds that either activate or inhibit channels, assessing their specificity to various KCNQ channels, their mechanism of action, and their use in research and therapy.

KCNQ Channel Activators

1. Retigabine 'RTG' (D23129)

In 2011, the drug retigabine (RTG) finished clinical trials as the first approved KCNQ channel opener for human use. RTG has a novel binding site and mechanism of action for activating the KCNQ 2-5 channels, but not the related cardiac KCNQ1 subunit (Fig.2) (98-101). RTG has an effect on a range of seizure disorders, and it has been approved by the FDA as an antiepileptic drug for the treatment of partial/focal seizures (98,102).

Retigabine also relieves behaviors related to anxiety (103,104), and other studies have shown pain-reliever effects of retigabine in several animal models (105-107). Still more studies have reported that RTG is a broad-spectrum agent for treating epilepsy and seizure in vivo, including chemically and electrically induced seizures in almost every animal seizure model (108,109). As an example, rats with complex partial seizures have been treated with RTG, which dose-dependently increases the threshold current for induction, and decreases the seizure severity, peak duration, total duration, and changes after discharge (110). It has also an agonistic action on GABAA receptors, the major inhibitory channels in the central nervous system, which are associated with epilepsy disorders (108,110,111).

RTG has shown interesting pharmacological action in potentiating KCNQ2/KCNQ3 potassium channels (Table 1). RTG's effects on the heterotetramer KCNQ2/KCNQ3 channels include enhanced activation rate, slowed deactivation rate and leftward shifting of the activation voltage curve by 30 mV (100,101,112). These effects cause neuronal hyperpolarization both during membrane resting and after an action potential (100). The binding with RTG could theoretically decrease the required energy for channel activation because opening the channel will require a lesser depolarization. (70,100,113-116).

A structural analog to the centrally acting analgesic flupirtine, RTG activates KCNQ channels by binding to TM5 and TM6 regions. The amino acid sequences of TM5 and TM6 segments are more than 90% conserved in KCNQ2 and KCNQ3, and RTG similarly affects the KCNQ2 and KCNQ3 homomeric channels (117). The TM5 and TM6 domains of KCNQ1 and KCNQ2 subunits differ by only 13 amino acids. A study has shown that the sensitivity of RTG to KCNQ2 channels was lost when tryptophan 236 in TM5 was mutated to the corresponding leucine 246 in the KCNQ1 subunit. KCNQ2 subunits with a TM6 sequence of KCNQ1 subunits make channels insensitive to RTG, however, the channels are still functional (101). These findings demonstrated that the conserved tryptophan residue in KCNQ2-5 channels, but not KCNQ1, is essential for retigabine sensitivity to M-current (117,118). The interesting mechanism of retigabine action has attracted much attention to discovery and screening of derivatives for the new class of drugs and treatments. The discovery of ligands with better subunit selectivity will improve ligand effectiveness in treating different disorders with minimal side effects (17,98,119-123).

Although RTG can prevent the excessive firing associated with seizures and the spontaneous firing that causes tinnitus (95,99), it has many adverse side effects, such as urinary retention, skin discoloration, and retinal disorders (124). These undesired side effects limit the uses of retigabine. Most of the undesired effects of retigabine arise because of the general lack of selectivity of KCNQ channels. Retigabine is effective for many forms of epilepsy because of its action on KCNQ2 and KCNQ3 channels, while its potentiation effect on KCNQ4 and KCNQ5 channels in smooth muscles, as an example, reduces contractile responses through membrane hyperpolarization (2,125). Agents that will selectively activate only KCNQ2 and KCNQ3 channels are urgently needed to treat neuronal hyperexcitability disorders related to M-current channels, such as epilepsy, migraine, and chronic pain. Retigabine is currently the only globally approved voltage-gated potassium channels opener (126). For attempts to discover analogues with better potency and specificity it is extremely important to understand the complex mechanism of channel activation by RTG.

2. SF0034

SF0034 was discovered by adding a fluorine atom to retigabine to achieve a more potent and selective molecule acting on KCNQ channels (Fig.2) (127). SF0034 is selective for KCNQ2/3 channels, and can manage seizure and reduce the number of side effects (Table 1) (127). SF0031 has displayed several times better potency than retigabine with heteromeric KCNQ2/3 channels in HEK293T cells. It has also been shown that SF0034 shifts the voltage dependence of KCNQ2/3 channels to more negative voltages. Unlike retigabine, it does not shift the voltage dependence of homotetramer KCNQ4 or KCNQ5 channels (127).

Interestingly, the lack of effect on KCNQ4 channels makes SF0034 an important drug candidate, because KCNQ4 is the main potassium channel that regulates the contractility of the smooth muscles in the bladder (2,125). Retigabine, but not SF0034, creates a major side effect by activating KCNQ4 in the bladder leading to membrane hyperpolarization, loss of contractility, and urinary retention. Persistent deafness can also occur when KCNQ4 functions are impaired (128). Also, KCNQ4 and -5 subunits are expressed in skeletal muscles, SF0034, which has no effect on either KCNQ4 or -5 channels, does not have the side effects of retigabine (2,129,130). The higher potency and selectivity of SF0034 could avoid many of retigabine's toxicities, making it a better choice as a KCNQ2/3 channel opener.

SF0034 may become a potential therapeutic candidate for encephalopathy because recently it was found that the KCNQ2 channels, expressed in neonatal brains are a regulator of neuronal excitability. Several genetic mutations in KCNQ2 potassium channels lead to epileptic encephalopathy in neonatal children and infants (131-134). SF0034 may be a better treatment for children with KCNQ2 encephalopathy than retigabine. KCNQ2/3 channels were also found to be directly related to tinnitus, and retigabine inhibits tinnitus development in a mouse (95). Tinnitus is experienced by one-eighth of the world's population (135), and SF0034 may also become an excellent clinical candidate for treating tinnitus. This ligand is not only promising as a new clinical candidate to treat many forms of epilepsy and tinnitus, but also a powerful experimental tool to study KCNQ channels.

3. Zinc Pyrithione (ZnPy)

Zinc pyrithione (Fig.2) was found by a relatively new experiment called function recovery after chemobleaching (FRAC) (136). The channels expressed on the surface of targeted cells were chemobleached, the replenished channel activity after chemobleaching was monitored, and the time for recovery was measured by nonradioactive rubidium flux assay. A pulse-chase assay monitored function recovery after bleaching with a specific chemical, to determine the time it took for the ion channel to reach the cell surface (136). This experimental combination was first tested to identify inhibitors for hERG and Kir2.1 with mechanism of action that are either to inhibit channel activity or regulate trafficking and half-life of channel proteins. This strategy was later used to screen KCNQ channels with many ligand libraries, searching for a ligand with agonist activity (137).

Zinc pyrithione (ZnPy) activates KCNQ1 channels ($EC_{50}=3.5 \mu M$), and it also activates other KCNQ channels, such as KCNQ2, KCNQ4, and KCNQ5 (Table 1). While ZnPy strongly potentiates M-current channels, it has shown no significant effects on voltage-gated potassium channels other than KCNQ (138). ZnPy does not show a significant effect on KCNQ3 channels, which may suggest that it does not bind to them (137,139).

ZnPy has shown the ability to manage some genetic mutations of neonatal epilepsy and myokymia patients (137). For years, ZnPy has been used clinically to treat dandruff and psoriasis (140). However, many studies on ZnPy in animal models, its mechanism of actions, and developing derivatives for clinical studies and uses may

be required.

ZnPy causes leftward shift in voltage dependent activation of KCNQ channels, and reduces the deactivation rate. In addition, ZnPy enhances channels currents at all physiological voltages (137). Unlike retigabine, which acts mostly by shifting KCNQ voltage dependence of activation but has minor potentiation effects at higher saturated voltages, ZnPy enhances maximum opening probability of KCNQ channels (101,117). Also, unlike retigabine, which loses effects on the W236L mutant KCNQ2, ZnPy is highly effective in potentiating the mutant channel, indicating that ZnPy and RTG do not bind to the same site (137). It was suggested that the presence of a zinc ion in the structure of ZnPy is important for its action in neuronal functions (Fig 2) (141).

Interestingly, ZnPy has been recently demonstrated to activate KCNQ channels after PIP2 depletion, suggesting that it competes with PIP2 for the same binding site. The potentiation effect by ZnPy was reduced when it was tested with channels mutated in the putative PIP2 binding site (142). This finding may suggest that ZnPy targets the PIP2 binding site, and plays a role in the VSD-PGD coupling. Thus, ZnPy represents a new class of ligand with a novel mechanism of action (82).

4. Flupirtine and N-ethylmaleimide (NEM)

The centrally acting, non-opioid analgesic flupirtine is widely used in Europe for the treatment of chronic pains, such as lower-back pain and cancer-associated pain (Fig.2) (143-145). Flupirtine affects the function of multiple ion channels and receptors. Although flupirtine is a neuronal potassium channel opener, it is a NMDA receptor antagonist and a GABAA receptor modulator (146). The mechanism underlying the clinic effects of flupirtine has not been fully revealed yet, however some studies have reported that its effects on neuronal excitability are mainly due to their actions by opening of voltage-gated KCNQ channels (147,148). Flupirtine has shown neuroprotective roles both in vitro and in vivo (17,149,150). It may be used to prevent memory and learning problems because it has been reported to treat seizures by activating KCNQ channels (151,152).

Flupirtine has been reported to have neuroprotective effects on spatial memory retrieval and hippocampal long-term potentiation (LPT). Applying acute stress has been noticed to decrease the expression of KCNQ2 and 3 channels in the hippocampus, leading to impair the functions of spatial memory retrieval and hippocampal LPT. The M-current activator, flupirtine prevent this

impairment from occurring. These results suggest that KCNQ channels are promising targets for protection of hippocampal function when it is affected by stress (153).

Over activation of M-current in cultured hippocampal neurons can mediate more K⁺ efflux, affecting the pro-apoptotic process. Flupirtine and N-ethylmaleimide (NEM) are believed to work as KCNQ channel openers in hippocampal neurons by causing the efflux of K⁺ in a dose-dependent manner, depleting the intracellular K⁺, and cell death in hippocampal culture (154,155). While both flupirtine and NEM induce cell death in hippocampal cultures, NEM also causes cell death in cortical cultures. The action of cell death by NEM was inhibited by the KCNQ channel blocker, XE991 (155). These findings suggest that M-current could play a regulatory role in neuronal apoptosis, and flupirtine and NEM can be used as research tools to study this role (155).

Antidystonic effects have been reported for flupirtine and retigabine in animal models with paroxysmal dystonia. These findings show the association of neuronal KCNQ channels in dystonia-associated disorders. Flupirtine and RTG also exert efficacious non-opioid analgesic effects that may help to alleviate disorders accompanied by muscles spasms such as dystonia (156).

5. L – 364373 ‘R-L3’

The benzodiazepine derivative L-364,373 (R-L3) (Fig.2), an activator of IKs channels, has been reported to shorten the action potential of cardiac myocytes in guinea pigs (157). The effects of R-L3 on IKs channels were also studied in precontracted mesenteric arteries where it produced concentration-dependent relaxation ($pEC_{50} = 6.3 \pm 0.4 \mu M$ (158)) (Table1). R-L3 displays moderate leftward shifts in the voltage dependence of channel activation, increases the rate of channel activation, and significantly decreases the rate of channel deactivation (157).

R-L3 activates KCNQ channels by increasing the amplitude of their currents (45). While it activates KCNQ1 at concentrations up to 1 $\mu mol/L$, it blocks the same channels at 10 $\mu mol/L$ (157). Many long QT syndrome-associated mutant KCNQ1 channels can be affected by R-L3 similarly as the KCNQ1 WT channels, consequently R-L3 has been shown to reverse the long QT by increasing IKs currents (45).

The molecular determinants of R-L3 interacting with KCNQ1 channels were revealed using molecular modeling and mutagenesis scanning of KCNQ1 channels with voltage-clamp analysis in *Xenopus* oocytes. R-L3 was found to interact with residues located at the S5 and S6 transmembranes segments of the KCNQ1 subunit (Y267, I268, L271, and G272 in S5, and F335 and I337 in S6) (45). The binding site of R-L3 may overlap with the site where KCNE1 subunits interact with S6, and the residues may not face the central cavity (159). When KCNE1 is used in excess, the effect of R-L3 in the IKs channel is abolished, which suggest that KCNE1 prevents binding of R-L3 to the KCNQ1 subunits by competing for a common interaction site on KCNQ1 subunits (157).

6. NSAIDs agents as openers with KCNQ channels

Fenamate compounds (Fig. 2) have been used clinically as an analgesic and anti-inflammatory (160). These fenamate ligands are NSAIDs (nonsteroidal anti-inflammatory drugs) that inhibit COX-1 and COX-2 non-selectively (161). Several derivatives of fenamate compounds were tested with KCNQ channels, such as mefenamic acid, flufenamic, tolfenamic, meclofenamic, niflumic acids, diclofenac, and 4,4'-diisothiocyanatos-tilbene-2,2'-disulfonic acid (DIDS) (Fig.2). Niflumic, mefenamic, fiufenamic acids, and DIDS can increase IKs current and reduce the deactivation rate at lower concentrations (10 μM) (160,162). These ligands presumably stabilize the open conformation of IKs channels. Mefenamic acid activates both IKs and KCNQ1 channels (163). It produces an approximately 20 mV leftward-shift in the activation curve of KCNQ1 currents (164). Mefenamic acid also affects the anti-contraction mechanism by activating KCNQ channels (160,163). At mM concentrations, mefenamic acid relaxes the mesenteric arteries in a concentration-dependent manner by activation of KCNQ channels and inhibiting Ca²⁺-activated Cl⁻ channels (158). The effect of mefenamic acid was only partially blocked by L-768673, a potent blocker on IKs channels, supporting that the mefenamic acid effects is due to a dual action by activating KCNQ channels and blocking Ca²⁺-activated Cl⁻ channels. Mefenamic acid antagonizes Ca²⁺-activated Cl⁻ channels at higher concentrations (5-10 mM) (165). The effects of these compounds on KCNQ channels suggest that they may restore the IKs channel function of some particular LQT-associated mutations in KCNE1 (164).

Meclofenamic acid and diclofenac have also been found as potent activators on KCNQ2/Q3 channels (161). They strongly potentiate KCNQ2/Q3 expressed in CHO cells,

Xenopus oocytes, and neurons (161). Both ligands shift the voltage dependent activation curve leftward and slow the deactivation rate. The actions of these ligands increase KCNQ2/3 currents and hyperpolarize the resting membrane potential of neurons. Meclofenamic acid and diclofenac decrease both the evoked and spontaneous spiking activity of rat cortical neurons. Animal studies have shown that meclofenamic acid and diclofenac inhibit the spontaneous neuronal action potential by improving the M-current (161). Both ligands are anticonvulsants in mice models, measured by MES (maximal electroshock-induced seizure) (161).

Fenamate's effects on potassium channels might be promising for understanding the mechanism of their actions on various receptors, and whether some of them are responsible for many treatment effects and side effects (100,113,114).

Interestingly, the diphenylamine functional group in fenamate compounds is fairly similar to the two phenyl rings in retigabine (Fig.2). Fenamate compounds and retigabine have two benzene rings linked through one or two atoms. Retigabine and diclofenac are selective activators of different KCNQ channels.

While retigabine is a potent activator of KCNQ3 homomeric channels (100), meclofenamic acid is potent on KCNQ2 homomeric channels. Co-application of retigabine and meclofenamic acid on KCNQ2/3 channels has displayed additive effects, which suggest that the two activators may act independently on two different binding sites of KCNQ2/3 channels (161). Meclofenamic and diclofenac are selective agents for KCNQ channels over other delayed rectifier channels, for instance, Kv1.2, Kv1.5, and Kv2.1 (161).

KCNQ Channel Inhibitors

1. XE991

XE991 is only a moderate inhibitor of almost all subtypes of KCNQ channels (Fig.3). However, XE991 blocks KCNQ channels at low μM concentrations, and it affects other types of potassium channels only at higher mM concentrations (72,166). XE991 is a tenfold more potent inhibitor of the KCNQ1 current than of the KCNQ1 + KCNE1 current. XE991 decreases activation and deactivation time constants, and shifts the activation curve of I_{Ks} channels to more positive voltages ($KD = 0.78 \mu\text{M}$ and $KD = 11 \mu\text{M}$ for KCNQ1 and I_{Ks} channels, respectively) (Table 3). It was also found that the inhibition effect of XE991 is both time and

voltage-dependent with I_{Ks} channels (167).

