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

CENTER HEARTBEAT

Newsletter | Cardiac Bioelectricity & Arrhythmia Center (CBAC) | Vol. 12 | Spring/Fall 2020

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Cardiac Bioelectricity & Arrhythmia Center (CBAC) Mission

The Cardiac Bioelectricity and Arrhythmia Center (CBAC) is an interdisciplinary center whose goals are to study the mechanisms of rhythm disorders of the heart (cardiac arrhythmias) and to develop new tools for their diagnosis and treatment.

Cardiac arrhythmias are a major cause of death (over 400,000 deaths annually in the US alone; an 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.

On the Cover

“Simulation of ion-channel function from its molecular structure using artificial intelligence machine learning”

By Smiruthi Ramasubramanian, PhD, Yoram Rudy Laboratory

Computing large numbers of ion-channel trajectories at an atomistic scale, a requirement for simulating ion-channel gating, is now possible with the help of artificial intelligence machine learning. This new approach includes: the creation of a structural library containing many (millions) of ion-channel conformations, “learning” the relationship between the ion-channel protein structure and its energy, generating an energy landscape for the protein conformational space, performing random walks on the energy landscape to simulate the structural changes during channel activation and computing the channel function in terms of ionic current. This image of the different protein structures with trailing binary numbers portrays the library and the novel machine learning approach. The jellyfish appearance of our protein gives this composition a deep-sea theme and a dream-like feeling of infinite space. It represents the random walk on the protein energy landscape. Does our ion-channel remind you of another deep-sea or mythical creature?

Ramasubramanian S, Rudy Y. The Structural Basis of IKs Ion-Channel Activation: Mechanistic Insights from Molecular Simulations. Biophys J. 2018 Jun 5;114(11):2584-2594. PMCID: PMC6129186

From the Director's Desk...

This volume of the Center Heartbeat is being issued at a time of uncertainty and unprecedented challenges caused by the COVID-19 pandemic. This global and deadly epidemic is a reminder of our vulnerability as human beings. I was hesitant to distribute the Newsletter at this time, but decided that it might contribute in a small way to feelings of normalcy and hope among our readers. The coronavirus epidemic and the struggle to control it, highlights the need for science as a guide at multiple levels, from understanding molecular mechanisms to patient support, diagnosis and treatment, to patterns of social interactions and behaviors at the population level. A multiscale approach is at the heart of the CBAC mission, as related to cardiac arrhythmias and sudden death. CBAC also provides a platform for interaction and collaboration between researchers and clinicians from various disciplines (biophysics and biochemistry, physiology, cardiology, radiology, radiation oncology and biomedical engineering). The articles and interviews in this issue of the Center Heartbeat reflect this philosophy and highlights the diversity of the CBAC membership.

In addition to this newsletter, our longstanding seminar series is available for viewing online. The CBAC Seminar Series was established in 2005 and has provided a steady platform for scientific exchange and discussion in the fields of cardiac electrophysiology and arrhythmia. The seminar speakers are leaders in these fields, from the US and abroad, in both the basic science and clinical aspects of cardiac electrophysiology. The archive of more than 150 seminar videos is an invaluable resource, available to all both on the CBAC website (cbac.wustl.edu) and on YouTube (just type "cbac seminars" in the youtube.com search bar) or click on this link:

https://www.youtube.com/channel/UCYz22ssMTrCTSva0n9uGfsA/

We hope that the cardiac electrophysiology community will take advantage of this treasure.

Many of us are operating in a "stay-at-home" mode, while others are at the frontline of patient care. To those who are in the trenches of the COVID-19 battle – a humble and appreciative thank you. Last year, while on a sabbatical in the UK, I visited many laboratories across Europe. Following the Gordon Research Conference in Barga, Italy, I visited the University of Florence and later the Universitat Politècnica de València in Spain. Both Italy and Spain have gone through unimaginable suffering and tragic times because of COVID-19; my thoughts are with colleagues and friends in these countries and other places around the globe that have been hit by the pandemic.

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Finally, my thanks to Huyen (Gwen) Nguyen who finalized editing this newsletter while working from home.

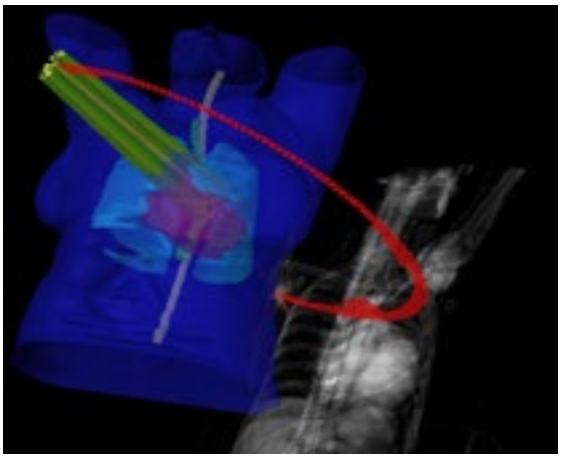
To all of you – stay healthy and safe!

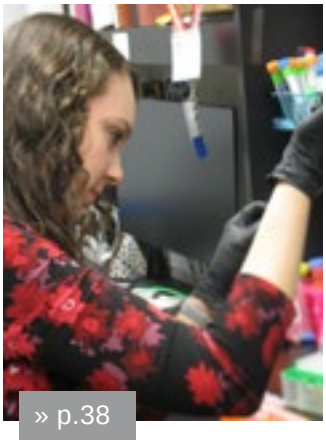
Yoram Rudy, PhD, FAHA, FHRS

Above: Sunrise in Barga, Italy, photographed during the Gordon Research Conference on Cardiac Arrhythmia Mechanisms in April 2019.

CONTENTS

CBAC NEWSLETTER





» p.38

» p.41

» p.35

BEYOND GENOMICS:
THE NEXT FRONTIER IN CARDIOVASCULAR PRECISION MEDICINE

By Kory J. Lavine[1*] and Michael J. Greenberg[2*]

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Abstract

Dilated cardiomyopathy (DCM) is a major cause of heart failure and cardiovascular mortality. In the past 20 years, there has been an overwhelming focus on developing therapeutics that target common downstream disease pathways thought to be involved in all forms of heart failure independent of the initial etiology. While this strategy is effective at the population level, individual responses vary tremendously and only approximately one third of patients receive benefit from modern heart failure treatments. We propose that DCM should be considered as a collection of diseases with a common phenotype of left ventricular dilation and systolic dysfunction rather than a single disease entity. We postulate that mechanism-based classification of disease subtypes will revolutionize our understanding and clinical approach towards DCM. We discuss how these efforts are central to realizing the potential of precision medicine and how they are empowered by the development of new tools that allow investigators to strategically employ genomic and transcriptomic information. Finally, we outline an investigational strategy to 1) define DCM at the patient level, 2) develop new tools to model and mechanistically dissect subtypes of human heart failure, and 3) harness these insights for the development of precision therapeutics.

KEYWORDS: Heart failure, engineered heart tissue, stem cells, next generation sequencing, personalized medicine

Cardiovascular diseases including heart failure and coronary artery disease represent important causes of morbidity and mortality worldwide. Over the past several decades, the predominant focus of cardiovascular medicine has centered on identifying common factors that contribute to the progression of these prevalent diseases. Such initiatives have formed the basis of our current approach to patient care, which is generally agnostic to the underlying cause of a patient's disease. For example, patients diagnosed with heart failure are offered essentially identical treatments regardless of whether their disease was caused by blockages in their coronary arteries or genetic mutations. Mechanistically, heart failure therapeutics target a process termed adverse remodeling, a common pathway by which the adult heart is thought to universally respond to injury. Pathologically, adverse remodeling is defined by cardiomyocyte hypertrophy and fibrosis (1, 2). Landmark clinical trials have established that therapeutics which target adverse remodeling including ß-adrenergic, angiotensin receptor II, and aldosterone signaling inhibitors reduce mortality and improve left ventricular systolic function in adult heart failure patients (3).

While this "one-size-fits-all' approach has led to improvements in clinical outcomes when large populations are examined, individual response rates vary tremendously, and it is difficult to distinguish patients who will achieve a favorable response from those who will experience disease progression and ultimately succumb to their illness. Consequently, many individuals are left inadequately treated and current 5-year transplant-free survival rates remain above 50% (4).

Intriguingly, therapies targeting adverse remodeling have substantially less efficacy in pediatric populations. The Pediatric Carvedilol Study failed to demonstrate improvements in clinical outcomes for children with symptomatic heart failure (5-7). Registry data further revealed that adult heart failure therapeutics have provided no survival benefit in children over digoxin and diuretic based regimens that were established in the 1970s (8). Our group has previously demonstrated that patients with pediatric heart failure displayed markedly reduced adverse remodeling at the histopathologic, electron microscopic, and gene expression levels compared to adult heart failure patients (9). These observations indicate that pediatric and adult heart failure represent distinct entities, provide a mechanistic rationale for why children display substantially lower rates of ventricular arrhythmias and sudden cardiac death compared to adults (10, 11), and highlight the clinically unmet need to identify novel approaches for pediatric cardiomyopathies.