When KCNQ1 and KCNE3 subunits are coexpressed in Xenopus oocytes, XE991 blocks the heteromeric channels more potently than KCNQ1 channels. The inhibition effect of XE991 on epithelial chloride transport is evidence for the blocking effect of this ligand on KCNQ1 + KCNE3 heteromeric channels (168). Thus, the selectivity of XE991 is dependent on the composition of accessory subunits in association with the KCNQ subunits in different channels complexes.

XE991 can evoke contraction of arteries and depolarization of smooth muscles in rodents and humans (169-172). Constriction of the intrapulmonary arteries of rats and mice (IPA) by XE991 is also evidence for functional KCNQ channels in modulating vascular vasoconstriction (173).

XE991 acts as a cognitive enhancer by releasing stimulant-evoked transmitter from the central nervous system (174). It is believed that the effect of XE991 is the results of inhibition of M-current (12,175). The inhibition effect of XE991 on KCNQ channels may be part of the resting conductance of the parasitophorous vacuole membrane (PVM). The ligand has also shown the ability to enhance portal vein excitability (176).

2. Linopirdine

Like its analogue XE991, linopirdine is a potent KCNQ channel inhibitor (Fig.3). At concentrations of a few μM , linopirdine inhibits almost all subtypes of KCNQ channels; nevertheless, its effects on other potassium channels have been noticed only at mM concentrations (10,72,166,177). Linopirdine can block heterologous KCNQ channels with different potencies, according to the assembled subunits.

Native PVM (portal vein myocytes) delayed-rectifier potassium currents were inhibited by linopirdine. In the presence of linopirdine, both the amplitude and duration of evoked depolarization in PVM were enhanced, giving the first evidence for functional KCNQ channels in vascular myocytes and a role of KCNQ channels in VSMC (vascular smooth muscle cell) repolarization (178). Linopirdine stimulates membrane depolarization and also induce excitability of isolated portal veins (176).

Linopirdine constricts the intrapulmonary arteries (IPA) of an endothelium and nerve terminal in the vessel wall from rat and mouse models at $IC_{50} = 1 \mu\text{M}$, predicting a role for KCNQ in regulating vasoconstriction. The effect of linopirdine is eliminated in the presence of nifedipine,

a selective L-type calcium channel blocker. This result suggest that inhibition of KCNQ channels may cause constriction of IPA via voltage-sensitive L-type calcium channels, possibly by increasing membrane depolarization and activating calcium channels (173).

IV administration of linopirdine to anesthetized rats produced increase in mesenteric vascular and systematic blood pressure, which was reversed by flupirtine. This study found a link between the modulation of vascular KCNQ channels and the control of systematic blood pressure and local blood flow, without affecting the heart rate (170).

KCNQ channel modulators such as linopirdine influence membrane potential, affecting the release of neurotransmitter (179).

Linopirdine raised epileptiform activity in brain slices from neonatal rats, whereas in slices from adult rats, it provoked erratic interictal-like activity. While linopirdine inhibits M-current *in vitro*, it can increase epileptiform activity in a pattern similar to BNFCs (benign neonatal familial convulsions). This inhibition effect of linopirdine may help to develop *in vitro* model to study the mechanism of epileptogenesis, and the developmental characteristics of BFCNs (180).

3. Chromanol 293B

I_{ks} selective inhibitors have been studied to discover more effective class III antiarrhythmic drugs (181-183). Chromanol 293B (Fig 3), a promising ligand in a new class of antiarrhythmics, works by inhibiting cardiac I_{ks} potassium channels (181,184,185).

In a two-electrode voltage clamp experiment using *Xenopus* oocytes, chromanol 293B inhibited KCNQ1 channels with a moderate IC_{50} ($IC_{50} = 26.9 \mu M$), while KCNQ1 + KCNE1 channels were fourfold more sensitive ($IC_{50} = 6.9 \mu M$) (Table 2). These results suggested that chromanol may play functional pharmacological roles as drug or a research tool in cardiac tissues because of its selective blocking of I_{ks} channels. KCNQ1 + KCNE3 channels were inhibited by chromanol 293B at $10 \mu mol/l$. In the human colon, chromanol 293B inhibited cAMP-stimulated secretion of chloride at similar concentrations ($10 \mu mol/l$) (186). Chromanol can block KCNQ1 channels which are expressed in the pancreas, leading to increased insulin secretion by glucose stimulation, and can raise the glucagon-like peptide-1 level in mice (187). KCNQ1 channel homologues from *Caenorhabditis elegans* were found sensitive to chromanol with a moderate potency ($IC_{50} = 28 \mu M$) (Table 2) (188).

Chromanol also inhibits KCNQ5 currents moderately (40% inhibited at $100 \mu M$ chromanol 293B); on the other hand, it only slightly inhibits KCNQ2, KCNQ3, KCNQ4, and KCNQ2/KCNQ3 heteromeric channels at $100 \mu M$ concentration (5%, 5%, and 10% inhibition of KCNQ2, KCNQ3, and KCNQ4, respectively) (Table 2) (184).

Mutations in KCNQ1, such as T312S, I337V, and F340Y, significantly reduced the blocking effect of chromanol. It has been suggested that hydrophobic interactions with residues I337 and F340 located in the S6 transmembrane segment, as well as electrostatic interactions with the innermost potassium ion in the selectivity filter (184) stabilize chromanol 293B to block the ion permeation pathway. This mechanism was consistent with the state-dependent binding study, in which chromanol blocked channels after opening, but not while the channel was closed (189). Chromanol can fully block I_{ks} channels in a voltage-independent fashion without significantly affecting channel kinetics (183,189).

4. Azimilide (NE-10064)

Azimilide is a unique antiarrhythmic agent which was used in human to prolong the time between recurrence of atrial fibrillation, paroxysmal supraventricular, and atrial flutter (Fig.3) (190). Azimilide is believed to have a novel mechanism that blocks both slowly activating (I_Ks) and rapidly activating (I_{kr}) channels (191-193). Azimilide has been reported *in vitro* to maintain rate-independent effects in ischemic or hypoxic conditions (e.g. in infarcted dogs, azimilide has similar effects at slower and faster pacing rates) (190,194).

Studies in animal cells have suggested that azimilide can be a potential ligand in a class of molecules with new mechanism of action, because it has effects on both the slow I_{ks} and rapid I_{kr} potassium currents (195). Azimilide's *in vitro* effects prolong the duration of the action potential makes it a candidate for a new class of *in vivo* antiarrhythmic agents (196-199). Many studies have reported the effect of azimilide on different potassium channels, for instance, it has displayed full inhibition of I_{ks} channel currents, but not I_{to1} or I_{kur} channel currents, at $100 \mu M$ (200). Many studies have reported that azimilide inhibits I_{kr} and I_{ks} channels in ventricular myocytes of guinea pigs. These studies have reported that azimilide is a more potent blocker of I_{kr} than I_{ks} channels (Table2) (200-202). Azimilide inhibits the slow component of the delayed potassium current (I_{ks}) in ventricular and SAN (sinuatrial node) cells of the guinea pig (193). Azimilide may allosterically interact

with beta adrenergic receptors or may keep step with a signal cascade of the beta-adrenergic receptors. These effects may happen at the threshold concentrations of drug (100 μ M), leading to potentiation of the I_{ks} current. With increasing concentrations of the drug, inhibition becomes dominant, possibly through the direct interactions between the drug and the KCNQ1 channel (193). The potentiation and inhibition of azimilide on I_{ks} channels seem to be underlined by independent mechanism, however, inhibition is the main component, with an overall reduction of steady state currents (193).

5. L-768673

The benzodiazepine analog L-768,673 (Fig. 3) is very potent on I_{ks} channels at nM concentrations ($IC_{50} = 6$ nM) (Table 2), whereas it is less potent on I_{kr} or I_{Ca} channels ($IC_{50} = 6\mu$ M and 1μ M on I_{kr} and I_{Ca} channels, respectively) (203). Conversely, L-768673 has no effect on I_{to} or I_{k1} channels. Therefore, the effects of L-768,673 with various tested channels revealed its selectivity for I_{ks} channels (204). These results suggested that L-768,673 can be a potential anti-arrhythmic therapeutic (158). This ligand was first reported to have no effect on the function or structure of rat cochlea after oral administration (205); however, another study reported an ototoxic side effect for L-768,673 after intravenous administration, predicting ototoxicity because of its effect on I_{ks} channels (206). Generally, L-768,673 is safe, with only slight effects on the studied animals with only moderate QT prolongation (204). L-768673 induces heterotaxia, predicting a functional role for KCNQ1 channels in early embryonic asymmetry (207). L-768,673 effects have been reported with granulosa cells (which have many roles, such as ovulation, implantation, and fertilization), suggesting that I_{ks} channels are involved in these cells (208,209).

The relaxant effect produced by the benzodiazepine R-L3 (Fig.2) on pieces of precontracted mesenteric arteries was completely reversed by L-768,673 at 10 μ M concentration. No effect was noticed on endothelium removal (158). The less potent relaxant effect of mefenamic acid was only partially reversed by L-768,673, which may be due to the inhibitory effect of mefenamic acid on Ca^{2+} -activated Cl channels (165). While L-768,673 has no effect on KCNQ5 currents, it has shown a remarkable inhibitory effect on KCNQ4 currents produced at potentials from positive to 0 mV, an action that has not been noticed with other blockers (158). These functional studies of L-768,673 may show that the KCNQ4 subunit is involved in many activities (158).

6. L-735821 (L-7)

L-735821 is an analog to cholecystokinin-B antagonists (specific antagonists that block the receptor sites for the peptide hormone cholecystokinin) (Fig.3) (203). L-7 is a potent blocker of both KCNQ1 and I_{ks} channels expressed in *Xenopus* oocytes. L-7 is slightly more potent on I_{ks} than KCNQ1 channels ($IC_{50} = 40$ nM and 200 nM on I_{ks} and KCNQ1, respectively) (Table 2) (210). Its action prolongs the duration of the cardiac action potential (210). L-7 has no effect on KCNQ2 channels at 10 μ M concentration (203,210). The effect of L-7 is voltage-independent (210).

L-735821 physically blocks the channel pore by binding to T312 of the pore helix, and I337, F339, F340, and A344 of the S6 transmembrane segment (210).

7. Clofilium

Clofilium is an antagonist on KCNQ1 channels (Fig.3), with an IC_{50} less than 10 μ M (Table 2) (211). It partially blocks murine KCNQ2 channels at 20 μ M when the current is elicited by depolarized voltage from -80 to +40 mV (77). At 10 μ M concentration, clofilium inhibits KCNQ3 currents by 30% (202). It inhibits KCNQ5 currents by 40% at 30 μ M concentration (77).

Clofilium is a blocker of cardiac I_{ks} and I_{kr} currents ($IC_{50} = 50$ μ M and $IC_{50} = 1$ μ M on I_{ks} and I_{kr} channel currents, respectively) (Table 2) (211,212).

Clofilium does not inhibit I_{ks} channels as effectively as it inhibits KCNQ1 channels. While it inhibits 25% of I_{ks} current at 30 μ M, it inhibits as much as 80-90% of KCNQ1 current at the same concentration (212,213).

Conclusions

The KCNQ voltage-gated potassium channels are involved in many physiology and pathophysiology functions. The KCNQ1 protein plays roles in the functioning of the heart, inner ear, and intestines. KCNQ2/3, and to some extent KCNQ5, are involved in M-current, and are distributed in neurons. KCNQ4 plays key roles in the vestibular and auditory systems. The KCNQ5 subunit may be involved in roles in skeletal muscles, however, this still needs to be confirmed. Modulating of KCNQ channels may help to manage many hyperexcitability disorders, for instance epilepsy, pain related disorders and cardiac arrhythmias (98,214).

Compounds either enhancing or inhibiting KCNQ channels have been used clinically to treat various diseases.

Ligands that work as activators on KCNQ2/3 or even KCNQ5, e.g., retigabine and SF0034 are therapeutics for some forms of epilepsy. Ligands that selectively inhibit KCNQ2/3 and 5 channels can be potential cognition enhancers. Ligands that selectively activate I_{Ks} channels can be promising for the treatment of arrhythmia, e.g., azimilide and L-7. Another treatment approach using agents that are selective for potassium channels may cure diseases associated with genetic mutations. The discovery of selective agents for specific homomeric or even heteromeric channels is urgently needed for better treatments with minimal unwanted side effects.

These compounds are also used as research tool to probe the expression of KCNQ channels in various tissues and their physiological roles. Flupirtine and NEM as an example, they induce cell death in hippocampal cultures, which was inhibited by XE991 (155). The actions of these ligands are due to their effects on KCNQ channel in hippocampal neurons. Inhibition of the spontaneous neuronal action potential by meclofenamic acid and diclofenac is an evidence for the action of these ligands in potentiating M-current in neurons (161).

The availability of specific openers and inhibitors on KCNQ channels help to confirm the involvement of KCNQ in many specific disorders, and to help in finding better treatments for these disorders. Expanding our knowledge and understanding of KCNQ subunits will facilitate the discovery of such required selective inhibitors and openers. Functional and structural studies of KCNQ channels will improve our understanding of drug binding and the mode of ligands actions (e.g. pore blocker, gating modifier, or expression modulator).

Figure 1.

A homology model of KCNQ1 channel based on the structure of Kv1.2/2.1 chimera and crystal structure of the Kv7.1 proximal C-terminal domain (215,216).

A. Enlarged view of a single subunit of KCNQ1 in the activated state.

B. Top view of the overall structure of channel formed by a four identical KNCQ1 subunits.

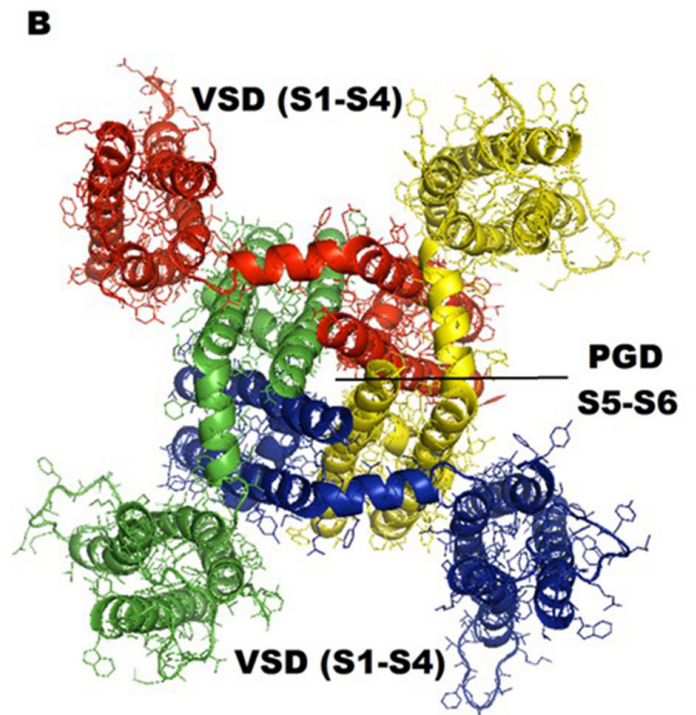
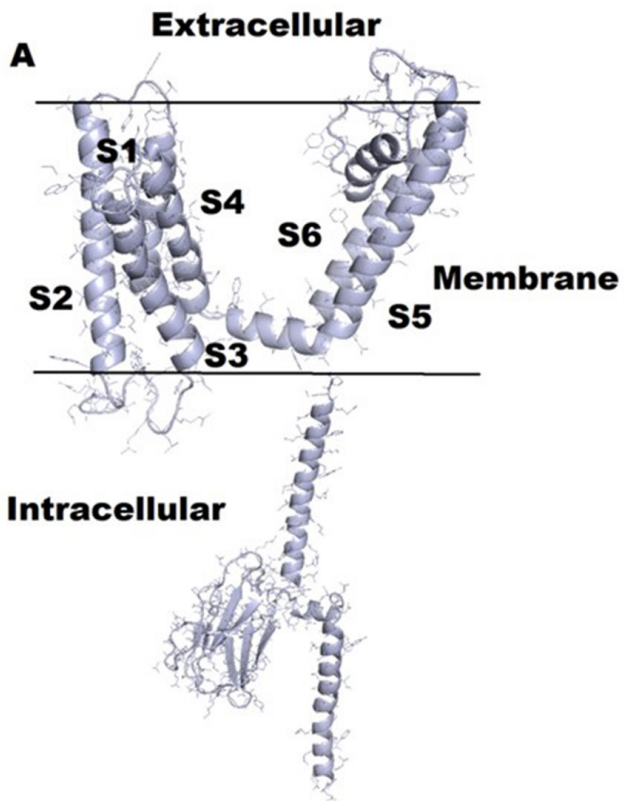
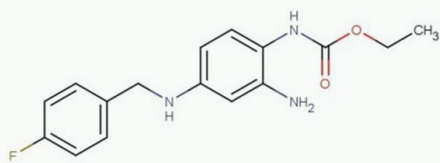
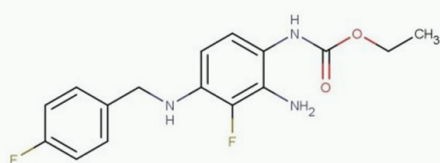


Figure 2.

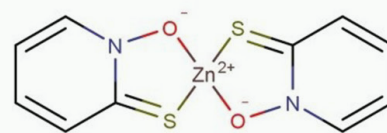
Molecular structures of activators on KCNQ channels.



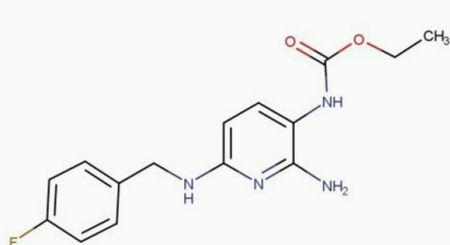
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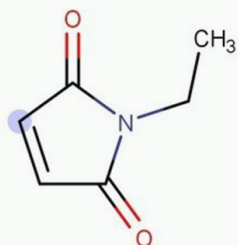
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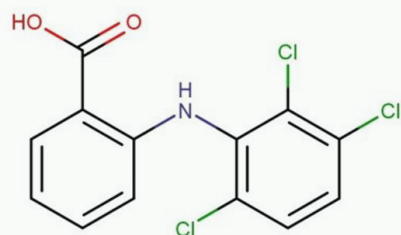
Flupirtine



N-Ethylmaleimide



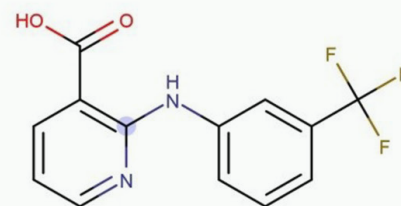
L-364,373



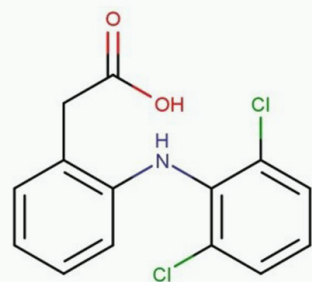
Meclofenamic acid



Mefenamic acid



Niflumic acid



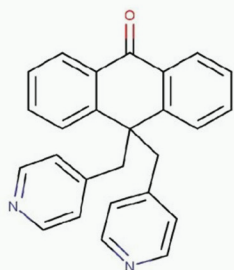
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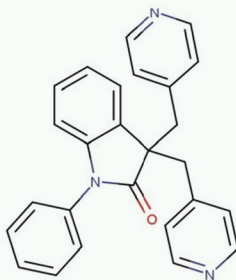
Flufenamic acid

Figure 3.

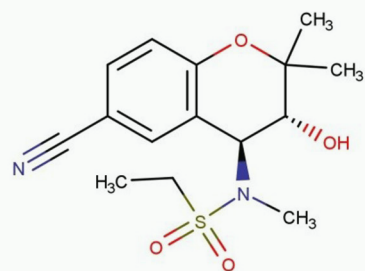
Molecular structures of inhibitors on KCNQ channels.



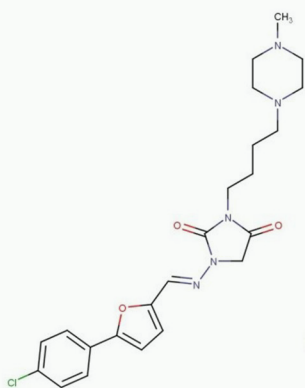
XE991



Linopirdine



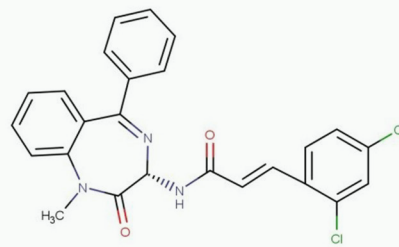
Chromanol 293B



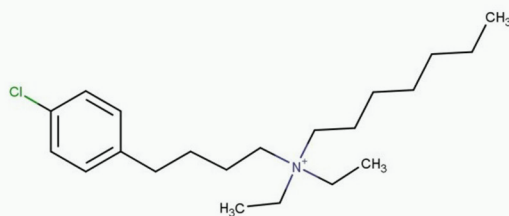
Azimilide



L-768-673



L-735821



Clofilium

Table 1.

The EC₅₀ values of activators on various KCNQ channels.

Ligand	KCNQ1	I _{Ks}	KCNQ2	KCNQ3	KCNQ2/3	KCNQ4	KCNQ5
Retigabine	-	-	4.1 μM (101)	11.6±0.4 μM (123)	6.5 μM (127)		
SF0034	-	-			1.3 μM (127)		
Zinc Pyrithione	3.5 μM	-	1.5 ± 0.3 μM (137)	-	2.4 ± 0.4 μM (137)	-	-
Flupirtine	N/A	N/A	N/A	N/A	N/A	N/A	N/A
L-364373		pEC ₅₀ = 6.3 ± 0.4μM (158)					

Table 2.

Inhibition values of inhibitors on various KCNQ channels.

Ligand	KCNQ1	I _{Ks}	KCNQ2	KCNQ3	KCNQ2/3	KCNQ4	KCNQ5
XE991	KD = 0.78 ± 0.05 μM (167)	KD = 11.1 ± 1.8 μM (167)					
Linopirdine							
Chromanol 293B	IC ₅₀ = 26.9 μM (184)	IC ₅₀ = 6 μM (184)	40% inhibited at 100 μM chromanol 293B (184)	40% inhibited at 100 μM chromanol 293B (184)	40% inhibited at 100 μM chromanol 293B (184)	40% inhibited at 100 μM chromanol 293B (184)	40% inhibited at 100 μM chromanol 293B (184)
Azimilide		IC ₅₀ = 3 μM (191-193)					
L-768673		IC ₅₀ = 6 nM (203)					
L-735821 (L-7)	IC ₅₀ = 200 nM (210)	IC ₅₀ = 40 nM (210)					
Clofilium	IC ₅₀ less than 10 μM (211)	IC ₅₀ = 50 μM (211,212)		30% inhibited at 10 μM Clofilium (202)			

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SPOTLIGHT

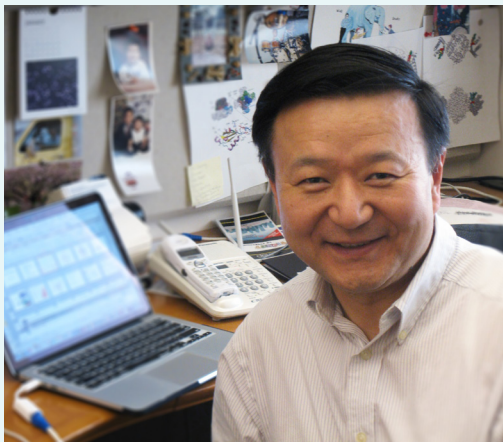
JIANMIN CUI, PH.D.

Professor of Biomedical Engineering

ION CHANNELS & DRUG THERAPY

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SPOTLIGHT



JIANMIN CUI, PH.D.

Professor of Biomedical Engineering

ION CHANNELS & DRUG THERAPY

Education:

- 1983 B.S., Physics
Peking University, Beijing, China
- 1986 M.S., Biophysics
Peking University, Beijing, China
- 1992 Ph.D., Physiology & Biophysics
State University of New York
Stony Brook, NY
- 1994 Postdoctoral Scholar,
Physiology & Biophysics
State University of New York
Stony Brook, NY
- 1998 Postdoctoral Scholar
Molecular & Cellular Physiology
Stanford University, CA

Research Interests:

- Molecular Mechanisms of
Ion Channel Activation
- Ion Channels in Association With
Diseases
- Discovery of Channel-Modifying
Compounds

I moved to Washington University in St. Louis in 2004 from Case Western University, and I have been on the faculty of the Department of Biomedical Engineering since then. I was an assistant professor in the Department of Biomedical Engineering at Case Western University before coming here. I moved here in the hope to find new research directions and opportunities given the larger research community here, and I did.

My lab studies ion channels. Ion channels are proteins in the cell membrane that pass ion fluxes across the membrane. The activities of these molecules generate electrical signals in cells that are essential for the function of almost all organs including nerve, heart, lung, blood vessel, kidney, skeletal muscle and immune systems. Consequently, aberrant ion channel function is linked to many human diseases and ion channels are important drug targets for therapeutics. Ion channels sense physical and chemical cell signals to open and close, and their exquisite molecular mechanisms are major interests of basic research. My lab is interested in the fundamental mechanisms of how ion channels sense stimuli such as voltage, intracellular signaling molecules, and ultrasound and then open in response to these stimuli. We are also interested in understanding the molecular mechanisms for how mutations in ion channel proteins link to diseases. The third area of our interests is to develop novel approaches to discover compounds that modify ion channel function and can be used as drugs for treating ion channel associated diseases.

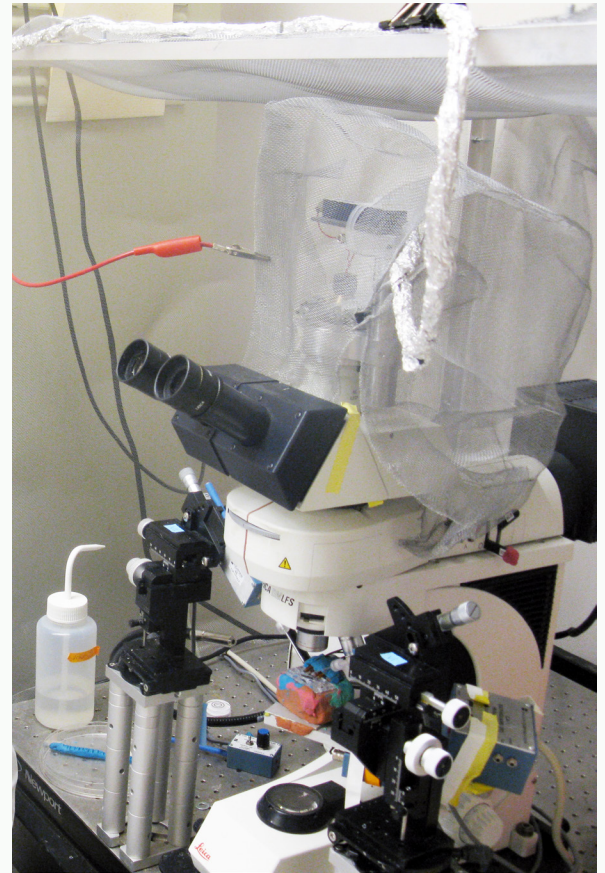
I grew up in China. In those years, Chinese society was full of changes and turmoil, and an individual's career could be shaped by many turns of events but not by his or her own choice. I was fortunate to have the opportunity to go to college and then come to the US for graduate school, and it was in graduate school that I decided to pursue a research career in academia.

However, I am pretty sure that my research interests in biophysics may have developed a lot earlier. In my childhood, I lived in a suburb and I spent much time playing in the woods and fields. The many forms of animals, insects and plants were a huge attraction and source of fascination for me.

Then in college, where I studied physics, the book “What Is Life” by Erwin Schroedinger led me to apply for the biophysics graduate program.

When I entered the Ph.D. program in 1986, the first ion channel had just been recently cloned. It was an exciting time because the molecular identity of so many ion channels was revealed at a rapid pace, and the new knowledge provided great opportunities to study ion channels in a much deeper and broader scale. What attracted me the most was how these channels sense physiological stimuli to open, a question that is still not fully understood even today. My Ph.D. mentor, Dr. Ira Cohen, inspired and encouraged me to learn molecular biology of ion channels, which was new to his lab at the time, and to try my own experiments. This experience made me confident that I could do research to answer my questions independently.

My post-doctoral training in Dr. Richard Aldrich’s lab at Stanford University was important for my career. I learnt to analyze the function of ion channels and correlate the function with structure.



“I tell my children that my career will be a good one if my research can directly benefit some real people”

I would say that wanting to know how things work, or curiosity, has been driving my research. Being on the faculty of an engineering department and more experienced with research, I now pay more attention to how my research can benefit other people’s research or life. I tell my children that my career will be a good one if my research can directly benefit some real people.

I hope that my next achievement is better than any previous ones. But to answer this question of what is my most important research achievement, I would like to mention one of our recent results:

The study was on how a beta subunit modulates a potassium ion channel to change its properties and

make it an important ion channel in the function of the heart. The potassium ion channel is called KCNQ1 and the beta subunit is KCNE1. When KCNQ1 is associated with KCNE1, all of its functional properties including its current amplitude, voltage dependence, pharmacology and posttranslational modulation are changed drastically. The KCNQ1+KCNE1 channel complex actually forms the I_{Ks} channel in the heart and these emerging properties due to KCNE1 association are important for the I_{Ks} channel to control heart rhythm. The question of how KCNE1 association causes such broad and drastic property changes has been studied for more than 16 years but no satisfactory answer was found.



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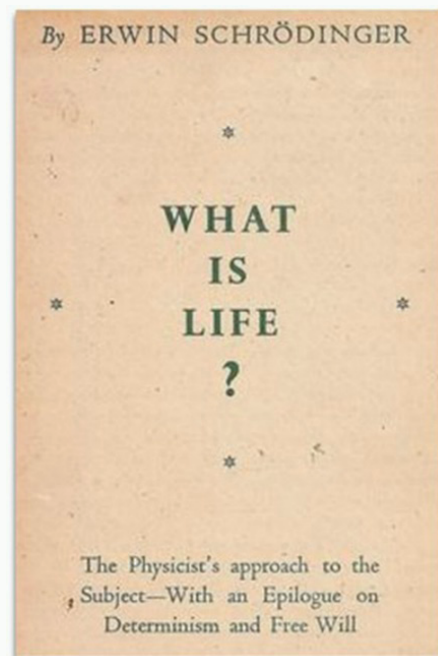
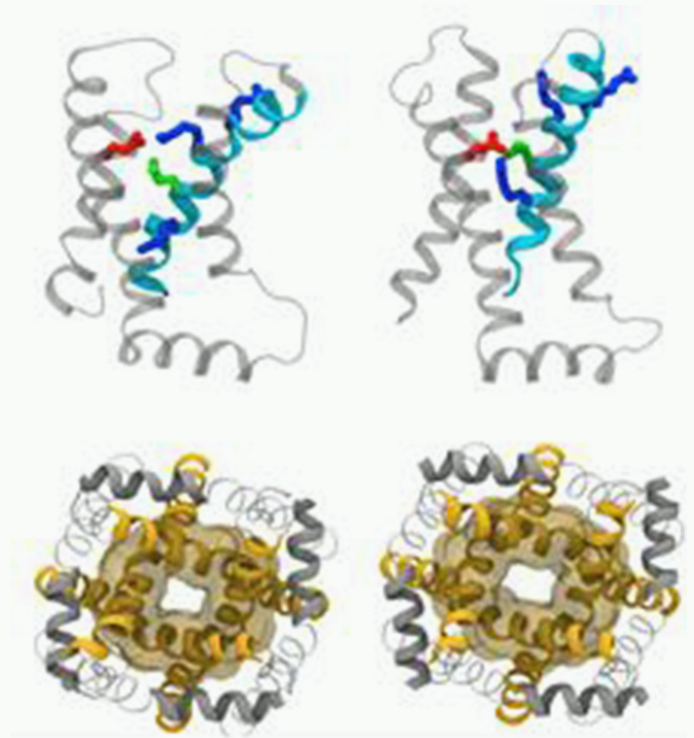
SPOTLIGHT CONTINUED

Recently, our lab found that the KCNQ1 channel has two open states, and the two open states differ in various properties, including voltage dependent activation, ion permeation and pharmacology. The effects of KCNE1 on channel properties can be well explained by the mechanism that KCNE1 association suppresses one open state but potentiates the other. Therefore, the properties of the channel are switched from being predominated by one open state to being predominated by the other open state. We are excited by this mechanism and are studying the ion channel further to test if all known property changes due to KCNE1 association can be explained by this simple mechanism.