In the cardiovascular field, we are now just beginning to appreciate that heart failure and coronary artery disease may actually represent a compilation of unique pathologies that are driven by complex interactions among a diverse array of genetic perturbations, environmental risk factors, and host responses to tissue injury or chronic disease. For example, due to the increased use of genetic sequencing in the clinic, inherited or spontaneously occurring mutations in genes important for cardiac contractility, structure, and metabolism are increasingly found in patients with idiopathic dilated cardiomyopathy (DCM), a common etiology of heart failure in adult and pediatric populations (12, 13). The vast majority of patients harbor heterozygous missense mutations that produce proteins with altered activity, abundance, cellular localization, and/or stability. It is likely that different mutations give rise to distinct disease entities with differing phenotypes, environmental interactions, and responses to current medical regimens. We believe that an individualized approach to cardiovascular medicine targeting the mechanisms that initiate disease and drive disease progression has the potential to be transformative and will ultimately lead to new treatments and hope for our patients.

Large gaps in knowledge must be overcome to realize the potential of cardiovascular precision medicine. Specifically, we must: reclassify cardiovascular diseases based on the mechanisms that drive pathogenesis; develop diagnostic strategies to identify patients with shared disease subtypes; and, generate therapeutics that target the specific mechanisms that underlie disease subtypes. Here, we will focus on the application of this approach to DCM, which represents a major cause of heart failure and mortality; however, these tools and approaches are broadly applicable to a host of cardiovascular diseases. We believe that this approach will reshape our clinical and research philosophy and realize the potential for precision medicine in the cardiovascular field.

Precision Medicine Beyond Genomics

Recent innovations in sequencing technology has made it feasible and reasonably inexpensive to sequence whole human exomes and genomes. The large volume of available sequencing data has revealed surprising diversity in the human gene pool, and as such, has become a focal point for precision medicine. Large scale sequencing and genome wide association studies (GWAS) have changed how we think about cardiovascular disease. They have helped to uncover the genetic bases of monogenic diseases with common presentations, such as DCM, Marfan's Syndrome, and Long Q-T syndrome, as well as polygenic risk factors for diseases including atherosclerosis and hypertension. In the case of DCM, at least 25% (14) can be attributed to specific mutations in a subset of genes that encode for sarcomeric (Troponin C, Troponin T, Myosin Heavy Chain, Tropomyosin, Myosin Binding Protein C3), structural (Titin, Desmin), mechanotransduction (Lamin A/C), calcium handling (Phospholamban, SERCA), signaling (Integrin-Linked Kinase), and metabolic or mitochondrial proteins (12, 13). The majority of genotype-positive patients have heterozygous missense mutations that produce proteins with altered activity, abundance, cellular localization, and/or stability.

While the genetic basis for DCM has become better understood, this advancement has yet to impact patient care beyond family screening. One challenge arises from the fact that despite sharing the common feature of cardiac remodeling and having a prevalence of 1:250 in the population, DCM can be caused by hundreds of mutations (12). For newly discovered mutations, it is difficult to determine whether a given variant is pathogenic, especially if examined families are not sufficiently large or the mutation occurred spontaneously. Genetic testing can be quite useful for individuals or families carrying a known or well-characterized variant that causes DCM. Individuals at risk for developing disease can easily be identified and subjected to either careful monitoring or aggressive treatment regimens focused on reducing cardiovascular risk factors and early initiation of anti-remodeling therapies. It is important to note that the genetic background and environment of a patient impact the presentation and prognosis of the disease. As a result, the timing of onset and heart failure phenotypes may differ between matched siblings and between parents and children. While some have suggested that genetic information alone could be used to decide whether to treat a patient with anti-remodeling therapies prophylactically, there is no consensus in the field as to the efficacy of such an approach with respect to the entire population of DCM or in regards to individual mutations (15).

Unfortunately, the direct translation of genomic data into precision medicine has been frustrated by several limitations. The most important limitation is that many genomic studies are correlative and do not necessarily provide actionable mechanistic insights into the disease pathogenesis. Surprisingly little is known regarding whether patients who

harbor mutations in different genes display distinct heart failure phenotypes and/or clinical outcomes. It is possible that DCM could be better reclassified based on the identification of mutations that give rise to common disease phenotypes. Moreover, mutations within the same molecule can lead to different gross phenotypes. For example, mutations within troponin T can lead to hypertrophic (16), dilated (17), restricted cardiomyopathy, or no effect depending on the specific variant (18). In fact, it has been shown that point mutations at the same residue with different amino acid substitutions can lead to different phenotypes (19).

Realizing the promise of precision medicine will require us to pair insights from genomic studies with mechanistic studies of the disease pathogenesis. Here, we discuss our approach and the fields progress towards precision medicine in 1) defining disease at the patient level, 2) developing new tools to mechanistically understand and model subtypes of human heart failure, and 3) harnessing these insights for the development of precision therapeutics (Figure 1).

Defining Disease at the Patient Level

The establishment of cardiac tissue biobanks have provided critical opportunities to explore cellular and molecular mechanisms that contribute to heart failure pathogenesis. Early histopathology and gene expression profiling studies have provided key evidence that heart failure is more heterogeneous and complex than previously appreciated (20). In fact, standard classification schemes dividing cardiomyopathies based on ischemic or non-ischemic etiologies are not sufficient to account for variability between individual patients (21). It is evident from rudimentary pathological analysis that dramatic differences exist between different forms of ischemic and non-ischemic cardiomyopathies (Figure 2). These observations highlight the need to develop new techniques and approaches to investigate, appropriately reclassify, and identify causative mechanisms that give rise to different forms of human heart failure.

Over the past several years, an explosion of molecular pathology techniques built on the shoulders of next generation nucleic acid sequencing technologies have revolutionized modern pathology. With the advent of single cell and single nuclei RNA sequencing approaches, it is now possible to measure gene expression at single cell resolution. Such technologies enable investigators to define the cellular composition of a given tissue, discover new cell types, and compare gene expression within a given cell type across experimental conditions or diseases within a single comprehensive and unbiased workflow. The introduction of single nuclei RNA sequencing has expanded these promising capabilities to encompass cell types that cannot be recovered from enzymatically digested tissues. Most importantly, single nuclei RNA sequencing is readily adaptable to cryopreserved specimens, fueling unprecedented exploration of biobanked tissues and reinvigorating enthusiasm for developing and expanding human tissue repositories. These technologies have already provided critical new insights into disease diversity and new cell types that contribute to the pathogenesis of diseases ranging from cancer to autism (22-25).

A limitation of single cell and single nuclei RNA sequencing approaches is the loss of spatial information, most notably the location of cell types within a tissue and the existence of unique tissue niches composed of various cell populations. Within current workflows, this information must be acquired retrospectively using either immunohistochemistry or *in situ*

hybridization. Spatial transcriptomics and advanced small sample input tissue acquisition systems offer viable solutions. These technologies provide transcriptomic level information from fresh or fixed tissue sections, respectively. Spatial transcriptomics provides an unbiased platform for spatial resolved transcriptional profiling (26). In this system, fresh frozen tissue sections are placed over a slide containing uniquely barcoded oligo-dT primers spaced every 40-100 microns printed over a 6mm X 6mm area. Co-registration of an H&E or antibody stained image with the position of the barcoded oligos allows the integration of spatial and transcriptomic data. Advanced laser capture and other small input tissue capture systems provide an alternative approach by allowing investigators to select particular regions of interest (27). These platforms have the unique advantage of working on an array of tissue types ranging from fresh frozen to formalin fixed paraffin embedded tissues.

Today, there is incredible opportunity to apply these technologies to cardiovascular diseases. Understanding, the cellular composition of the healthy and diseased human heart is likely to provide unprecedented opportunities to identify disease potentiating cell types and delineate the functional diversity of human heart disease. For example, we know very little regarding the exact immune and fibroblast cell types that orchestrate myocardial fibrosis, whether mutations in distinct DCM genes produce unique tissue pathologies, or the underlying signaling pathways that contribute to rare cardiomyopathies including cardiac sarcoidosis, giant cell myocarditis, and cardiac amyloidosis. Most importantly, next generation molecular pathology will undoubtedly allow investigators to glean critical information directly from the human disease itself rather than relying on oversimplified or potentially inaccurate animal or cellular models.

New Tools to Mechanistically Understand and Model Subtypes of Human Heart Failure

Recent technological advances have also opened the door to modeling human heart failure subtypes *in vitro*. These new tools can be leveraged for the development of precision therapeutics for heart failure. Here, we will focus on recent advances in stem cell technologies, gene editing, and tissue engineering, and their translational potential for cardiovascular precision medicine.

Gene Editing and Human Pluripotent Stem Cells

There are several model systems that have been applied to model heart failure. Each of these systems comes with its own set of advantages and caveats. Tissue from patients provides useful information about the specific patient phenotype in human tissues (28); however, it is often not possible to obtain genetically matched control tissues for functional experiments, and it is difficult to obtain sufficient volumes of tissue for most functional experiments. Moreover, human tissue is usually only available from patients in the end-stages of the disease, either after the implantation of a ventricular assist device, heart transplantation, or postmortem. Transgenic animals including drosophila, zebrafish, and mice are excellent systems for studying some genetic forms of cardiovascular disease (15); however, they do not always recapitulate the disease phenotype seen in humans due to physiological differences between species (19, 29-34). In the case of mice, mouse hearts beat 500-600 times per minute, compared to approximately 60-80 times per minute for humans. To achieve this faster heart rate, murine hearts have different proteins isoforms for calcium handling, ion channels, and contractile proteins. For example, murine hearts express the alpha myosin isoform (MYH6), which has a speed (as measured by the ADP

release rate from actomyosin) that is ~10-times greater than the beta cardiac isoform (MYH7) expressed in human ventricles (35). These differences can make it so that mouse models of heart failure do not recapitulate the human disease phenotype, and efforts have been made to make more humanized mice (30, 36, 37). Given known limitations of rodent and other model systems, there has been a great push to develop new experimental platforms that focus on human tissues or cell-based systems.