I hope to contribute to the understanding of how the channels open in responding to physiological stimulation, and to be able to use the knowledge we have on ion channels to find drugs for therapeutic uses.

CBAC brings together basic scientists and physician scientists to exchange results on cardiovascular research. It has been very helpful for me to understand many clinical and physiological issues that are related to my research at the molecular level. I hope that our research benefits other CBAC members reciprocally.

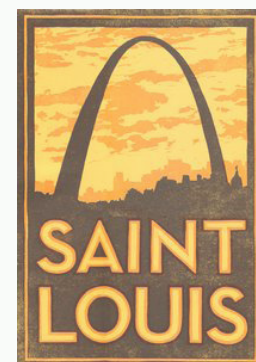
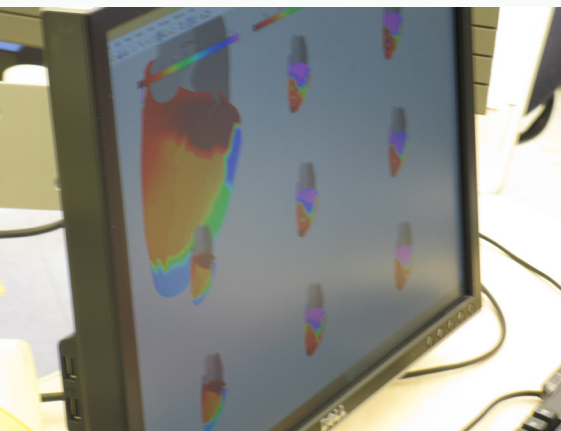
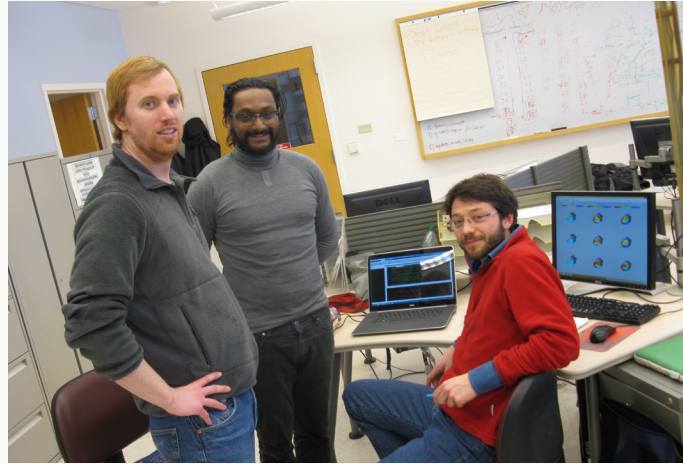
I am most satisfied with that I have a warm and loving family. I like reading, swimming and hiking. I do not find time to do these everyday except that I have been swimming almost daily for the last three years.



VISTORS FROM ACROSS THE POND

SPOTTED IN THE YORAM RUDY LAB

Members of the Yoram Rudy Laboratory are currently collaborating with two researchers – Drs. Neil Srinivasan and Michele Orini from the laboratories of Professors Peter Taggart and Pier Lambiase, University College London (UCL) & The Barts Heart Centre London.



(Top Image) Christopher Andrews, Neil Srinivasan, Michele Orini. (Right Image) Neil Srinivasan, Michele Orini. (Left Image) ECGI images on a lab computer. (Bottom Image) Left to Right: Neil Srinivasan, Michele Orini, Christopher Andrews, Junjie Zhang and Ramya Vijayakumar.

VISTORS FROM ACROSS THE POND

SPOTTED IN THE YORAM RUDY LAB CONTINUED

Michele Orini and Neil Srinivasan were here to perform analysis of a collaborative study using Noninvasive Electrocardiographic Imaging (ECGI) in patients with Brugada syndrome, investigating the relationship between electrical parameters attained with ECGI and myocardial fibrosis seen on MRI in these patients.

Michele Orini, Ph.D. is the Marie-Curie Research Fellow at the Institute of Cardiovascular Science, University College London, United Kingdom. He has an extensive experience in signal processing. He is studying the electrical activity of the human heart by placing a multi-electrode sock over the heart of patients undergoing cardiac surgery. Specifically, he investigates electrical alternans and the effect of stretch.

Neil Srinivasan, M.B., Ch.B. is a Cardiology Electrophysiology Fellow with an interest in inherited cardiac arrhythmias and VT/VF. He performs catheterization laboratory based research, using catheter mapping to investigate electrical heterogeneity within the heart. He is currently taking time out to complete a Ph.D. before finishing his clinical training.

Recently, they were seen in the Rudy Lab and Dr. Srinivasan was able to let us know a bit about his background:

How long have you been in your current position?

Three years

Can you give us an overview of what it is you do in your research and clinical work?

I am a cardiology fellow, with an interest in inherited arrhythmias, sudden cardiac death and ventricular arrhythmias. My primary research interest is electrical heterogeneity within the heart in health and disease, and how this interplays to cause arrhythmia. My research consists of invasive cardiac mapping in healthy and diseased ventricles and its relation to surface ECG markers of risk.

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

Wanted to be a professional soccer player rather than a cardiologist!!!

What is your training experience?

I have worked as a doctor since 2006, and have been doing a Ph.D. since 2013 while continuing to train clinically. I started medical school in 2000 and qualified as a doctor in 2006. I have worked in all aspects of general medicine for the last ten years, and have specialized in cardiology since 2010. During medical school I also did a BSc in one year that largely revolved around the study of cellular electrophysiology. With Professor Arun Holden, I worked with the Luo Rudy cellular computational model, investigating the effects of electrical heterogeneity in LQT2 and the effects of drugs such as Sotalol and Amiodarone on the ventricular wall. This inspired me to pursue a career in cardiac electrophysiology after medical school.

How did you come about being part of Professor Pier Lambiase's laboratory?

After three years as a cardiology Fellow, I moved to Professor Pier Lambiase's team in London, to study the electrical heterogeneity of the heart in health and disease and its relation to surface ECG markers of risk in our patients with

inherited cardiac arrhythmia. We have previously collaborated with Chris Andrews in the Rudy lab studying ARVC, and we have now visited to look at our Brugada patients and the role of ECGI and scar in cardiac MRI in relation to this disease. We are interested to see if we can use ECGI to characterize the Brugada substrate better.

What motivates you to do what you do?

I am motivated by my experiences in the National Sudden Cardiac Death clinic at the Barts Heart Center. I see many patients who have survived a sudden arrhythmic event, as well as families who have tragically lost loved ones to inherited cardiac arrhythmia. I also see many patients where the diagnosis is unclear/difficult, and some where the decision as to whether to implant an ICD is challenging. I'm motivated by a desire to give these people better answers, clearer diagnosis and better risk stratification.

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

We have learnt extensively about ECGI, and I now appreciate the years of heart research that have gone into such an amazing tool. We have also learnt skills in mesh generation of the heart.

What do you feel is your most important personal achievement?

Playing soccer for my school in the Kent Cup final twice. We never won it!!!

Any hobbies?

I watch soccer all the time in the UK. In fact I watch all European soccer and can describe the intricacies of the English, German, French, Italian and Spanish leagues. I like to drink beer while watching soccer.

How have you or will you benefit from collaborating with members of the CBAC?

This is a wonderful establishment, and a great hub for intellectual thought and further research to improve cardiac care. We do not have such a set-up in the UK and we must aspire to something like this. It has been a wonderful experience and we hope to come back soon.

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

I aim to become an academic interventional cardiac electrophysiologist with an interest in ventricular arrhythmia both inherited and acquired.

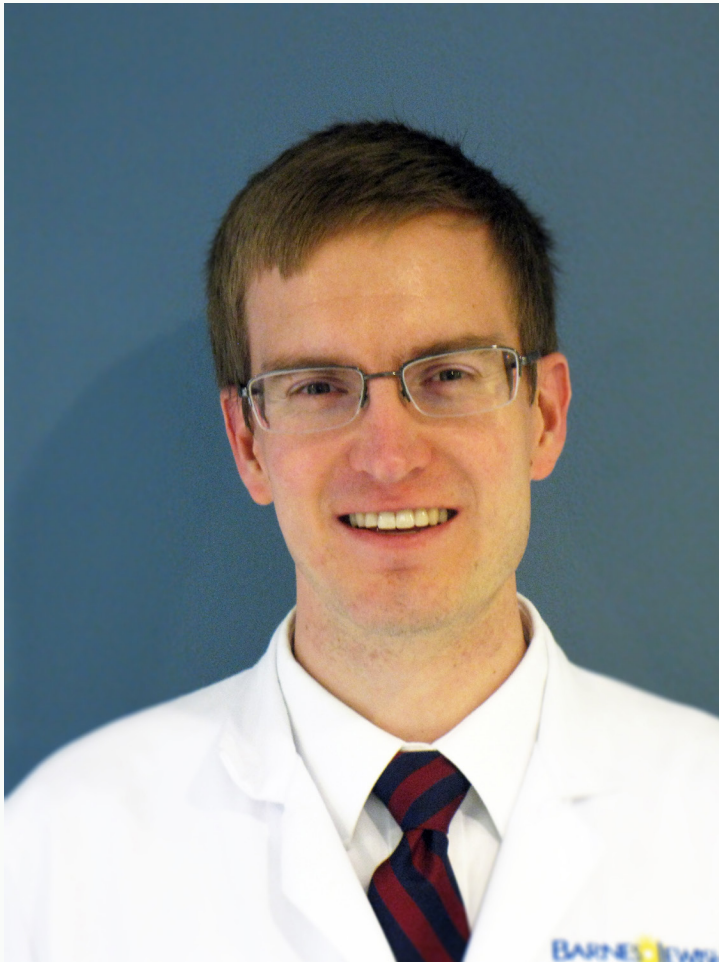
What is your most important research achievement that you are most proud of?

Its top secret!!! You'll have to wait and see...



CBAC RESEARCH FELLOW

SPOTLIGHT



MATTHEW SCHILL, M.D.

RESEARCH FELLOW

DIVISION OF CARDIOTHORACIC SURGERY

DEPARTMENT OF SURGERY

RALPH DAMIANO LABORATORY

CARDIAC SURGERY

I have been a research fellow in Dr. Ralph Damiano's laboratory for ten months. I work on several projects. Our laboratory's research currently centers on investigating the pathophysiology of atrial fibrillation that develops in patients with mitral regurgitation. My primary project involves examining patients referred for mitral valve repair with electrocardiographic imaging (ECGI) before and after surgery. Some of these patients have atrial fibrillation, and they are treated with a Cox-Maze IV procedure as well. I am looking for differences in these patients' atrial conduction patterns before and after surgery. We are also studying the onset of atrial arrhythmias associated with mitral regurgitation in a large animal model. Finally, the Washington University cardiac surgeons have vast experience with surgery for atrial arrhythmias, and our laboratory is actively engaged in clinical outcomes research in this patient population.

Background

It may be a cliché, but I've always enjoyed science and working with my hands, and I wanted to help people. The first thing that I did that was anything like surgery was building electronics. I was messing with circuits and computers from a very young age. I think that gave me an appreciation for fine technical work and for the art of fine-tuning a complex system. I became interested in medicine as a teenager. For me, medicine is a way to solve interesting problems while having an immediate impact on people's lives – there's nothing else like it.

I think the moment I knew that surgery was the right discipline for me came when I was an undergraduate. I was working in a nephrologist's laboratory, and one of my projects was developing a mouse model of acute kidney injury to see if there was a phenotype for a gene they

had knocked out. This sort of model had been done many times before, but the hard part was in the details of getting it to work in our hands. I ended up choosing a surgical ischemia-reperfusion injury model. I found myself dissecting out fine vessels under an operating microscope, mainly guided by textbooks. Producing a meaningful injury while still keeping the animals alive and comfortable was a real challenge – I loved coming to work every day. Once I figured out that one could make a career out of actually making people better, I was set on surgery. Cardiac surgery is the epitome of everything I love about surgery – taking sick patients and performing a challenging operation to help them feel better.

I attended medical school at Washington University. The learning environment was fantastic – the institution’s commitment to medical student education shows. I think the best part of being at a place like this is being part of a community of smart and motivated people. The faculty taught me about medicine; my patients taught me about life.

After that, I was fortunate to match into the general surgery program at Barnes-Jewish Hospital. I’ve done two years of a five-year program. It’s the hardest job you’ll ever love.

Current Work

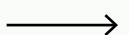
I committed to a career in cardiac surgery at the end of my first year of residency. Most of us spend two years or so doing research as part of our clinical training – it’s a privilege to get to do that. I chose Dr. Damiano’s lab mainly because he has accomplished something rare and difficult in surgery – significantly improving an operation and proving that it worked, first in the laboratory and then in the operating room. It’s my dream to make a contribution like that to our field someday, and I thought that the way to learn how to do that would be to study under someone who had changed our field.

I think the best thing is when patients get better. There is nothing more rewarding than seeing someone come back to the clinic feeling better a few weeks after an operation.

I’m not yet to the point where my current research is bearing fruit. I think the best thing I’ve done yet is taking a prospective clinical study that was making very slow progress and getting things moving – we’ve collected almost half the data we need in a few months. It took a lot of coordination with other departments to make this happen, and I’ve picked up a lot of new skills.

To me, the CBAC means a group of basic and clinical scientists from a variety of disciplines who are focused on studying cardiac arrhythmias. The sort of work I am doing can’t be done in isolation; it requires experts from multiple fields to make it happen. I’ve collaborated with individuals from surgery, biomedical engineering, cardiology and radiology. Everyone has been very open and helpful. The CBAC Seminar Series and last year’s symposium were great opportunities to learn from leaders in arrhythmia research and to keep apprised of the latest developments in the field.

“There is nothing more rewarding than seeing someone come back to the clinic feeling better a few weeks after an operation.”





Recent Publications with CBAC Members

Schill MR, Melby SJ, **Schuessler RB**, **Damiano RJ**. Surgery for atrial fibrillation and other SVTs. In *Cardiac Electrophysiology: From Cell to Bedside*, 7th ed. Zipes DP and Jalife J, eds. Philadelphia: Saunders, future. *Accepted, under review.*

Henn MC, **Schill MR**, Ruaengsri C, **Schuessler RB**, **Damiano RJ**. Surgical ablation for atrial fibrillation. In *Practical Cardiac Electrophysiology*, 1st ed. Bhargava K, ed. New Delhi: Jaypee Brothers Medical Publishing, future. *Submitted, awaiting review.*

Lancaster TS, **Schill MR**, Greenberg JW, Moon MR, **Schuessler RB**, **Damiano RJ**, Melby SJ. Potassium and magnesium supplementation do not protect against atrial fibrillation after cardiac surgery: a time-matched analysis. *Annals of Thoracic Surgery*. 2016. *Submitted, awaiting review.*

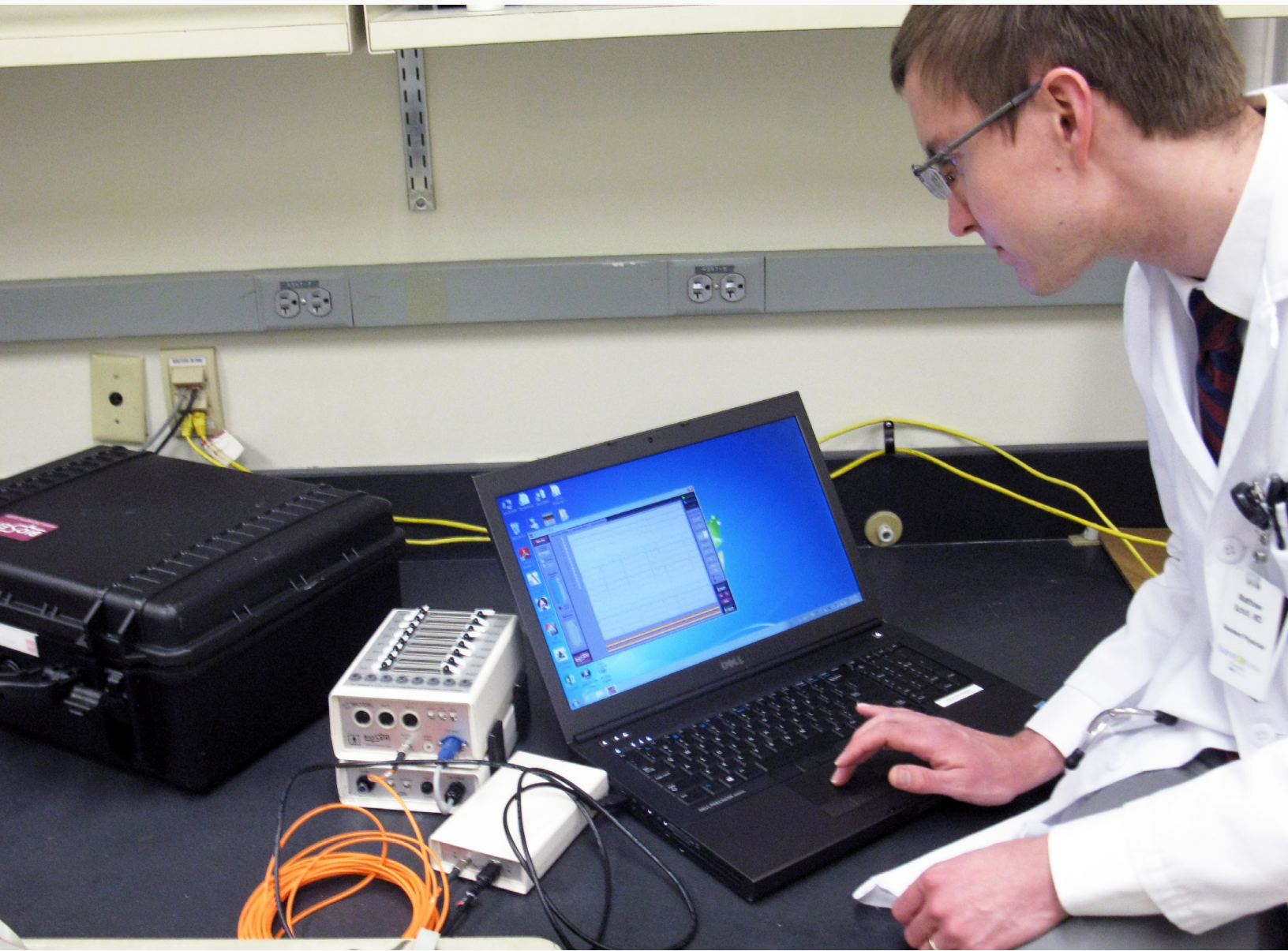
Learning and the Future

Well, probably the most significant thing was learning how to be a physician. I've lived here for over six years now. My wife Ellen and I met here and were married here. As far as medicine and research go, I've learned almost everything I know here.

I'd like to see my current project through to completion and finish a few smaller research projects as well. As far as the long term, I see myself pursuing an academic career in cardiac surgery. If my career stays on its current path, I see myself finding a faculty position in 2022 or so.

Hobbies

I golf and run, although not competitively. I really enjoy fixing things around the house – there's nothing better than a job well done. Ellen and I recently discovered that we both really enjoy assembling furniture! I also like to read outside of work – primarily biographies, but also politics, economics and history.

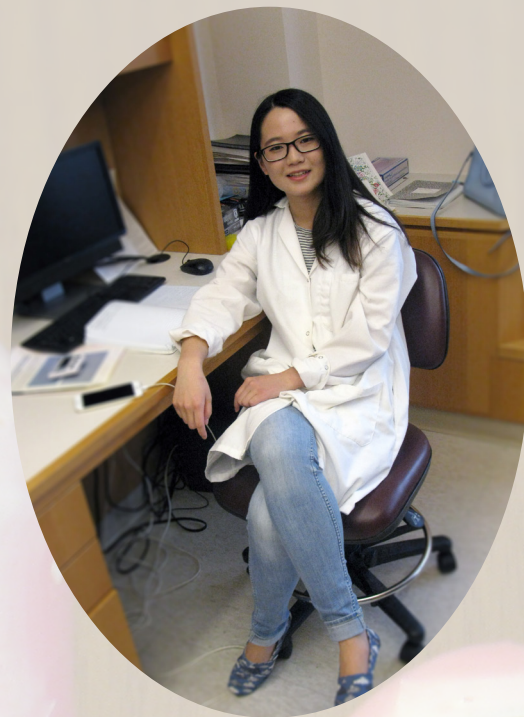


WANDI ZHU

PH.D. CANDIDATE

AMERICAN HEART PRE-DOCTORAL FELLOW
DEPARTMENT OF BIOMEDICAL ENGINEERING
JONATHAN SILVA LABORATORY

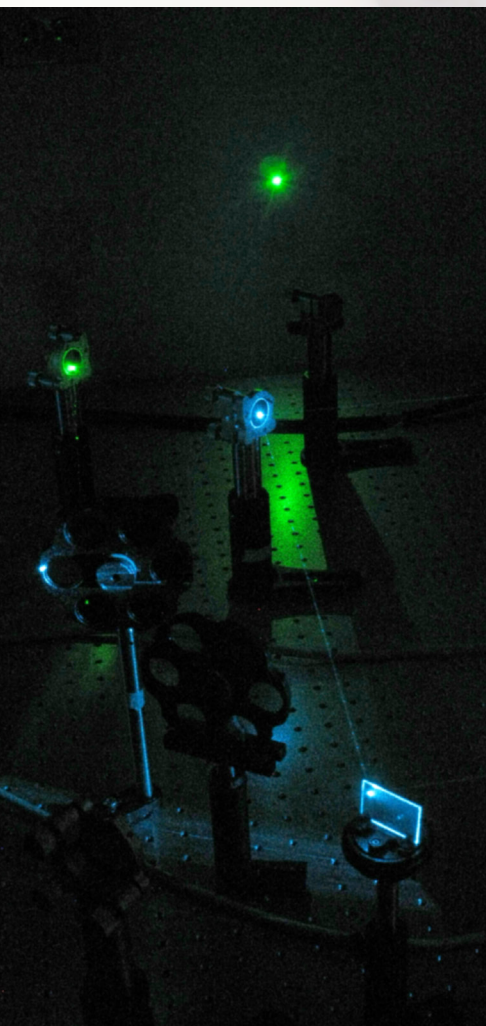
NAV CHANNELS



“When I came to visit here, I felt there was a very collaborative and friendly environment, in particular the focused research centers...”

I am a third year Ph.D. student in Dr. Jonathan Silva’s lab. I am currently working on understanding the post-translational modulation mechanism of cardiac NaV channels. NaV channels, being essential for maintaining regular cardiac function, have been well characterized. However, recent studies revealed that the system is more complex than what we understood, as many accessory proteins form a macromolecular complex with the NaV channel, altering channel gating and pharmacology. We use a technique called voltage clamp fluorometry to probe how the accessory proteins, in particular NaV β subunits, alter the channel conformational changes during gating. I am also working on developing the patch clamp fluorometry technique, to track the milliseconds channel conformational changes in mammalian cells, which can eventually be used to correlate channel molecular motions to cellular action potential of cardiac iPS cells.

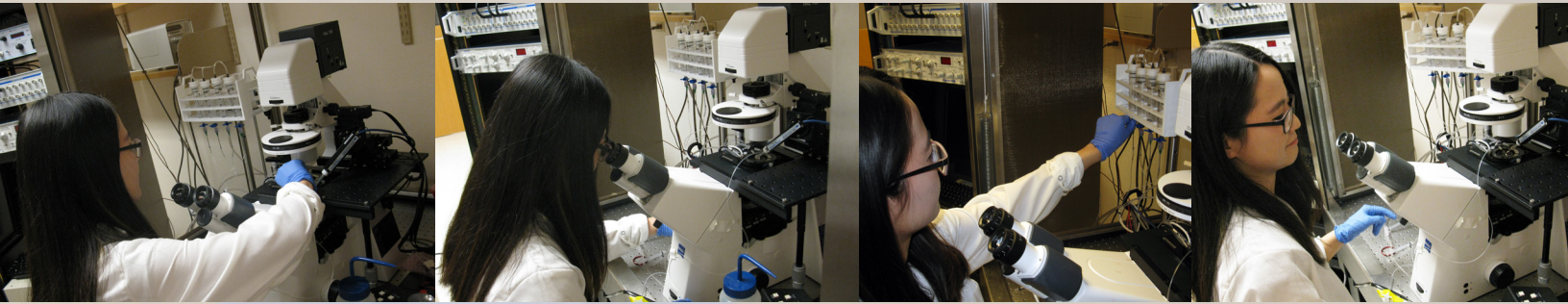
I grew up in a family where no one works in the science field. My mom is an editor and my dad is a judge. My mom has always wanted to me to pursue a career in literature. She bought me many books to read and taught me to write when I was a kid. Despite her efforts, I never got interested in literature, instead, I always loved all of my science classes, especially lab classes, so I thought it would be nice to do a job related to that. My parents were very understanding and supportive of the choices



Total Internal Reflection Fluorescence (TIRF) Microscope

CBAC PH.D. STUDENT

SPOTLIGHT



I made. They also supported me going to college in the States.

Since physics and biology were my favorite subjects in high school, I knew immediately that biomedical engineering was the right major for me. During my undergraduate years at Stony Brook University, I worked in Dr. Emilia Entcheva's lab working on optogenetics for cardiac applications, such as pacemaking and defibrillation. I also did a research fellowship at SUNY Upstate Medical University, where I worked in Dr. Patricia Kane's lab in the Department of Biochemistry and Molecular Biology doing studies of V-ATPase structure and regulation. From my undergraduate research experiences, I realized that both molecular and cardiac engineering are intriguing to me.

I heard of Washington University from a post-doctoral student in my undergraduate research lab, who graduated from the BME program here. I learned that Wash. U. has a very strong cardiac research program that focuses on many different aspects. When I came to visit here, I felt there was a very collaborative and friendly environment, in particular the focused research centers, such as the CBAC. Dr. Silva's research topics are very interesting to me, because it is a merge of two interests, where I get to study molecular protein kinetics, and associate them with the physiology of the heart. After rotating in Dr. Silva's lab, I decided to stay, because he is an incredible mentor who inspires ideas, and gives a lot of guidance and freedom to do the research projects I am interested in.

I guess the most exciting part of my research is that we can get a lot of clinical insights from the basic

research we do. For example, I started my current project trying to understand the NaV β subunits regulation mechanisms of the NaV channels, which later on leads to the findings of β subunits' differential modification of the channel responses to anti-arrhythmics, which potentially underlies the heart chamber and patient specific responses to different anti-arrhythmics.

I think St. Louis is a city that you slowly grow to like. It is not the nicest city, but it has great history and culture. I learned that ooey gooey butter cake was actually invented by accident, but it is one of the best thing ever.

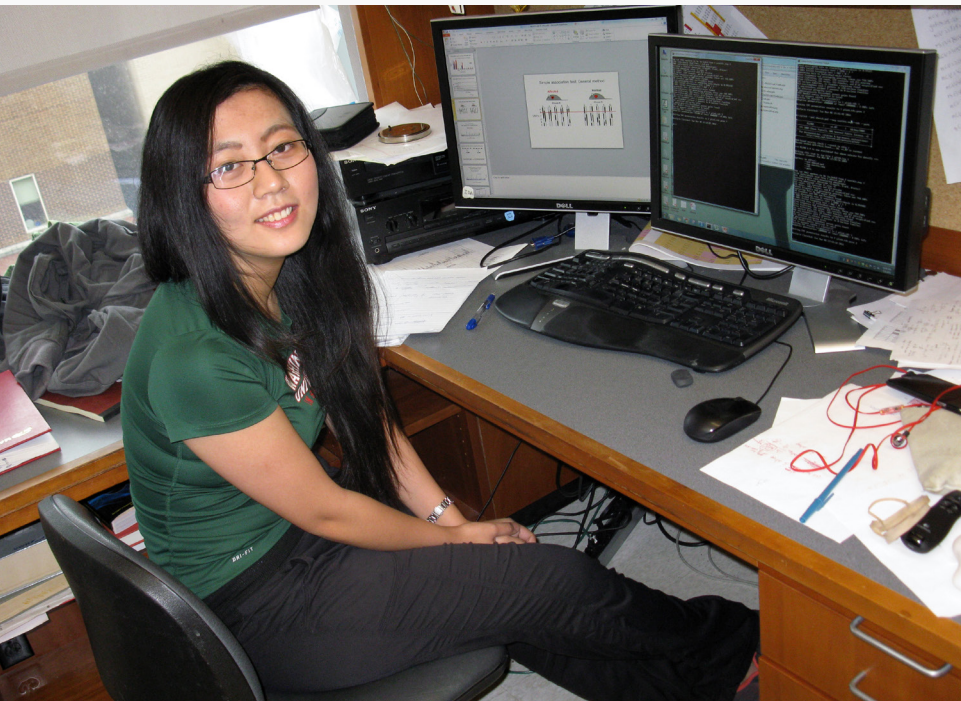
My biggest personal achievement is adopting my sweet dog Rizzo, who has given me a lot of love and support, especially on frustrating days.

I look forward to publishing my work on NaV β subunits, and to continue exploring different directions and possibilities that this project may open.

I love painting, pottery, or anything related to art. I also enjoying outdoor activities, such as hiking - thanks to the mystery Christmas gift "Best Hikes Near St. Louis" I received in the BME holiday party. CBAC is a great place that bring the cardiac community together from clinical, engineering, and biophysics fields. I learned so much from attending the CBAC seminars, probably more than any conference I have ever went to. One of my main project ideas was actually inspired by a CBAC talk. Being part of CBAC, I feel like we have a lot more resources for research and opportunities for collaboration.

CBAC STUDENT

SPOTLIGHT



YIDAN IDA QIN

BIOMEDICAL ENGINEERING, B.S.
MAGNA CUM LAUDE
DEPARTMENT OF BIOMEDICAL
ENGINEERING
PATRICK JAY LABORATORY

GENETIC BASIS OF CONGENITAL HEART DEFECTS

I joined Dr. Patrick Jay's lab in September 2014, two weeks after I transferred to Washington University from China. Since then, I have been working in the Jay lab for one and a half years. My current research focus is the genetic basis of the co-occurrence patterns observed among various congenital heart defects and pleiotropic modifier genes that are associated with multiple congenital heart defects.

At the age of fifteen, I was admitted to the Special Class of Gifted Youth in Xi'an Jiaotong University (XJTU), one of the nine most premier universities in China. I started working as an undergraduate research assistant in the Bio-Inspired Engineering and Biomechanics Center in XJTU, where I first learned the beauty of biomedical engineering research. I gained basic knowledge about biomechanics and bio-inspired materials. Moreover, I acquired necessary skills for researchers, including a systematic mind for designing experiments and data analysis skills, etc.

Although my first research position was in the field of biomechanics, I have been interested in genetic research since I was a freshman in XJTU. Genetic research requires a strong mathematical background, programming skills and most importantly, a solid understanding of the biological mechanisms behind gene transmissions and genotype expressions. Since there is no lab in XJTU that carries out genetic research, I trained myself in math and programming, hoping that I can join a genetic lab in the future.

Before I traveled to the U.S., I researched labs that studied genetics at Washington University. I was very interested in Professor Patrick Jay's research focus about the genetic factors that affect the risk of developing a heart defect. I read recent papers by the Jay lab and found my skill set to be suitable for this lab: statistical analysis and programming. Professor Jay is a great physician-scientist with abundant accomplishments, published papers, and successful trainees. I believed that his mentorship would help me grow as a researcher.