Recent advances in stem cell technologies and gene editing have made it easier to study mutations that cause human heart failure in experimentally tractable systems. The derivation of human induced pluripotent stem cells (hiPSCs) (38) from a patient blood sample, urine sample, or skin biopsy, has enabled the study of patient-specific disease-causing mutations. hiPSCs can be differentiated into cardiomyocytes (hiPSC-CMs) using small molecules that activate developmental pathways (39-41). hiPSCs can undergo genome editing using the CRISPR/Cas9 system (42) to enable the modeling of human disease on a controlled genetic background. One caveat of this system is that hiPSC-CMs are developmentally immature compared to adult cardiomyocytes (43, 44). These cells differ from mature cardiomyocytes in several ways. For example, hiPSC-CMs have a lower mitochondrial content, minimal t-tubular structures, show sarcomeric disarray, have higher membrane resting potentials, generate less force in response to activation, and have altered action potentials (45, 46). That being said, the field is actively developing approaches to promote maturity, including providing hiPSC-CMs with mechanical (47-54), electrical (55-57), and chemical (43, 58) cues that mimic the native environment of the heart.

Single hiPSC-CMs can be extensively characterized using deep phenotyping tools. Transcriptional profiles can be probed using RNA sequencing. Precise measurements of contractility can be obtained using tools such as traction force microscopy or atomic force microscopy (47, 59, 60). Cellular metabolism can be measured using tools such as the Seahorse Analyzer. Cellular and sarcomeric structural organization can be examined in fixed cells using immunofluorescence or in live cells using fluorescently tagged proteins (61). E-C coupling can be investigated using single cell patch clamping and voltage/calcium sensitive dyes (62). Moreover, these profiling techniques can be used for drug screening of individual patient-specific cell lines.

Using genome edited hiPSC-CMs, it is now possible to engineer single cells carrying disease-causing mutations on a controlled genetic background. The CRISPR/Cas9 system (42) can be used both to introduce mutations into control lines or to correct mutations found in patient cells (i.e., generate a genetically matched healthy control lines). The use of gene editing on a controlled genetic background removes confounding factors that arise when comparing two non-matched patients or even siblings. This gene editing approach has been used to model several forms of cardiac diseases at the single cell level including hypertrophic cardiomyopathy, long QT syndrome, Duchenne's Muscular Dystrophy, and dilated cardiomyopathy (63). While hiPSC-CMs are developmentally immature (43) and do not currently capture the late stages of the disease, single cell assays have been able to recapitulate many features of the early disease phenotype including cellular hypertrophy, disrupted calcium transients, altered gene expression, and altered action potentials (64). This can be seen as a key advantage to study disease initiation.

In the case of DCM, several patient-specific mutations have been modeled in hiPSC-CMs, including mutations in troponin T (60, 65), lamin A/C (66), titin (67), dystrophin (68), and

phospholamban (69). Moreover, hiPSC-CMs have been used to model diabetic cardiomyopathy (70, 71). These studies have been used to identify new mechanisms involved in the disease pathogenesis, such as aberrant PDGFR signaling (66) and disrupted responses to mechanobiological cues (65). hiPSC-CMs have also been used to test the effects of potential therapeutics for individual patient-specific mutations (60), revealing interesting similarities and differences between specific mutations, supporting the power of this experimental system for precision medicine approaches.

One place where this technology shows great promise for precision medicine is in determining whether a given variant is pathogenic. For many DCM-associated variants, there are not enough patients with a particular variant to definitively determine whether it is likely pathogenic or not using linkage analysis. Gene edited hiPSC-CMs were recently used to demonstrate the likely pathogenicity of a mutation that causes cardiomyopathy (72). Cells from both healthy and diseased patients were obtained, reprogrammed, and differentiated to form hiPSC-CMS. The hiPSC-CMs from the diseased patients showed alterations in calcium transients, contractility, sarcomeric structure, and gene expression compared to healthy controls. Next, the healthy lines underwent gene editing to introduce the mutation, and the diseased patient line underwent editing to fix the mutation. The data clearly demonstrate that cellular dysfunction is dependent of the presence of the mutation, establishing that the mutation is likely pathogenic.

Human Engineered Heart Tissues

Human engineered heart tissues (EHTs) provide a unique system for human disease modeling and the development of novel therapeutics. EHTs are in vitro systems that recapitulate aspects of the 3D environment of the heart (73, 74). As such, they provide a more physiologically relevant environment for studying cardiomyocyte function. The heart is a complex environment, consisting of many cell types including cardiomyocytes, fibroblasts, endothelial cells, and immune cells. These cells interact with each other, and these interactions can affect the contractile and electrophysiological properties of the myocardium (75). In EHTs, cardiomyocytes are mixed with desired stromal cells in the presence of extracellular matrix proteins. These tissues will self-assemble in engineered devices where they can undergo extensive phenotyping. EHTs can be assembled using hiPSC-CMs, giving flexibility to examine patient-specific mutations that cause cardiovascular disease.

Multiple EHT platforms have been designed (Figure 3), each with its own set of strengths and weaknesses (56, 76-79). These platforms have varied geometries for tissue formation and are designed to examine different functional parameters (80). These platforms can incorporate elements for measuring contractility, tissue organization, perfusion, electrophysiology, and conduction velocities. Moreover, systems have been designed to provide various cues to promote tissue maturity and to model environmental interactions including electrical stimulation (55, 81), afterload (52), exogenous chemicals, and specific extracellular matrix scaffolds. hiPSC-CMs cultured in EHTs show improvements over single cells in mitochondrial content, sarcomeric organization, gene expression, T-tubule structure, electrophysiology, and contractility (55). EHT systems have also been designed for higher throughput drug screening (82, 83). As such, EHTs show great promise for human disease modeling and drug discovery.

EHT systems have been used to model patient-specific mutations in several forms of heart disease. These studies have revealed diversity in the disease pathogenesis and highlight the potential role for EHTs in cardiovascular precision medicine. For example, an EHT model of DCM-causing truncations of the muscle protein titin revealed that these mutations likely exert their effect through haploinsufficiency (67). EHTs were also used to model hypertrophic cardiomyopathy caused by mutations in myosin binding protein C (MyBPC), and it was used as a platform to demonstrate that expression of a phosphomimetic MyBPC could restore cardiac function in a particular mutant (84). EHTs have also been used to study patient specific sensitivity to the chemotherapeutic agent, sunitinib, and to reveal that some heart specific effects of the drug become more pronounced with increased cardiac afterload (85).

Control of the genetic, chemical, cellular, and mechanical environment in EHTs gives them unique qualities that can be harnessed for precision medicine. For example, these systems could be used for diagnostic purposes, testing whether a given variant identified in a patient is pathogenic or for dissecting how multiple genetic polymorphisms contribute to the development of complex polygenic diseases. Moreover, one can completely define the EHT environment to mimic different physiological or pathological conditions. For example, it is possible to examine the effects of different cell types in the heart, and their relative roles in disease. One can examine how changes in mechanics, such as increased afterload in hypertension or stiffening of the myocardium in fibrosis affects the disease development (52, 85, 86). Moreover, it is now possible to examine how changes in the extracellular matrix that accompany disease affect EHT function.

Road to Precision Therapies

The ultimate goal of precision medicine is to develop and appropriately match therapeutics to patients. This approach requires upfront knowledge of the patient's diagnosis, disease classification, and therapeutic options. Thus, the generation of new diagnostic tools is an essential element that cannot be ignored. Diagnostic classifications based on genetic testing, imaging, and/or serum biomarkers represent feasible options. For example, genetic testing for DCM variants or molecular imaging for particular immune cell populations would provide physicians with the requisite information to prescribe tailored or individualized therapies that target specific genotypes of DCM or inflammatory mediators, respectively. As opposed to our current practice, this approach maximizes benefit for a given individual and minimizes risk associated with adverse effects. These tools can be applied to other diseases with cardiac involvement. For example, hiPSC-CMs from cancer patients were recently screened for cardiotoxicity to tyrosine kinase inhibitors (87). Moreover, precision diagnostic tools are also likely to yield useful prognostic information regarding the anticipated natural history of an individual's disease.

As highlighted above, EHTs provide a human model of heart disease for drug discovery, development, and cardiotoxicity studies. By using patient specific hiPSC-derived cardiomyocytes or engineering an individualized mutation into an established hiPSC cell line, EHTs can be used to predict an individual's response to a particular therapy. The use of human EHTs has several advantages over animal systems for early drug discovery, including fewer ethical concerns, easier scaling for high throughput screening (82, 83), and lower cost per experiment. Moreover, murine hearts do not express the hERG channel that is expressed in humans. Many drugs bind to this channel, and as such, undetected cardiotoxicity in mouse models is one of the leading causes for clinical trial failures (87, 88).