Congenital heart defects still affect a lot of newborns. While surgeries help fix most heart defects, these patients may not live normal lives, most require constant medical attention throughout their lives. The research in the Jay lab aims at preventing these defects from developing. What I am most passionate about is the fact that the research we are doing is making a difference. The goal I hope to accomplish, and what I am working on now, is to contribute to the understanding of how congenital heart defects developed so that preventive strategies can be designed against these defects.

Since the genetic basis of congenital heart defects is complex, it requires a large sample population to discover an association between genes and the development of congenital heart defects. Studying the gene transmission from parents to offspring is a widely-used genetic analysis method. This method, however, requires genotype data of parents, which was not collected. I developed an algorithm that deduces parental genotype data using offspring genotype and pedigree data. This algorithm can achieve a 92% deduction accuracy. I am also cooperating with a venture company in St. Louis about the commercialization of this algorithm's application in plant genetics.

By far, the most important personal achievement of mine would be to graduate from college at the age of nineteen. After graduation, I will be applying to MD-PhD programs this year. I hope to be accepted to an MD-PhD program (at Washington University, hopefully) and continue my research in graduate school.

CBAC faculty members study cardiovascular diseases from multiple perspectives: genetics, ion channels, imaging and modeling, etc. The diversity in CBAC helps me understand cardiovascular diseases in a more systematical way. I have worked under the supervision of two CBAC faculty members: Professors Jay and Silva. Their knowledge and attitudes toward research deeply influenced me.

“What I am most passionate about is the fact that the research we are doing is making a difference.”





NEWS & ANNOUN

CONGRATULATIONS TO..



Congratulations to the CBAC faculty that have been placed on the Best Doctors List in America for 2015. Best Doctors in America uses peer-to-peer surveys to identify specialists considered by fellow physicians to be the most skilled in their fields and most qualified for reviewing and treating complex medical conditions. This list is also published every August by St Louis Magazine. Link: <https://www.stlmag.com/health/Best-Doctors-2015>

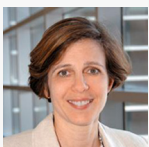
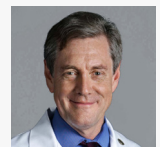
2015: St. Louis Magazine “Best Doctors in America” List (August 2015):

Phillip S. Cuculich, MD - Cardiovascular Division
Sanjeev Bhalla, MD – Radiology
Daniel H. Cooper, MD – Cardiovascular Division
Ralph J. Damiano Jr, MD - Thoracic Surgery
Mitchell N. Faddis, MD, PhD - Cardiovascular Division
Douglas Mann, MD - Cardiovascular Division

Clifford G. Robinson, MD - Radiation Oncology
Gautam K. Singh, MD - Pediatrics
Timothy W. Smith, D Phil, MD - Cardiovascular Division
George F Van Hare III, MD - Pediatric Cardiology
Pamela K. Woodard, MD - Radiology

The American College of Cardiology has named CBAC faculty member **Douglas Mann**, MD the first editor-in-chief of its newest journal, JACC: Basic Translational Research. A monthly, open-access publication, the new journal launched its inaugural issue in December 2015.

Link: <https://source.wustl.edu/2015/08/mann-named-editorinchief-of-new-cardiology-journal/>



On February 17, 2016, **Jean E. Schaffer**, MD, received the Washington University in St. Louis' Distinguished Investigator Award for her contributions in advancing the understanding of cardiovascular pathophysiology in metabolic disease. She was nominated by her peers to recognize her achievements in clinical care, community service, research and teaching.

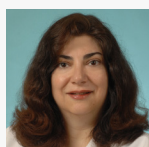
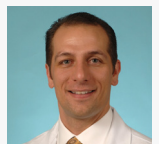
Link: <https://medicine.wustl.edu/news/distinguished-faculty-goldstein-honors-awarded/>

Jianmin Cui, PhD and two other faculty members, Daniel Moran, PhD and Rohit Pappu, PhD were inducted to the College of Fellows of the American Institute for Medical and Biological Engineering (AIMBE) on April 4, 2016 in Washington, D.C. The AIMBE represents the top two percent of medical and biological engineers in the country. Link: <https://engineering.wustl.edu/news/Pages/Three-biomedical-engineering-professors-elected-as-AIMBE-Fellows-.aspx>



Richard Gross, MD, PhD was awarded the Solomon A. Berson Medical Alumni Achievement Award in Basic Science from the New York University School of Medicine on April 16, 2016. The Solomon A. Berson Medical Alumni Achievement Award in Basic Science is awarded to a graduate of the NYU School of Medicine who has distinguished himself or herself by major accomplishments in fundamental scientific research. Link: <http://www.med.nyu.edu/school/alumni/achievement/solomon-berson-medical-alumni-achievement-award/past-honorees>

Phillip Cuculich, MD, was promoted to Associate Professor of Medicine effective July 2016.

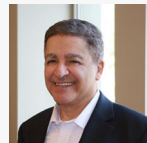


Pamela Woodard, MD, FACR, FAHA, FCCP was awarded the Distinguished Investigator Award, given by the Academy of Radiology Research in 2015 and named to the Council of Distinguished Investigators of the Academy. In November 2016, Woodard will also receive the American Heart Association (AHA) Charles T. Dotter Award, and will give the Charles T. Dotter Memorial Lecture at the American Heart Association Scientific Sessions in November 2016, New Orleans, LA – title “Precision plaque imaging: Are we there yet?”

ACCEMMENTS (JULY 2015- JULY 2016)

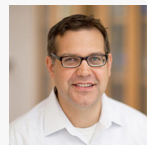
IN THE NEWS

Arye Nehorai, PhD, the Eugene and Martha Lohman Professor of Electrical Engineering, The Preston M. Green Department of Electrical & Systems Engineering, and his team have developed the first 3-D multiscale mathematical model of the electrophysiology of a woman's uterus contractions as they begin from a single cell to the myometrium, or uterine tissue, into the uterus. Link: <https://source.wustl.edu/2016/05/researchers-create-first-mathematical-model-uterine-contractions/>



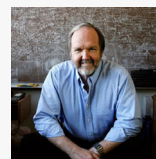
Medtronic acquired Cardiolinsight Technologies, developer of a clinical noninvasive imaging system, called ECGI, for noninvasive mapping of the electrical activity of the heart and cardiac arrhythmias. ECGI was developed in Professor **Yoram Rudy's** laboratory with support from the NIH – National Heart, Lung and Blood Institute. Link: <https://www.radcliffcardiology.com/gallery/new-insights-mechanisms-human-cardiac-arrhythmias-interview-yoram-rudy>

Jonathan Silva, PhD, Assistant Professor, Department of Biomedical Engineering received a two-year, \$154,000 grant from the American Heart Association to take a close look at the changes at the molecular level in the heart that are behind the Brugada Syndrome - a genetic mutation behind the second-leading cause of death in Southeast Asian males under age 40. Link: <https://engineering.wustl.edu/news/Pages/Heart-of-the-matter-Silva-studying-genetic-mutations.aspx>



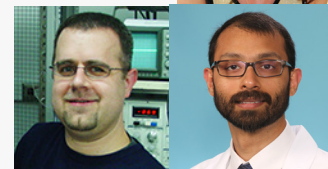
NEW POSITIONS

Martin Arthur, PhD, Newton R. and Sarah Louisa Glasgow Wilson Professor of Engineering as of July 2016, is now Interim Department Chair of The Preston M. Green Department of Electrical & Systems Engineering, succeeding Arye Nehorai.



Happy one year anniversaries to:

- **Maria S. Remedi**, PhD, Assistant Professor of Medicine and Cell Biology & Physiology, Department of Medicine;
- **Amit Noheria**, MBBS, SM, Assistant Professor of Medicine, Department of Medicine in the Cardiovascular Division and
- **Scott Marrus**, MD, PhD, Research Assistant Professor., Department of Electrical and Systems.

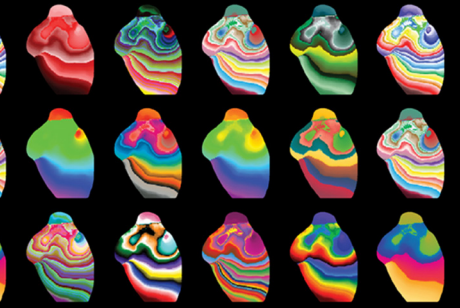


NOTABLES

Amit Noheria, MBBS, SM won 2nd Prize, Jeopardy at Heart Rhythm Society's ABIM Clinical Cardiac Electrophysiology Board Review Course, Chicago, IL. on August 19, 2015.

Wandi Zhu, PhD student in Jonathan Silva's lab, won the best poster award at the Washington University School of Medicine's Cardiovascular Research Day on Friday, October 23, 2015. Her poster title was, "How mutations to the Nav β 1 and β 3 subunits cause Atrial Fibrillation and alter the Nav1.5 responses to anti-arrhythmics. **Jonathan Silva**, PhD received the award for Best Translational Poster at the annual Joseph "Bo" Koster Memorial Symposium hosted by the Center for the Investigation of Membrane Excitability Diseases (CIMED), Washington University in St. Louis on May 25, 2016.

Charu Ramanathan, PhD, alumna of Yoram Rudy's lab, inducted into Medtronic Inc.'s Bakken Society on August 25, 2016.



PUBLICATIONS

JULY 2015 - JULY 2016

R. MARTIN ARTHUR, Ph.D.

Arthur RM, Zhao W. System for 2D Ultrasonic Temperature Imaging (TI) based on the change in backscattered energy in real-time with or without motion compensation. *Ultrasonic Imaging*, October 2015; vol. 37(4), pp. NP15, 2015.

C. WILLIAM BALKE, M.D.

Lindman BR, Tong CW, Carlson DE, Balke CW, Jackson EA, Madhur MS, Barac A, Abdalla M, Brittain EL, Desai N, Kates AM, Freeman AM, Mann DL. National Institutes of Health Career Development Awards for Cardiovascular Physician-Scientists: Recent Trends and Strategies for Success. *J Am Coll Cardiol*. 2015 Oct 20;66(16):1816-27. Review. PMID: 26483107, PMCID: 4615587

PHILIP V. BAYLY, Ph.D.

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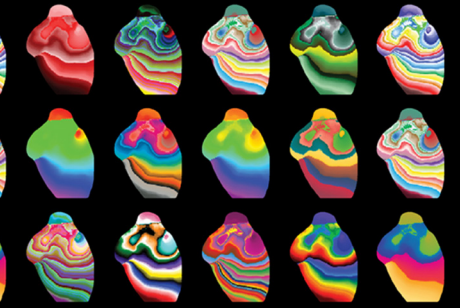
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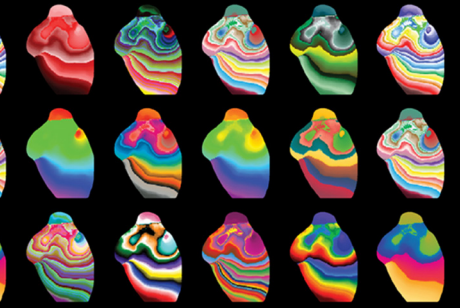
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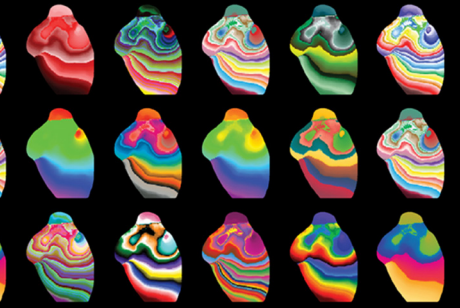
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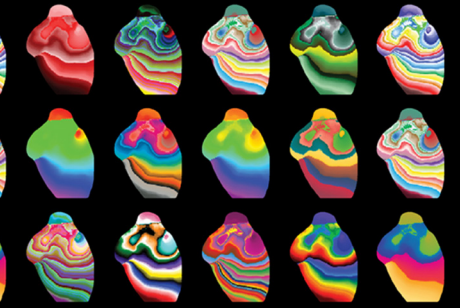
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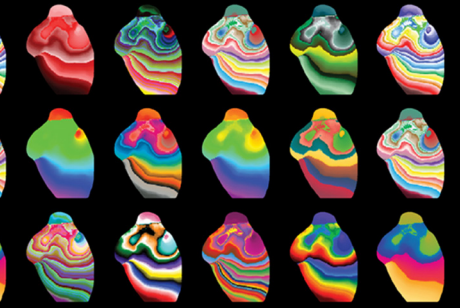
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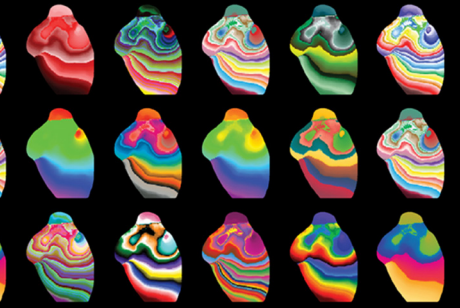
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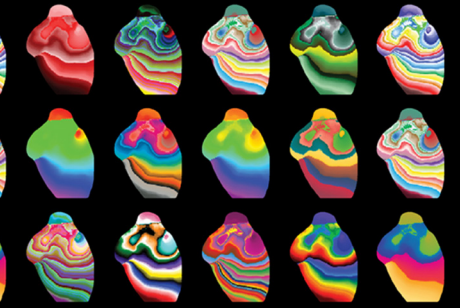
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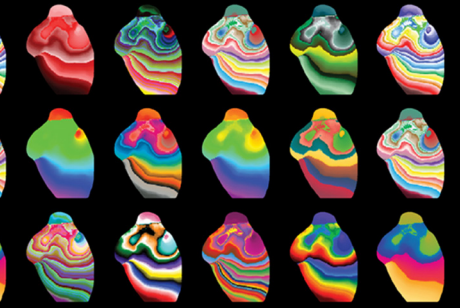
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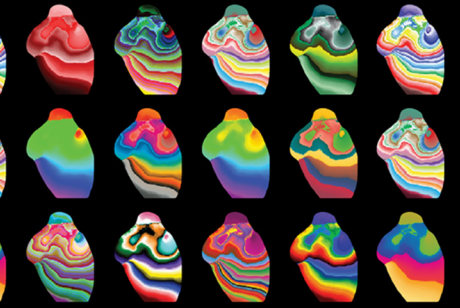
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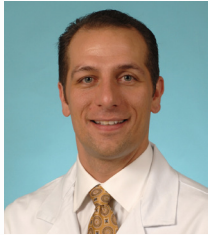
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LECTURES & PRESENTATIONS

JULY 2015 - JUNE 2016



PHILLIP S. CUCULICH, M.D.

- 2015 Cuculich MD. Cardiology Review for Primary Care, Montego Bay, Jamaica.
- 2015 Cuculich MD. "Left Atrial Appendage Closure." Advanced Revascularization Chapter VIII (ARCH VIII), St. Louis, MO.
- 2015 Cuculich MD. "Preventing Sudden Cardiac Death & Treating Ventricular Tachycardia." Cox Health Heart & Vascular Summit, Branson, MO.
- 2015 Cuculich MD. "Substrates and Mechanisms of Ventricular Arrhythmias: Lessons from Noninvasive Mapping with ECGI." Cardiac Bioelectricity & Arrhythmia Center (CBAC) 10th Anniversary Symposium, Washington University, St. Louis, MO (August).
- 2015 Cuculich MD. Cardiology Review for Primary Care, San Francisco, CA.
- 2016 Cuculich MD. "Controversies in Atrial Fibrillation." Session Chair, American College of Cardiology Scientific Sessions, Chicago, IL
- 2016 Cuculich MD. "Three-Dimensional Electrophysiology of the Uterus: Early Electrical Maturation in the Etiology of Preterm Birth." March of Dimes/Washington University Prematurity Think Tank, Washington University, St. Louis, MO.
- 2016 Cuculich MD. Cardiology Review for Primary Care, Orlando, FL.
- 2016 Cuculich MD. "Novel Imaging Technologies to Study Preterm Birth." Pediatric Academic Societies, Baltimore, MD.
- 2016 Cuculich MD. "Firing Solutions: Combining Noninvasive Electrical Mapping to Guide Noninvasive Cardiac Ablation." Stanford BioDesign in Electrophysiology Symposium, Palo Alto, CA.
- 2016 Cuculich MD. "How to Become a Cardiovascular Investigator." Heart Rhythm Society Scientific Sessions, San Francisco, CA (May).
- 2016 Cuculich MD. "First Report of Entirely Noninvasive Cardiac Radioablation for VT in Humans (ENCoRe-VT Pilot)." Heart Rhythm Society Scientific Sessions, San Francisco, CA (May).