There are several opportunities for the development of precision treatments for DCM, that expand beyond the current "one-size-fits-all" treatments that target remodeling. It is likely that therapeutics which correct the activity of individual DCM variants, prevent their incorporation into sarcomeres, or promote their removal through selective degradation would constitute a highly effective strategy to delay or reverse the natural history of DCM. For example, there are several new compounds in development that target the sarcomere to correct altered contractile protein function (89-91). Moreover, gene therapy and exon skipping strategies to correct or mitigate the functional effects of mutant proteins have continued to evolve (92, 93); however, there are substantial challenges that still must be overcome before these technologies can be brought to the clinic. Alternatively, since the vast majority of DCM patients harbor heterozygous missense mutations that display reduced or absent activity, it might be possible to target mutant proteins for selective degradation. For many but not all of these mutants, the incorporation of these mutant proteins into sarcomeres (or other complexes) occurs in a stoichiometric fashion and results in a dominant effect on contractile function. For example, the TNNT2 K210 variant encodes a mutant protein with markedly reduced sensitivity to calcium (65). Incorporation of this mutant protein into sarcomeres containing wild type TNNT2 leads to reduced force generation and abnormal relaxation (17, 94). Targeting of mutant protein for degradation or removal from the sarcomere has the possibility of rescuing the disease phenotype. Taken together, there are multiple exciting avenues for the development of precision therapeutics for cardiovascular disease.

We anticipate that the application of precision medicine to cardiovascular diseases will have profound translational impacts and result in paradigm shifts that will ultimately reshape our approach towards treating heart failure and other cardiovascular diseases. We envision that these initiatives will yield new diagnostics that define specific disease subtypes with differing etiologies, prognoses, and treatment responses. Ultimately, the deployment of precision therapies will finally arm physicians with the appropriate tools to treat disease on an individual rather than a population level. While these "forward-looking" initiatives may appear futuristic, technological advances are propelling the field at unprecedented speed and investigators are now only limited by their imagination and creativity rather than technical expertise.

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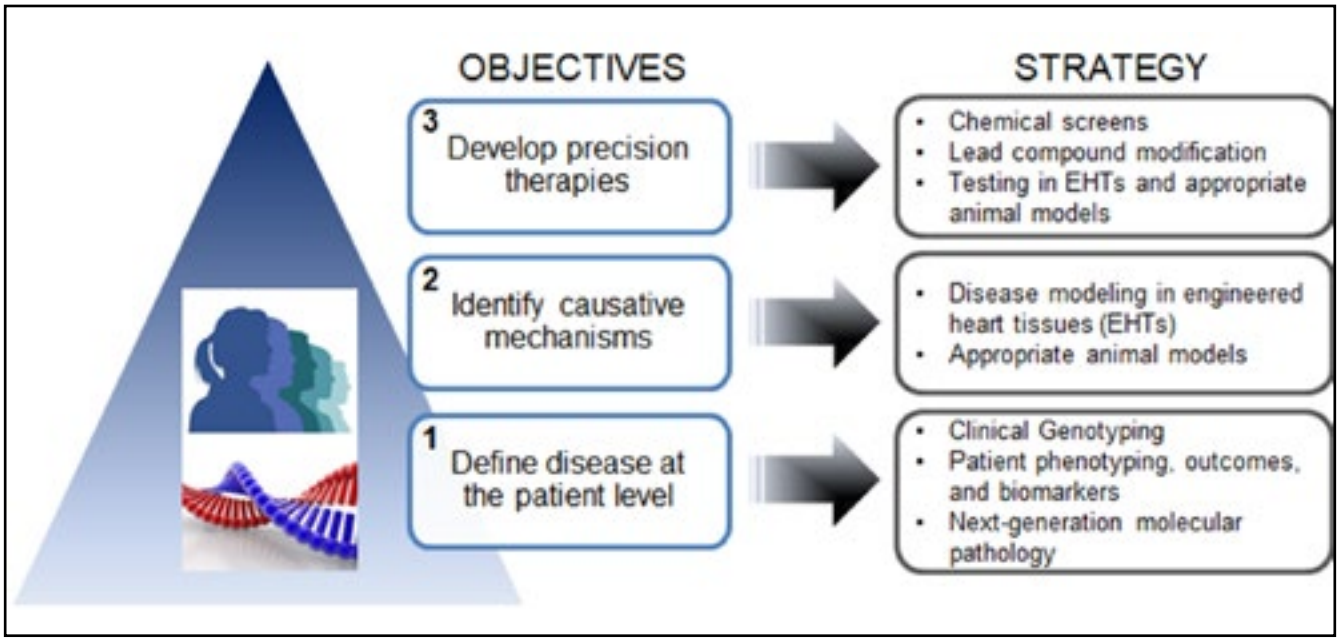

Figure 1: Schematic describing a precision medicine approach to heart failure and other cardiovascular diseases.

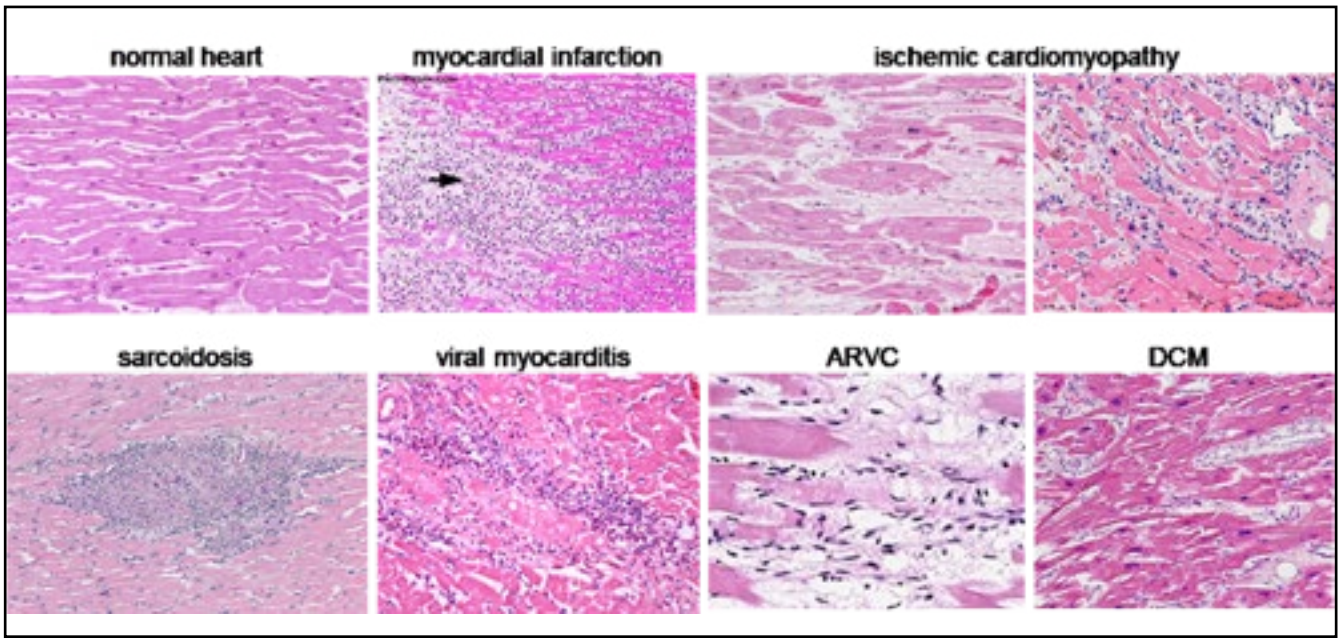

Figure 2: Individual heart failure etiologies display distinct histopathology features. Arrow denotes site of myocardial infarction. ARVC: arrhythmogenic right ventricular cardiomyopathy, DCM: dilated cardiomyopathy. Images from Wikipedia and Pathpedia.

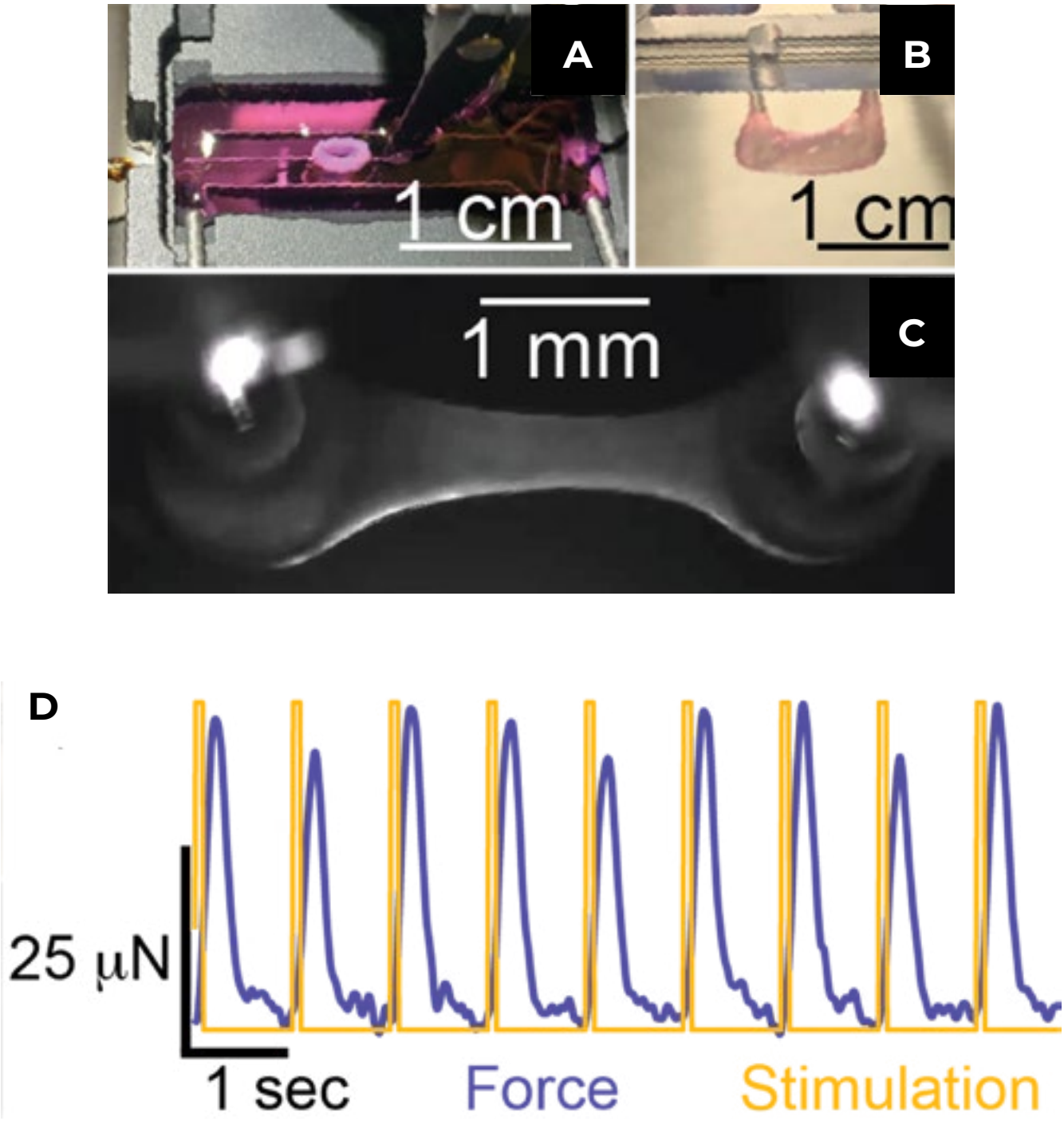

Figure 3: Examples of engineered heart tissues (EHTs) generated for disease modeling. (**A**) A circular EHT consisting of hiPSC-CMs and fibroblasts was mounted in between a force transducer and a length mover (Aurora Scientific) for active mechanical measurements. (**B-C**) An EHT consisting of hiPSC-CMs and fibroblasts was grown between two PDMS posts (EHT Technologies). The tissue self assembles and contracts spontaneously within 5 to 7 days after seeding. (**D**) An EHT grown between two PDMS posts was electrically stimulated (yellow). As the tissue contracts, it displaces the PDMS posts, enabling the calculation of the force of contraction (blue) for the tissue.

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NONINVASIVE CARDIAC RADIOABLATION TO TREAT VENTRICULAR TACHYCARDIA

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The field of clinical cardiac electrophysiology has grown substantially in the past three decades. A major reason for this growth is the now-routine use of invasive catheters to map arrhythmias and deliver ablative energy to the critical structures of the arrhythmia focus or circuit. Techniques and tools have been refined such that a routine catheter ablation procedure is generally a positive patient experience. For most types of supraventricular tachycardia and some forms of idiopathic ventricular tachycardia (VT), the procedure times range from 1-4 hours with high rates of success and low procedural risk.

For patients with life-threatening VT related to structural heart disease, the patient experience of catheter ablation is generally not positive. Mapping and ablation components require considerably more time, often extending the procedure beyond seven hours. With the increased procedural complexity and duration comes increased procedural risk. The procedural risk is further amplified by the fact that patients with structural VT are among the sickest, with severely reduced cardiac function and substantial comorbidity. As a result, even in the most experienced centers, 7% of patients experienced a complication related to a VT ablation procedure and 5% of all patients who underwent VT ablation died within a month of the procedure (1). This highlights both the complexity of the procedure and the grave prognosis of patients with refractory VT.

For patients who survive the procedure and recover successfully from the subsequent hospitalization, recurrence of VT is too common. There are several reasons for this. Frequently, certain regions of the heart are difficult to reach with the necessary energy for ablation. Alternatively, cardiac maps may tell an incomplete story of the arrhythmia circuit. Either of these will result in acute procedural failure. After the procedure, the underlying cardiomyopathy continues to evolve, leading to the formation of new circuits. In response to this, the field continues to develop new ablative tools and new strategies to approach myocardial scar. The evolution of this process can be summarized as “more ablation” and “deeper ablation,” usually with more invasive tools, longer procedures, and increased risk.

To improve the overall patient experience, we developed EP-guided Noninvasive Cardiac Radioablation (ENCORE), an entirely noninvasive way to map and treat cardiac arrhythmias (2). This method combines multiple noninvasive cardiac imaging modalities to best identify the arrhythmogenic region. This location is then targeted for treatment with Stereotactic

Ablative Radiotherapy (SAbR), a technique that delivers precise, high doses of radiation to targets in the body with minimal damage to normal adjacent tissue, and is not constrained by the depth or location of the target.

The concept of using ionizing radiation as a therapy for arrhythmia is not novel. In fact, Walt Disney in a prescient and beautiful manner illustrated the concept in his 1956 pictoral book, "Our Friend the Atom" (Figure 1, right). After witnessing the destructive power of nuclear energy at the end of World War II, the public was fearful of atomic energy. Disney saw the important positive opportunities that controlled nuclear energy could bring to humankind, so he partnered with leading physicist Heinz Haber to teach the lay public about the generative rather than destructive force of atomic power.

Figure 1: Illustration from "Our Friend the Atom" by Heinz Haber (ill. Walt Disney Studios)

Enabling precise noninvasive ablation with images, a process called "radioablation," requires accurate noninvasive cardiac mapping. Early inspiration for the partnership between a Heart Rhythm specialist and a Radiation Oncologist began in the laboratory of Yoram Rudy, with the development and testing of Electrocardiographic Imaging (ECGI). As ECGI was refined over years, it proved to be sufficiently accurate in identifying the location of the circuits causing VT (2) and the abnormal ventricular substrate harboring VT circuits (3). As a result, ECGI forms the basis for noninvasive targeting for radioablation (Figure 2, below)

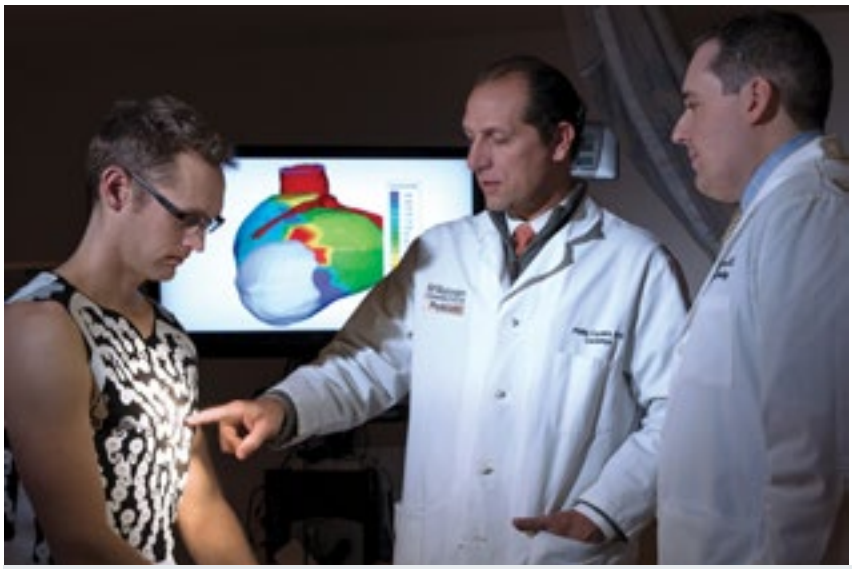

Figure 2: CardioInsight noninvasive cardiac mapping vest, the commercial version of ECGI manufactured by Medtronic.

ENCORE addresses many of the current shortcomings of catheter ablation procedures. The noninvasive mapping component is performed ahead of the treatment, allowing operators to comfortably analyze the relationship between the arrhythmia and the abnormal myocardial substrate without the time constraints of an invasive procedure. Noninvasive mapping incorporates 3D scar topology from MRI and/or CT scans, metabolism from PET or SPECT scans, and identification of surrounding structures from a CT scan

to give the treating physicians a more complete assessment of the myocardial substrate. Electrical mapping of the VT is initially provided by analysis of a standard 12-lead ECG (for exit site) and in greater detail by ECGI (for full reentry characteristics of exit site, reentry site, and putative diastolic isthmus). The electrical map created with ECGI can then be layered over the combined anatomic map to develop an intelligent ablation strategy.

Once the arrhythmogenic region of the heart is targeted for treatment, a virtual plan is developed by the radiation oncology team following largely standardized SAbR practices. For example, as shown in Figure 3 (bottom), it is now common to develop SAbR plans using continuous sweeping arcs of radiation with simultaneous shaping of the beam to the target, bringing treatment times down to minutes. Ultimately, energy is delivered to the entire thickness of the targeted myocardium at once, bringing forth the concept of treating a target "volume" to the electrophysiology community. In our experience, the delivery time is now as short as five minutes, without any sedation or anesthesia. After treatment, patients stand up, walk out, and go home.