RALPH J. DAMIANO, J.R., M.D.

- 2015 Damiano, J.R., M.D. "Surgical Ablation for AF: Technique, Indications and Results." Samsung Medical Center International Symposium: Arrhythmia 2015. Seoul, South Korea (October).
- 2015 Damiano, J.R., M.D. "How I Do It: Minimally Invasive Cox-Maze IV Procedure." Samsung Medical Center International Symposium: Arrhythmia 2015. Seoul, South Korea (October).
- 2015 Damiano, J.R., M.D. "Surgical ablation for AF: Techniques, Indications, and Results." Persistent AF Think Tank 2015. Orlando, FL (November).
- 2015 Damiano, J.R., M.D. "New Approaches to Surgical Management of HCM. Management of Hypertrophic Cardiomyopathy for the Clinical Cardiologist." Orlando, FL (November).
- 2015 Damiano, J.R., M.D. "The Surgical Treatment of Persistent AF: Current Controversies." ISMICS Winter Workshop. Istanbul, Turkey (December).



LECTURES & PRESENTATIONS

JULY 2015 - JUNE 2016



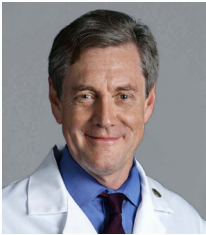
RALPH J. DAMIANO, J.R., M.D. (Con't.)

- 2016 Damiano, J.R., M.D. "Maze Surgery in 2016: Why, When and How. Meet the Expert." Ramathibodi Hospital. Bangkok, Thailand (January).
- 2016 Damiano, J.R., M.D. "MIS Cox Maze IV." CCIT-Rama Joint Live Case Session. Central Chest Institute of Thailand. Bangkok, Thailand (January).
- 2016 Damiano, J.R., M.D. "Evaluation of Surgery: Update of Current Advances." The Society of Thoracic Surgeons of Thailand. 30th Annual Meeting 2016. Bangkok, Thailand (January).
- 2016 Damiano, J.R., M.D. "The Ultimate AF Approach." Valvular & AF Surgery. The Society of Thoracic Surgeons of Thailand. 30th Annual Meeting 2016. Bangkok, Thailand (January).
- 2016 Damiano, J.R., M.D. "Surgical Therapy of Atrial Fibrillation." 2016 Miami Cardiac & Vascular Institute Cardiovascular Summit. Baptist Health South Florida. Miami, FL (February).
- 2016 Damiano, J.R., M.D. "Minimally Invasive Valve Surgery." 2016 Miami Cardiac & Vascular Institute Cardiovascular Summit. Baptist Health South Florida. Miami, FL (February).
- 2016 Damiano, J.R., M.D. "Prophylactic surgical AF ablation feasible in high risk patients?" Ninth Annual Western Atrial Fibrillation Conference. Park City, UT (February).
- 2016 Damiano, J.R., M.D. "Surgical Maze: What Lesion Sets? What Outcomes?" The Heart Valve Society. New York, NY (March).
- 2016 Damiano, J.R., M.D. "Minimally Invasive Valve Surgery." Grand Rounds. Blessing Hospital. Quincy, IL (March).
- 2016 Damiano, J.R., M.D. "Structural Session; Live Case: Transcatheter Valve Replacement." Moderator. Advanced Revascularization – Chapter IX Symposium. Saint Louis, MO (April).
- 2016 Damiano, J.R., M.D. "Surgical Approach to Left Atrial Appendage Ligation." Left Atrial Appendage Exclusion Conference. Stritch School of Medicine, Loyola University. Maywood, IL (April).
- 2016 Damiano, J.R., M.D. "Advances in Surgical Ablation for Atrial Fibrillation." Stanford Biodesign Retreat. Stanford University School of Medicine, Stanford, CA (May).
- 2016 Damiano, J.R., M.D. "Role of Clinical Research in Atrial Fibrillation Programs." Featured Symposium – Patient-Centered Atrial Fibrillation Care. Heart Rhythm Society. San Francisco, CA (May).



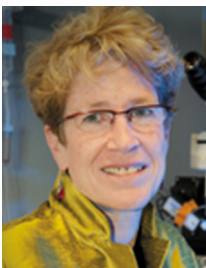
RICHARD W. GROSS, M.D., Ph.D.

- 2016 Gross, M.D., Ph.D., "Membrane-mediated Alterations in Diabetic Cardiomyopathy." CME presentation. New York University School of Medicine, New York, NY (April).
- 2016 Gross, M.D., Ph.D., "Adventures in Shotgun Lipidomics and the Chemical Biology of Diabetes." Medical University of South Carolina, Charleston, SC (April).



DOUGLAS L. MANN, M.D.

- 2015 Mann, M.D. "The Role of Innate Immunity in Cardiac Injury and Repair" The Methodist Research Institute, Houston, TX (July).
- 2015 Mann, M.D. "The Role of Innate Immunity in Cardiac Injury and Repair," 6th Cardiovascular Symposium on Cardiovascular Regeneration, National Institutes of Health, Bethesda, MD (September).
- 2015 Mann, M.D. "Macrophages and Myocardial Injury," University of Alabama Symposium on Inflammation and Cardiovascular Disease, Birmingham, AL (August).
- 2015 Mann, M.D. "Load, Unloading, Remodeling and Recovery." Moderator and Discussant. Scientific Sessions of the Heart Failure Society of America, National Harbor, MD (September).
- 2016 Mann, M.D. "The Role of Innate Immunity in Cardiac Injury and Repair," Special Seminar, Rikshospitalet, Oslo, Norway (February).
- 2016 Mann, M.D. "Precision Medicine Intensive." ACC Co-Chair. ACC:16 Scientific Sessions, Chicago, IL (April).



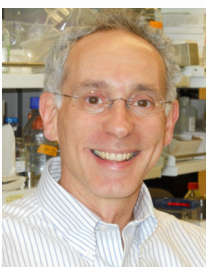
JEANNE N. NERBONNE, Ph.D.

- 2015 Nerbonne, Ph.D. National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD.
- 2016 Nerbonne, Ph.D. Department of Anatomy and Neurobiology, Washington University Medical School, St. Louis, MO.
- 2016 Nerbonne, Ph.D. Department of Physiology and Pharmacology, University of Iowa, Cedar Rapids, IA.
- 2016 Nerbonne, Ph.D. "Cardiac K⁺ channel regulation: functional studies." Fourth UC Davis Cardiovascular Symposium: Systems Approach to Understand Cardiac E-C Coupling and Arrhythmias – K⁺ Channels and Regulation, University of California at Davis, Davis, CA (March).
- 2016 Nerbonne, Ph.D. "Electrical remodeling in the failing heart." Second Sudden Cardiac Death Symposium, Bern, Switzerland (October).



COLIN G. NICHOLS, Ph.D.

- 2016 Nichols, Ph.D. "smFRET Analysis of Ion Channel Dynamics." Ligand Recognition GRC, Il Ciocco, Italy (January).
- 2016 Nichols, Ph.D. "smFRET Analysis of Ion Channel Dynamics." Biophysical Society Symposium (February).
- 2016 Nichols, Ph.D. "Cardiac KATP channels and Cantu Syndrome." C Davis Cardiology symposium (February).



DANIEL S. ORY, Ph.D.

- 2015 Ory, Ph.D. "Histone Deacetylase Inhibitors as NPC1." Therapeutics, National Niemann-Pick Disease Foundation Family Conference, Chicago, IL (August).
- 2015 Ory, Ph.D. "Diagnostic advances with novel biomarkers in NP-C." SSIEM Satellite Symposium, Lyon, France (September).
- 2015 Ory, Ph.D. "New Approaches to Diagnosis and Treatment of Niemann-Pick C: A Neurodegenerative Cholesterol Storage Disorder." Department of Nutrition Science, Purdue University, West Lafayette, IN (October).
- 2015 Ory, Ph.D. "The Future of NP-C: Research and Therapy." 4th NP-C LATAM, Rio de Janeiro, Brazil (October).
- 2015 Ory, Ph.D. "Development of a newborn screen for Niemann-Pick C." Fundacion Niemann-Pick de Espana, Talavera de la Reina, Spain (November).



LECTURES & PRESENTATIONS

JULY 2015 - JUNE 2016



DANIEL S. ORY, Ph.D. (Con.'t)

- 2015 Ory, Ph.D. "Snow in the Forecast: Noncoding RNA Regulation of Cholesterol Homeostasis." Cardiovascular Medicine Grand Rounds, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH (December).
- 2016 Ory, Ph.D. "Bile acid biomarkers for NP-C." 8th Scientific Symposium on Niemann-Pick Type C (NP-C), Budapest, Hungary (March).
- 2016 Ory, Ph.D. "Regulation of cholesterol trafficking by snoRNA U17." Bortree Seminar Series, Penn State University, University Park, PA (April).
- 2016 Ory, Ph.D. "Measurement of bile-acids as new marker for NPC." Session Chair, Workshop on Biomarkers for Niemann-Pick C Disease, Rome, Italy (May).
- 2016 Ory, Ph.D. "Biomarkers for NPC diagnosis and clinical trial endpoints." 2016 Parseghian Scientific Conference for Niemann-Pick Type C Research, Tucson, AZ (June).
- 2016 Ory, Ph.D. "Regulation of cholesterol trafficking by snoRNA U17." 2016 Lipoprotein Metabolism Gordon Research Conference, Waterville Valley, NH (July).

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



- 2015 Rentschler, M.D., Ph.D. "Programming and Reprogramming Cardiac Conduction." University of Washington, Center for Cardiovascular Biology Distinguished Lecture Series, Seattle, WA (December).
- 2016 Rentschler, M.D., Ph.D. University of Michigan, Center for Organogenesis, Ann Arbor, MI.
- 2016 Rentschler, M.D., Ph.D. Brown University, Electrophysiology Grand Rounds and Cardiovascular Research Institute, Providence, RI.
- 2016 Rentschler, M.D., Ph.D. "Human Pluripotent Stem Cells as Models of Cardiovascular Disease." Session Chair. Keystone Symposia on Molecular and Cellular Biology, Cardiac Development, Regeneration and Repair (Z2), Snowbird, UT (April).

CLIFFORD ROBINSON, M.D.



- 2015 Robinson, M.D. "PET for Esophageal Cancer." Nuclear Medicine Residents Conference, Washington University in St. Louis, St. Louis, MO (August).
- 2015 Robinson, M.D. "Clinical Implementation of MR-IGRT for Stereotactic Body Radiotherapy." Continuing Medical Education (CME), Webinar for The Radiosurgery Society (August).
- 2015 Robinson, M.D. "Radiation for Spine Metastases." Continuing Medical Education (CME), Marilyn Fixman Conference, Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO (September).
- 2015 Robinson, M.D. "SBRT for early stage NSCLC." Continuing Medical Education (CME), Updates on Evaluation and Management of the Pulmonary Nodule and Peripheral Bronchoscopy, Washington University in St. Louis, St. Louis, MO (October).
- 2015 Robinson, M.D. "Thoracic Oncology highlights from ASCO 2015 and WCLC 2015." Continuing Medical Education (CME), Webinar, IASLC (October).
- 2015 Robinson, M.D. "Advanced Treatment of Non Small Cell Lung Cancer: Novel Imaging." Continuing Medical Education (CME), Advanced Treatment of NSCLC: Using all the tools, ASTRO Annual Meeting, San Antonio, TX (October).

CLIFFORD ROBINSON, M.D. (Con.'t)

- 2015 Robinson, M.D. "Adaptive Therapy/Retreatment for Lung Cancer." Continuing Medical Education (CME), Clinical Commissioning and Workflow for Adaptive Therapy, ASTRO Annual Meeting, San Antonio, TX (October).
- 2015 Robinson, M.D. Continuing Medical Education (CME), Cape lung symposium, Cape Town, South Africa (December).
- 2015 Robinson, M.D. "Updates in radiation for brain metastases." Continuing Medical Education (CME), Neurosurgery Grand Rounds, Washington University in St. Louis, St. Louis, MO (April).

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



- 2015 Rudy, Y. "Noninvasive Imaging of Cardiac Electrophysiology and Arrhythmias in the Intact Human Heart." The Astor Lecture, University of Oxford, United Kingdom (September).
- 2015 Rudy, Y. "Theoretical Concepts in Cardiac Conduction." Department of Computer Science, University of Oxford, United Kingdom (September).
- 2015 Rudy, Y. "New insights in mechanisms of human cardiac arrhythmias gained by non-invasive mapping." Top Ten in Cardiology, an International Cardiology Meeting, Lausanne, Switzerland (October).
- 2015 Rudy, Y. "Noninvasive ECG Imaging (ECGI) to Identify VT Substrate." University of Pennsylvania School of Medicine, 10th International Symposium on Ventricular Arrhythmias: Pathophysiology and Therapy, Philadelphia, PA (October).
- 2015 Rudy, Y. "Substrates and Mechanisms of Cardiac Arrhythmias: Insights from Noninvasive Mapping in Patients." Washington University Center for Cardiovascular Research, St Louis, MO (December).
- 2016 Rudy, Y. "Noninvasive Imaging of Cardiac Electrophysiology and Arrhythmias." Keynote Presentation. Israel Society for Medical and Biological Engineering Annual Meeting, Israel (February).
- 2016 Rudy, Y. "New Developments in Noninvasive Mapping with ECG Imaging (ECGI) Selected Examples of Applications." The 13th International Dead Sea Symposium on Innovations in Cardiac Arrhythmias and Device Therapy, Tel Aviv, Israel (March).
- 2016 Rudy, Y. "Cardiac Electrophysiological Substrate Underlying the ECG Phenotype and Electrogram Abnormalities in J wave Syndrome Patients." The 13th International Dead Sea Symposium on Innovations in Cardiac Arrhythmias and Device Therapy, Tel Aviv, Israel (March).
- 2016 Rudy, Y. "Noninvasive ECG Imaging of Ventricular Arrhythmogenic Substrate." The 13th International Dead Sea Symposium on Innovations in Cardiac Arrhythmias and Device Therapy, Tel Aviv, Israel (March).
- 2016 Rudy, Y. "The Inverse Solution: How is it measured, limitations, and spatial resolution." Heart Rhythm Society 37th Scientific Sessions, San Francisco (May).
- 2016 Rudy, Y. "Multi-scale modeling and imaging cardiac electrophysiology: A potential approach for drug development and evaluation." Keynote Presentation. Sanofi – Mount Sinai Systems Pharmacology Symposium. New York, NY, June 2016.



JEAN E. SCHAFFER, M.D.

- 2015 Schaffer, J. Keynote Speaker, Society for Heart and Vascular Metabolism, Tarrytown, NY, September (September).



LECTURES & PRESENTATIONS

JULY 2015 - JUNE 2016



JEAN E. SCHAFFER, M.D. (Con.'t)

- 2015 Schaffer, J. Indiana University Diabetes Research Center, Indianapolis, IN (October).
- 2016 Schaffer, J. Cardiovascular Medicine Grand Rounds, Harrington Heart and Vascular Institute, Case Western Reserve University, Cleveland, OH (April).
- 2016 Schaffer, J. Diabetes Journal Symposium, American Diabetes Association Meeting, New Orleans, LA (June).
- 2016 Schaffer, J. Harrison Visiting Professor, Vanderbilt University, Nashville, TN (June).
- 2016 Schaffer, J. Riboclub Annual Meeting, Magog-Orford, Canada (September).



JONATHAN R. SILVA, Ph.D.

- 2015 Silva, Ph.D. " I_{Na} and I_{NaL} , the Na^+ Currents." Cardiac Bioelectricity and Arrhythmia Center 10th Anniversary Symposium, Washington University in St. Louis, St. Louis, MO (August).



GEORGE F. VAN HARE, M.D.