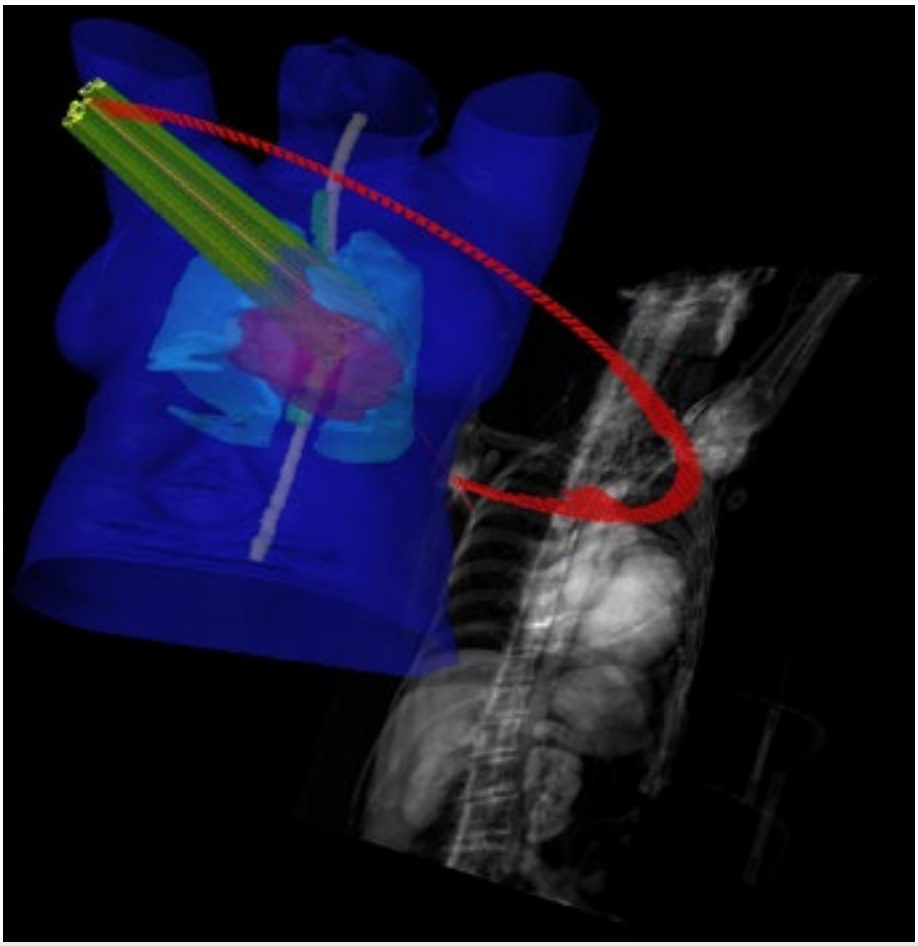

Figure 3: 3D rendering of a patient undergoing virtual treatment planning for ENCORE. The projected path of a continuous arc of radiation (red) is seen, with one position in the arc (yellow lines) delineating the required beam shape at that position to conform to the target. A virtual digital radiograph behind the patient represents what would be "seen" by x-rays passing through the patient at that position. Other 3D structures highlighted include the external surface of the patient (dark blue), lungs (light blue), heart (red), esophagus (green), and spinal cord (tan).

Without doubt, the patient experience is faster and more comfortable than traditional catheter ablation. But is it safe? And does it work? The initial experience in patients with a high VT burden who failed standard therapies demonstrated a strong signal for efficacy (4). To carefully test key questions about longer-term safety and efficacy, we completed an investigator-initiated and funded, prospective Phase I/II clinical trial (ENCORE-VT trial, NCT02919618). The results of this trial were published late 2018, in coordination with a Late-Breaking Science presentation at American Heart Association Scientific Sessions and subsequent publication in Circulation (5). In short, ENCORE-VT confirmed the early safety and efficacy of ENCORE for refractory VT, with 94% of patients having any reduction in VT, coupled with significant decrease in dual antiarrhythmic medication (59% to 12%) and concomitant improvements in quality of life at 6 months.

Important questions remain to be answered:

- How is cardiac radioablation actually antiarrhythmic? What are the mechanisms involved?
- What are the longer-term risks with focused cardiac radiation? How can we apply historical lessons learned from radiation oncology?
- How much is too much? Is there a threshold ablation volume or treatment dose above which the risk for complication escalates?
- Is the treatment effect similar in different types of cardiomyopathy?
- Can advances in cardiac imaging, in silico modeling, and artificial intelligence better identify the critical regions to target for treatment noninvasively?
- Can we automate the process of noninvasively mapping and treating VT?
- Can cardiac radioablation be helpful earlier in the management of VT?
- Can cardiac radioablation be useful in other arrhythmias, such as atrial fibrillation?
- What is the best collaborative workflow and compensation model between radiation oncologists and cardiac electrophysiologsts?

Answers to these questions will require meticulous science, dedicated effort from radiation oncology and cardiology teams, and a strong willingness to collaborate between centers interested in exploring this further. Toward this effort, we have created the Center for Noninvasive Cardiac Radioablation (CNCR), the world's first multidisciplinary Center exploring the biology, clinical implementation, and population impact of cardiac radioablation. CNCR is already fueling new molecular discoveries and technical innovations, with two licensed patents, a NIH R01, and AHA Collaborative Sciences Award within the first year of its inception. To date, CNCR has helped over 25 medical centers worldwide to safely and reproducibly treat patients. In 2020, CNCR is scheduled to lead a multinational, multicenter prospective trial for cardiac radioablation of VT.

As we move forward with careful testing of noninvasive cardiac radioablation, we must always keep the patient in the center of the discussion and be prepared to answer the questions they are already asking: "Hours with catheters inside my body? Or minutes without?"

→

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Before 1959	Grew up in Brooklyn, NY	**1959**	**BARNARD COLLEGE, NEW YORK** Graduated with an AB Phsyics Degree	**1962**	**WASHINGTON, DC** Realizes true passion: knowledge that can prevent unnecessary suffering

The Many "Lives" of...

1968

VIRGINIA
While living in a log cabin, realized need to get PhD; enrolls at UVA

1985

UNIVERSITY OF VIRGINIA (UVA)
Studies exercise physiology

1987

M. Ed DEGREE
Obtains M. Ed in Exercise Physiology at UVA

1990

PhD DEGREE
Obtains PhD in Health Promotion at UVA

WASHINGTON UNIVERSITY IN ST. LOUIS!

BY CHANCE
meets Dr. Robert Kleiger from WU at a conference and gets a postdoc offer

1991

HRV
Offered to Dr. Robert Carney in Cardiology. Starts work on Heart Rate Variability (HRV)

Phyllis K. Stein, PhD

Director, Heart Rate Variability Laboratory
Associate Professor of Medicine (Cardiovascular Division)

Heart Rate Variability Expert

CBAC FACULTY PROFILE: Phyllis K. Stein, PhD

Director, Heart Rate Variability Laboratory
Associate Professor of Medicine
(Cardiovascular Division)

Heart Rate Variability Expert

I have been at Washington University in St. Louis since 1990. The year after I arrived in Saint Louis as a brand new post-doc, and after failing to fit into my first lab, I was "given" to Dr. Robert Kleiger in Cardiology, then at Jewish Hospital. My PhD thesis was about exercise training and cardiovascular reactivity to mental stress, but I had literally never heard of heart rate variability (HRV). Dr. Kleiger's revolutionary paper reporting that decreased HRV was an independent predictor of mortality in post-Myocardial Infarction (MI) patients had only been published in 1987. So, I continued as, a postdoc, a research instructor, a research assistant professor and as an associate professor to become the "go to" person here for HRV studies.

The actual annotation of the continuous ECGs that we study falls to my assistant Beverly Vanderheyden. After she generates the basic results - which we call a beatfile, the associated graphical displays of the heart rate patterns, and in the case of a Holter, the report itself, I overread them and suggest any necessary changes. These results are stored by study, in our huge database that is now on a server.

Meanwhile, I am editing papers, supervising the work of students in the lab, keeping up with the latest findings, if possible, and writing up our results. In active studies, the Holter report is shared with the originating investigator.

Growing Up

I grew up in Brooklyn, NY and, literally, was in the same high school class as Bernie Sanders (but I do not remember him). My graduating class had 1,404 students. There were enough bright kids to fill several classes. Being very bright and good at science and math just seemed normal. Almost all the bright kids were second-generation descendants of Eastern European Jewish immigrants and education was a primary value. However, my maternal grandmother, who was very bright and knew five languages, did not have any professional opportunities. She talked about getting into a bitter fight, back in the "old country" with her stepfather who did not believe that women should be educated. My parents would have been professionals (chemists) except their ambitions were quashed by the great depression. My father, who eventually became a high school industrial arts teacher, after doing outdoor construction work, finished his BA at Brooklyn College at the age of 85. My mother was deeply opposed to my going to an out-of-town school, afraid that I would "change." So I went to Barnard College, commuting by subway over an hour each way. I planned to major in physics and since Columbia and Barnard shared a physics department, I was, I thought, going to be in one of the best departments anyway. Also, my boyfriend, and eventual first husband, was a physics major at Columbia, a year ahead of me.

Barnard was a shock, because everyone had been at the top of their class, not just me. I continued to declare my major as physics, partly because people were so impressed when I said it. I thought that it was the most fundamental science, the basis for everything, so it was the most worth studying. When I got to theoretical physics, in my 3rd year, I became disillusioned. Theoretical physics turned out to be pages of equations, and if there were a mistake on the third line, it would be pages of garbage. More than that, the true theoreticians were so "out there" that the faculty could not be sure if they were brilliant or insane! I knew I was not in their league.