- 2015 Van Hare, M.D. "Paediatric ablation: atypical AVNRT; JT & atypical 'Mahaim'." Asia Pacific Heart Rhythm Society Scientific Sessions, Melbourne, Australia (November).
- 2015 Van Hare, M.D. "The future of Paediatric EP: Expect the unexpected!" Asia Pacific Heart Rhythm Society Scientific Sessions, Melbourne, Australia (November).
- 2016 Van Hare, M.D. "ECG Pearls." The 13th International Dead Sea Symposium on Innovations in Cardiac Arrhythmias and Device Therapy, Tel Aviv, Israel (March).
- 2016 Van Hare, M.D. "Learning how the heart works by destroying stuff." The 13th International Dead Sea Symposium on Innovations in Cardiac Arrhythmias and Device Therapy, Tel Aviv, Israel (March).
- 2016 Van Hare, M.D. "ECG Screening in Young Patients: Health Policy, Cost Effectiveness and Bayesian Considerations." The 13th International Dead Sea Symposium on Innovations in Cardiac Arrhythmias and Device Therapy, Tel Aviv, Israel (March).
- 2016 Van Hare, M.D. "Long QT Syndrome: ECG screening should be NOT performed in infancy and early childhood." 12th Annual Congress of the European Cardiac Arrhythmia Society (ECAS), Paris, France (April).



PAMELA K. WOODARD, M.D., F.A.C.R., F.A.H.A., F.C.C.P.

- 2015 Woodard, M.D., F.A.C.R., F.A.H.A., F.C.C.P. "Receptor Targeted Molecular Imaging of Atherosclerosis." New York University, New York, NY (July).
- 2015 Woodard, M.D., F.A.C.R., F.A.H.A., F.C.C.P. "Coding and Billing in Cardiovascular CT and MRI: Update – 2015." North American Society for Cardiovascular Imaging (NASCI), San Diego, CA, (September).
- 2016 Woodard, M.D., F.A.C.R., F.A.H.A., F.C.C.P. "Cardiovascular PET-MRI." Massachusetts General Hospital, Boston, MA (March).
- 2016 Woodard, M.D., F.A.C.R., F.A.H.A., F.C.C.P. "Pursuing research in an academic setting: Personal reflections." American college of Radiology Annual Meeting, Marriott Wardman Park, Washington, DC (May).



Mon. 10/31

Héctor H. Valdivia, M.D., Ph.D. - Frank N. Wilson Professor of Cardiovascular Medicine & Professor of Internal Medicine
Professor of Molecular & Integrative Physiology
Co-Director, Center for Arrhythmia Research
University of Michigan



Mon. 11/21

William Catterall, Ph.D. - Chair & Professor
Department of Pharmacology
University of Washington

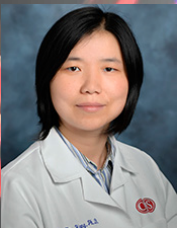


Mon. 11/25

Phillip S. Cuculich, M.D. - Associate Professor
Cardiovascular Division
Washington University in St. Louis School of Medicine



Clifford G. Robinson, M.D. - Associate Professor
Department of Radiation Oncology
Chief of Service, Stereotactic Body Radiation Therapy (SBRT)
Washington University in St. Louis School of Medicine



Mon. 12/5

TingTing Hong M.D., Ph.D. - Assistant Professor of Medicine
Cedars-Sinai Heart Institute
Cedars-Sinai Medical Center
University of California, Los Angeles (UCLA)



Mon. 12/12

Francis E. Marchlinski, M.D. - Richard T. & Angela Clark President's Distinguished Professor & Director of Electrophysiology Laboratory
Hospital of the University of Pennsylvania
Director of Electrophysiology
University of Pennsylvania Health System



Mon. 12/19

Richard Verrier, Ph.D. - Associate Professor of Medicine, Harvard Medical School
Associate Professor, Department of Medicine, Beth Israel Deaconess Medical Center
Harvard University

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

CBAC 2016 FALL SEMINAR SCHEDULE

Mondays @ 4:30 pm
Whitaker Hall
Room 218*

*Unless indicated otherwise.
Refreshments will be Available



 Washington University in St. Louis



NEW CBAC MEMBERS



Amit Noheria, M.B.B.S., S.M.

Assistant Professor of Internal Medicine, Cardiovascular Division
Washington University in St. Louis

Research Interests:

Dr. Noheria's research interests include the improvement and optimization of catheter-based treatments of heart rhythm disorders, specifically, electrophysiologic mapping and ablation techniques for ventricular arrhythmias including premature ventricular beats and ventricular fibrillation. He is interested in epidemiology, treatments and clinical outcomes of heart rhythm disorders in complex heart disease populations like congenital heart disease, heart failure, and patients with mechanical circulatory support.

Education and Training:

- 2006 M.B.B.S., Medical School, All India Institute of Medical Sciences (AIIMS), New Delhi, India
- 2007 S.M., Epidemiology, Harvard School of Public Health, Boston, MA
- 2010 Internship and residency, Internal Medicine, Mayo Clinic, Rochester, MN
- 2013 Fellowship, Cardiovascular Diseases, Cedars-Sinai/VA Medical Center, Los Angeles, CA
- 2015 Fellowship, Cardiac Electrophysiology, Mayo Clinic, Rochester, MN



Clifford G. Robinson, M.D.

Associate Professor
Radiation Oncology
Chief of Service, Stereotactic Body Radiation Therapy (SBRT)
Washington University in St. Louis

Research Interests:

Dr. Robinson's research interests include optimizing dosing and delivery of radiotherapy with or without the addition of biologic modifiers for purposes of tumor control and normal tissue protection. He has written and opened several institutional prospective trials through the Siteman Cancer Center with topics ranging from neuroprotection after cranial radiotherapy, hypofractionated proton radiotherapy for locally-advanced non-small cell lung cancer, and MRI-guided stereotactic radiotherapy for ovarian cancer. Recently, he has collaborated with CBAC member Dr. Phillip Cuculich to explore the use of SBRT for treatment of ventricular tachycardia, and have initiated development of a phase I protocol on the same topic. He is excited to bring his experience in advanced radiotherapy delivery and clinical trial design to the CBAC, and more importantly, to learn from the wealth of experience within the consortium.

Education and Training:

- 2000 B.S., Molecular Biology, University of Pittsburgh, Pittsburgh, PA
- 2004 M.D., Case Western Reserve University School of Medicine, Cleveland, OH
- 2005 Intern, Cleveland Clinic, Departments of Medicine and Surgery
- 2008 Chief Resident, Cleveland Clinic, Department of Radiation Oncology
- 2009 Resident, Cleveland Clinic, Department of Radiation Oncology



Maria S. Remedi, Ph.D.

Assistant Professor of Medicine
and Cell Biology & Physiology
Washington University in St. Louis

Dr. Remedi was born and raised in Argentina. She obtained a dual degree, a M.S. in Biochemistry (equivalent) and a Pharmacist Degree at National University of Cordoba in Argentina. Dr. Remedi obtained a Ph.D. in Chemical Sciences at the same university. As a Ph.D. student, she was awarded with a prestigious fellowship from the Science and Technology Council in Argentina to study metabolic pathways in a parasite that causes Chagas disease. Dr. Remedi then moved to the USA to study Diabetes Mellitus and Congenital Hyperinsulinism with CBAC member Dr. Colin Nichols. During her postdoctoral training, she obtained an American Diabetes Association Minority Fellowship Award to work in the progression of diabetes with former Wash. U. faculty member, Dr. Michael McDaniel. Dr. Remedi joined the Department of Medicine faculty at Washington University in St. Louis in July of 2015.

Research Interests:

Dr. Remedi studies in vivo physiology in various mouse models of diabetes to unravel the underlying mechanisms of pancreatic β -cell failure in glucotoxic stages, and their consequences in both pancreatic and extra-pancreatic tissues. Development of secondary loss of β -cell mass and antidiabetic drug sensitivity in long-standing diabetic patients is not completely understood.

Education and Training:

- 2001 Post-doctoral Fellow, Washington University in St. Louis
- 2001 Post-Doctoral Fellow, Universidad Nacional de Cordoba





CBAC MEMBER DIRECTORY

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

The Fred Saigh Distinguished Professor of Engineering;
 Professor of Biomedical Engineering, Cell Biology &
 Physiology, Medicine, Radiology, and Pediatrics
 Phone: (314) 935-8160
 Websites: rudylab.wustl.edu, cbac.wustl.edu
Email: rudy@wustl.edu

Jianmin Cui, Ph.D.

The Spencer T. Olin Professor of Biomedical Engineering

Email: jcui@wustl.edu

R. Martin Arthur, Ph.D.

Newton R. & Sarah Louisa Glasgow Wilson Professor &
 Interim Chair, Preston M. Green Department of
 Electrical & Systems Engineering; Professor of
 Biomedical Engineering **Email: rma@wustl.edu**

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

Evarts A. Graham Professor of Surgery
 Chief of Cardiothoracic Surgery
Email: damianor@wustl.edu

Philip Bayly, Ph.D.

The Lilyan & E. Lisle Hughes Professor of Mechanical
 Engineering; Chair, Dept. of Mechanical Engineering &
 Materials Science; Professor of Biomedical Engineering
Email: pvb@wustl.edu

Victor G. Davila-Roman, M.D., F.A.C.C. F.A.S.E.

Professor of Medicine, Anesthesiology, Radiology
 Medical Director, Cardiovascular Imaging and Clinical
 Research Core Laboratory
Email: vdavila@wustl.edu

C. William (Bill) Balke, M.D.

Professor of Medicine, Cardiovascular Division
 Chief of Cardiology, St. Louis Veterans Affairs Medical
 Center (VAMC) & Health Care System
Email: bill.balke@wustl.edu

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

Associate Professor of Medicine, Cardiovascular Division
 Director of Electrophysiology
Email: faddism@wustl.edu

Sanjeev Bhalla, M.D.

Prof. of Radiology; Chief, Cardiothoracic Imaging
 Section; Co-Chief, Body Computed Tomography;
 Assist. Radiology Residency Program Director, MIR
Email: sanjeevbhalla@wustl.edu

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

Elvera and William Stuckenburg Professor & Chair
 Department of Biomedical Engineering
Email: scg@wustl.edu

Daniel H. Cooper, M.D.

Assistant Professor of Medicine, Cardiovascular
 Division; Director, Electrophysiology Fellowship
Email: cooperdh@wustl.edu

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

Professor of Medicine & Developmental Biology
 Washington University School of Medicine
 Professor of Chemistry
Email: rgross@wustl.edu

Phillip S. Cuculich, M.D.

Associate Professor of Medicine, Cardiovascular
 Division
Email: pcuculic@wustl.edu

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

Associate Professor of Pediatrics and Genetics
 St. Louis Children's Hospital
Email: jay_p@wustl.edu

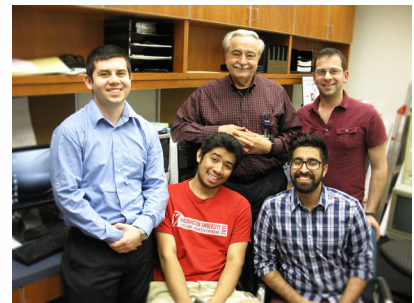
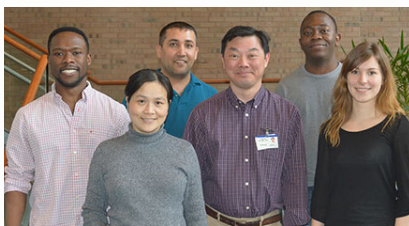
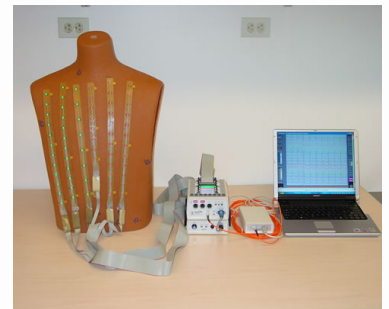
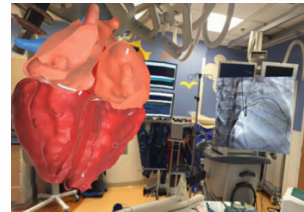
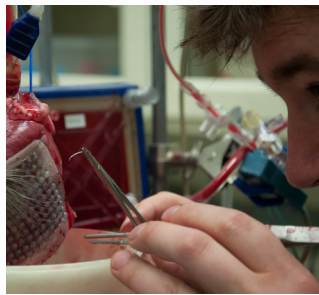
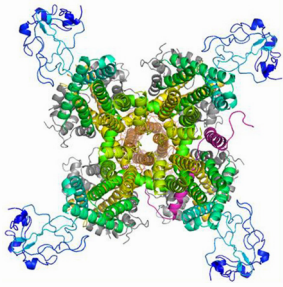
<p>R. Gilbert Jost, M.D. Professor of Radiology Department of Radiology Email: jostg@wustl.edu</p>	<p>Amit Noheria, M.B.B.S., S.M. Assistant Professor of Medicine, Cardiovascular Division; Clinical Cardiac Electrophysiologist, Barnes-Jewish Hospital Email: anoheria@wustl.edu</p>
<p>Sándor J Kovács, M.D., Ph.D. Professor of Medicine, Cell Biology & Physiology Adj. Prof. of Physics & Biomedical Engineering Director & Founder, Cardiovascular Biophysics Laboratory Email: sjk@wustl.edu</p>	<p>Joseph A. O’Sullivan, Ph.D. Samuel C. Sachs Prof. of Electrical Engineering; Prof. of Biomedical Engineering & Radiology; Dean of the UMSL/WUSTL Joint Undergrad. Engineering Program Email: jao@wustl.edu</p>
<p>Douglas L. Mann, M.D. Tobias and Hortense Lewin Professor and Chief, Cardiovascular Division; Cardiologist-in-Chief, Barnes-Jewish Hospital Email: dmann@wustl.edu</p>	<p>Daniel S. Ory, M.D. Alan A. & Edith L. Wolff Distinguished Professor of Medicine, Cell Biology & Physiology; Co-Director, BioMed 21 Diabetic Cardiovascular Disease Center Email: dory@wustl.edu</p>
<p>Scott B. Marrus, M.D., Ph.D. Research Assistant Professor, Preston M. Green Department of Electrical & Systems Engineering Email: smarrus@wustl.edu</p>	<p>Maria S. Remedi, Ph.D. Assistant Professor of Medicine, Endocrinology, Metabolism & Lipid Research Division; Assistant Professor of Cell Biology & Physiology, Department of Cell Biology & Physiology Email: mremedi@wustl.edu</p>
<p>Arye Nehorai, Ph.D. The Eugene & Martha Lohman Professor, Preston M. Green Department of Electrical & Systems Engineering Director, Center for Sensor Signal & Information Processing Email: nehorai@wustl.edu</p>	<p>Stacey L. Rentschler, M.D., Ph.D. Assistant Professor of Medicine & Developmental Biology, Cardiovascular Division Email: stacey.rentschler@wustl.edu</p>
<p>Jeanne M. Nerbonne, Ph.D., F.A.H.A. Alumni Endowed Professor of Molecular Biology & Pharmacology; Director, Center for Cardiovascular Research; Co-Director, Center for the Investigation of Membrane Excitability Diseases; Departments of Developmental Biology & Internal Medicine Email: jnerbonne@wustl.edu</p>	<p>Clifford G. Robinson, M.D. Associate Professor, Radiation Oncology Chief of Service, Stereotactic Body Radiation Therapy (SBRT) Washington University School of Medicine Email: crobinson24@wustl.edu</p>
<p>Colin G. Nichols, Ph.D. Carl Cori Professor Department of Cell Biology & Physiology; Director, Center for the Investigation of Membrane Excitability Diseases Email: cnichols@wustl.edu</p>	<p>Jean E. Schaffer, M.D. Virginia Minnich Distinguished Professor of Medicine Director, Diabetic Cardiovascular Disease Center & Diabetes Research Center Email: jschaff@wustl.edu</p>



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<p>Timothy W. Smith, D.Phil., M.D., F.A.C.C., F.H.R.S. Associate Professor of Medicine, Cardiovascular Division Email: tsmith@wustl.edu</p>																							
<p>Jason W. Trobaugh, D.Sc. Lecturer, Department of Electrical & Systems Engineering Email: jasont@wustl.edu</p>																							



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Cardiac Bioelectricity & Arrhythmia Center (CBAC)

Whitaker Hall, Room 290
CB 1097
1 Brookings Drive
St. Louis, MO 63130-4899

hbnguyen@wustl.edu
(314) 935-7887
<http://cbac.wustl.edu>



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