However, I finished Barnard in three years in order to catch up with my now husband at the time. Millicent MacIntosh, the president of Barnard, was a strong proponent of married women having careers. She had five children and it did not stop her! She was also wealthy enough to have full time household help, but who is counting! This was the '50s. Living with or literally even sleeping with one's boyfriend was not acceptable and the subject of gossip. I was 18 when I got married and finally able to leave home.

We were both accepted at Rutgers as graduate assistants in Physics and during that year, I realized that there was nothing in physics that really interested me. My then husband also decided that a PhD in physics was not his goal, so he got a job at the National Bureau of Standards. As a result, we moved to Washington, DC.

Research Interests:

- Extracting prognostic markers for cardiovascular mortality, non-cardiovascular mortality and autonomic dysfunction from continuous ECG recordings
- Use of Holter recordings to detect sleep apnea and analysis of ECGs from sleep studies

Knowledge that can Prevent Unnecessary Suffering

None of this history directly relates to my career choice, because I had become passionate about the possibility of giving birth without suffering or needing to be put out of my misery (i.e., the Lamaze method). When I talked about it, people said, "How do you know if you haven't had a baby?" So, I did have a baby! I taught myself from whatever (pre-internet) resources were available and found a reasonably supportive OB and a hospital, where my husband could stay with me *and* my baby could stay with me from birth. Labor was the hardest physical work I could ever imagine, like running around the block and then knowing in less than a minute, I was going to run around the block again, whether I wanted to or not. The intensity of the sensations was also astounding, but never more than I could handle, and I did have one real labor pain when I tried a position that did not work. I am glad that happened, because it showed me the reality of what women had endured. The pain was so bad that I did not know how I was going to live through it, and yet I knew I would. I went back to what was working. Without realizing it, this experience was the first round of my true passion, knowledge that can prevent unnecessary suffering.

I went on to help start a formal Lamaze group in Washington, DC, teach Lamaze to couples in my home, and have a second baby (at home with a physician present). When I did the stats, after seven years of teaching, nearly 90% of couples were able to use Lamaze to deliver their babies without needing drugs. This was before the days of 30% C-section rates, and most couples who did not have a supportive OB had changed doctors. I also became involved with La Leche League, a lay organization that supports nursing mothers.

My world changed in 1968, and I "dropped out." The pre-programmed life that I was dutifully following suddenly became uninhabitable. My husband and I split up. I had never really asked the question of what my life could be. I will skip over this phase in detail, except to say that I learned a lot about different therapy modalities, like bioenergetics and even primal scream. When my sons were ready to leave for college, we were living in a log cabin in the woods of Virginia. That was when I had to decide what I wanted to be when I grew up. This was in 1985. I knew, at the time, that any knowledge that promised to prevent unnecessary suffering excited me and that I needed a PhD to become "credible" in whatever I decided to do.

I decided, after realizing that medical school would not be a good fit for me, to go to the University of Virginia (UVA), which was about a 45 minute drive from the cabin. Although I had no idea what I should get a PhD in, fate sent me to exercise physiology. The program director was new and looking for students and did not care what else they were interested in beyond the core curriculum. I was the only non-athlete in the program, but what I learned, including how to write a scientific paper, which we did every two weeks after the entire group did something like lactate threshold testing, or strength testing in our regular lab, was invaluable. I got my MEd in Exercise Physiology and then joined the PhD program in health promotion.

I went to many conferences and was especially drawn to psychophysiology, i.e., determinants of the physiologic response to mental stress. A moment that stands out was an early conference where someone said that by looking at the effect of respiration on heart rate, it is possible to quantify "vagal tone." Now I already knew that recovery and better health were associated with "better" vagal tone and suddenly I saw that there would be a way to quantify whether people were getting better because of an intervention rather than relying on subjective data from

questionnaires. My PhD thesis title was "The Effect of Exercise Training on Cardiovascular Responses to Mental Stress in Previously Sedentary Middle-Aged Men." I commuted from the cabin (chestnut logs, built in 1910 before the blight) until the last year of my studies when I moved to Charlottesville, Virginia. By then, I had given up the goats, chickens, geese and horse, but I moved to town with two older dogs and two older cats.

When I received my degree in 1990, I assumed I would find a faculty position somewhere, but again, pre-internet, I had no idea how this even worked. By a stroke of complete luck, I had met Robert Carney, now a professor of psychiatry here at WashU, at what I remember to have been a psychophysiology conference, and he had a slot for an interdisciplinary postdoc, which he offered to me. So, this totally East Coast person moved to Saint Louis, a place I never imagined living, and a place I found to have just the right balance of resources and affordability. I came with the same two dogs and two cats. And I am still here.

Career in Heart Rate Variability (HRV) Research at WashU

I landed at Jewish Hospital as a postdoc and I never left, even though Jewish became Barnes-Jewish. It seems like once I found HRV — my evolution was set. However, in my first two years I collected up all of the known papers about HRV and put them, alphabetically, in binders. There were nearly 2,000. I still have the binders, but looking back at the days when I thought I could know all there was to know about the topic, I shake my head. Keeping up is now impossible, and that does not count the endless supply of the "Journals of Advanced Whatever" that sound so legitimate and beg me to contribute. What struck me the most about being at Wash U, however, is that, somehow, I had wound up in "the big leagues." I am glad it happened that way.

When I came to Saint Louis, the obvious place for me to start my postdoc was in applied physiology. Within months, it was clear that who I was then was not a good fit. I was offered to Robert Kleiger in cardiology (then at Jewish Hospital) who was becoming known for work that showed that markedly decreased heart rate variability (HRV) is a powerful independent predictor of mortality post-MI. In 1991, he was part of a data collection of normative values for 24-hour HRV in healthy adults. He was happy to take me, and I recruited subjects for that study and put Holter monitors on them. Even though I was interested in cardiovascular reactivity, I had never heard of HRV. Indeed, my dissertation advisor, who had returned to his native Australia, was skeptical about its validity. Nevertheless, information from applications of HRV became my career.

Research Goals

I have joked that torturing the continuous ECG until it admits everything is my life's goal. Now, I think it is closer to using HRV research findings to guide alleviation of and prevention of physical and emotional suffering both in health and disease and in all age groups.

We have increasingly been involved with NICU data and are involved in a project in Malawi where HRV data is being used to discover optimal treatment for babies with cerebral malaria. As I write this, I think what motivates me is the understanding of our basic physiology as reflected, in part, by information from the heart, gives us solid guidance towards a path of better lives because this information does not lie.

Right: Stein's log cabin in Virginia

Challenges

Too much data, too little time to fully analyze it and write it up. (Students at all levels and IMGs welcome to help me in this undertaking!) I want to create an online database so that people can apply to do projects within our datasets, none of which have been fully explored. We probably have over 25,000 annotated continuous ECG recordings, mostly Holters, but also sleep studies, lab studies, animal studies, NICU and ICU studies etc.

The earlier recordings are just the beat-to-beat files from which HRV is calculated. When more storage became available, we stored the digitized multichannel ECG. Now we can store the analyzed recording saved directly from the Holter scanner (which will read any continuous ECG recording) as well. There are huge and frustrating HIPPA issues about doing this, even though the data are de-identified, and, post-HIPPA, nearly impossible to connect to the actual person. It is an active area of effort.

Most Important Research Achievement

I have been very much oriented to looking at beat-by-beat heart rate patterns, even if they are obtained from a 24-hour (or longer) continuous ECG recording. We routinely create a heart rate tachogram, on a scale that is interpretable, for every recording, even for very short ones. Seeing these patterns result in insights that cannot come from numbers alone. I think one of my most important research achievements, possibly being somewhat undone now by the commercialization of self-monitoring HRV apps and the oversimplification of what they can be used for, is to promote a much deeper understanding of the complex physiology that HRV reflects. This has been further guided by the work of Stephen Porges (polyvagal theory) and Julian Thayer (neurovisceral integration).

One way to explore a deeper understanding of HRV is to plot it, using power spectral analysis. As a result, I was able to detect a form of higher HRV that should reflect better vagal functioning and therefore better health, but it does not. Unlike the earlier lesson that got me into the field, sometimes the changes in HRV with breathing are actually disorganized and unrelated to breathing. I called this erratic sinus rhythm (ESR). This HRV actually reflects a higher risk of mortality, at least in older adults, and can now be captured by some novel non-linear HRV measures that reflect the organization, rather than just the amount of HRV, but at the time I published on it, that was not known.

Shortly after I had begun to observe ESR, I saw a poster at a cardiology meeting, from the Cardiovascular Health Study (CHS), reporting the higher “vagal” HRV is associated with healthy aging, because, cross-sectionally, the oldest participant had higher values. I asked the presenter “How do you know that this is truly respiratory sinus arrhythmia, maybe it is a more disorganized sinus rhythm?” The person I asked contacted me later and said “We need you in the CHS.”

The result was an R0-1 to re-analyze all of the 2,500 or so Holter recordings in the CHS, and a renewal to analyze the two cycles of overnight sleep studies from the same participants in the Sleep Heart Health Study (SHHS). I also discovered that heart rate patterns could detect sleep onset and detect sleep disordered breathing from outpatient recordings. This was validated in the SHHS and we continue to update prior studies to include sleep-disordered breathing in risk models, including, currently, a predictive model for higher fasting glucose in the CHS. In all active studies, we notify the investigators who notify participants and encourage them to seek follow-up.

Currently, we are exploring abnormalities in circadian rhythms, specifically sleep time heart rate patterns which indicate that the person is not getting normal rest at night. In CHS, patterns at baseline and changes over five years in people with two Holter recordings appear to be associated incidents of dementia. We are also exploring the application of artificial intelligence (AI) to Holter-derived beat-to-beat files in order to detect clinical characteristics. In the first such effort, AI could successfully classify CHS participants as currently having no cardiovascular disease (CVD), subclinical CVD or clinical CVD with 96% accuracy. This was done as a pilot study on a smaller number of participants, but was just validated on the entire dataset of about 1,400 people with usable 24-hour recordings. Errors were always in the direction of classifying people who were supposedly free of CVD as having CVD. The potential applications of this methodology to our different datasets, e.g., to identify higher risk of mortality, or to detect subjects with depression, boggles the mind. And, since most of our datasets have the actual digitized ECG available as well, this further explodes the potential applications of AI.

Learning and Life in St. Louis

It had never occurred to me that I might live in the Midwest, but, of course, St. Louis is the perfect balance. It is big enough and cosmopolitan enough to have everything I might want, without nightmarish traffic and pollution and the cost of living is affordable. Also, now, social media and easy calling and VOIP means that we do not have to lose contact with people in other places. When I came here, I rented an apartment near Tower Grove Park, still one of my favorite places. I have grown so much since I got here. Partly, of course, since I got here in 1990, the world and what is possible, have changed. Also, in 1994, when the RFT was still ubiquitous and had a personals section, I met my second husband, an Indian man, who is a member of the Chemistry faculty at UMSL. We were together for 10 years and then divorced. During the time we were together, my first son, Daniel, who lived in Yellow Springs, Ohio, was diagnosed with brain cancer (ologdendroglioma) and died 10 years later, teaching all of us so much in that journey. His widow, after he died, went to medical school and is now the Medical Director of the Dayton Area Hospice. He left two children.

After our divorce and some recovery time, my ex- and I remained friends, and 2 ½ years ago we became a couple again, both of us very different people capable of so much more together. During that period also, I had been deeply involved in different modalities of personal growth (preventing unnecessary suffering) but felt like I was not very “good at” what they required me to do, e.g., release my anger by beating on pillows. Several years ago, I took a class at U College (Somatic Awareness) and one of the three modules was called Somatic Experiencing (SE). SE is about addressing and rewiring the underlying autonomic consequences of trauma (e.g., being stuck in a highly activated sympathetically mediated flight or fight mode mode). I got it, and suddenly my passion for HRV, a measure of autonomic functioning and my passion for using knowledge to prevent unnecessary suffering came together.

I no longer needed to be “good at” a modality to heal, because modalities like SE take into account my *actual* physiology instead of what someone else thinks it should be. I now knew why I was doing what I was doing in my research and in helping others. I did complete the 3-year SE certification program and it led me to other related modalities where my expertise in HRV and my earlier passion for optimizing childbirth and attachment of mother and baby all came together. I am now in a role, among others, of being able to help develop and guide trauma-healing research, where HRV can evaluate the baseline physiology and document healing that takes place.

What Does the Future Hold?

I would like to be able to continue my research into making the continuous ECG admit to everything, including research in the ICU where changes in HRV patterns might warn of an impending event before the patient becomes symptomatic. I want to continue to contribute to the science-based prevention and alleviation of unnecessary suffering, and to our application of autonomic physiology to promoting the increased ability of humans to love and support each other.

As mentioned before, I would love to find a way to make the incredible amount of clinical HRV data and research that we have done available so that others can further explore it or apply novel and yet to be discovered methods to deepen the insights from it.

I have mentored many foreign medical students and graduate students. I would love to continue to build on these collaborations. We are all learning to deal with this new world of information overload, but I am trying to learn how to navigate it with kindness to myself. As an example, I went off Facebook a couple of months ago, because it was taking up too much of my life, but I continue to manage the Somatic Experiencing Research Coalition page so that I can share relevant research findings with a large community. We also have a WUSM HRV Lab page where I post personal updates from anyone who has spent time in the lab.

Hobbies

I do not have a lot of spare time, partly because I am and have always been someone who needed almost nine hours of sleep every night, one of the reasons I decided not to try to get an MD. I do love classical music and have a very good sound system. When I do my nightly treadmill exercise, there is always something interesting on YouTube, or a saved webinar, often related to trauma healing, but sometimes comedy. I have become able; recently, to watch Rachel Maddow and/or Lawrence O'Donnell again, but there was an unbearable period too. Weekends, I spend as much time as I can with my partner, just being together or going to events together, dealing with the necessary and getting ready for the week ahead.

Surprising Thing to Know about Phyllis

I would say they might be surprised to know about the several different "lives" I have led.

Below: Photographs by Robert Kleiger, Professor of Medicine, Cardiovascular Division

GETTING TO KNOW:
NATHANIEL HUEBSCH, PhD

Assistant Professor, Department of Biomedical Engineering

Education:

- 2003 BS, Bioengineering
  University of California,
  Berkeley, CA
- 2010 PhD, Engineering
  Science and Medical Engineering
  Harvard University, MA

Research Interests:

- Pluripotent-stem cell derived cardiac micro-tissues for modeling cardiac development, drug toxicity and cardiomyopathy
- Synthetic extracellular matrix mimetics with defined presentation of adhesion ligands and growth factors

I have been at WashU for just about two years. Previously, I was a research scientist at UC Berkeley working on a heart-on-a-chip team to develop iPSC-based models of disease. I was attracted to WashU because of its strengths in electrophysiology and collaborative science.

My lab uses human induced pluripotent stem cell technology, micro-fabrication, and tissue engineering to study how mechanical loading influences electrophysiology of heart muscle. We primarily rely on high-speed video microscopy, using fluorescent indicators of voltage and calcium, to monitor tissue conduction, calcium handling and contractility. We develop elastomer and hydrogel-based synthetic materials to change the extracellular matrix environment of cardiomyocytes, as well as to model changes in preload and afterload.

The most challenging aspect of making tissue-engineered models of disease is figuring out ways to test whether the *in vitro* models are actually predicting the biology that happens in the human body.

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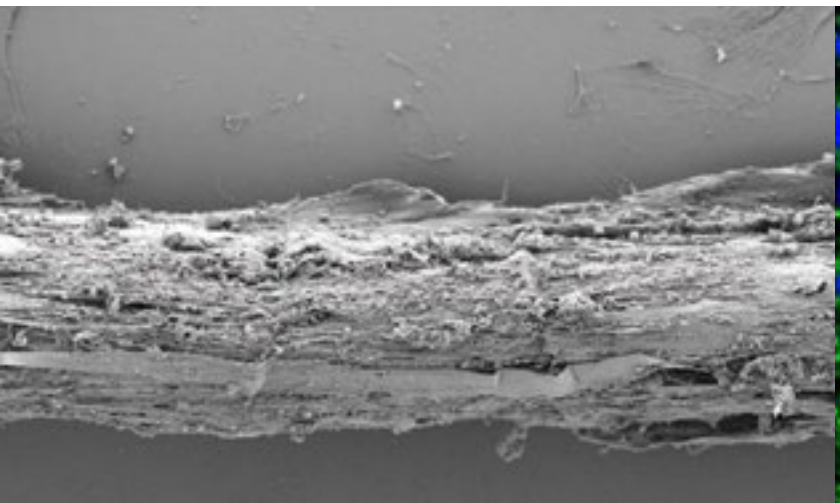
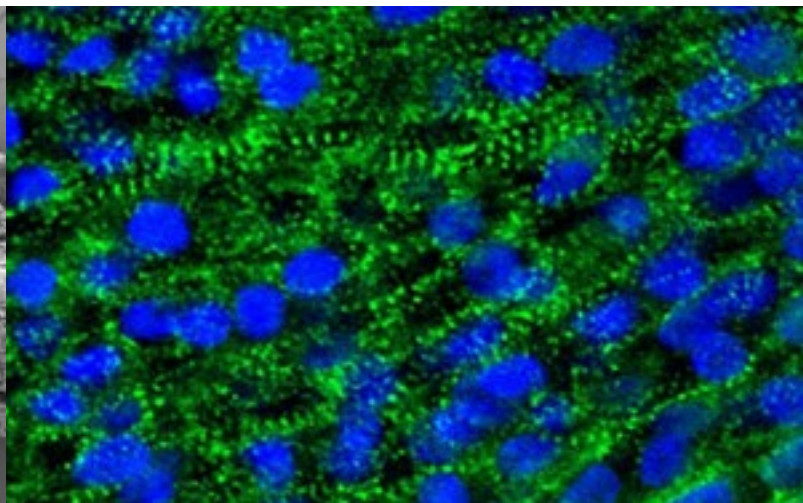




Research Interests and Professional Development

I was an undergraduate when the field of tissue engineering was growing rapidly. While trying to form tissue by putting cells on various polymer scaffolds and exposing them to growth factor cocktails meant to induce differentiation, researchers kept seeing that the scaffolds themselves had a very strong influence on differentiation – sometimes an even stronger influence than the growth factors had. I became fascinated by the idea that mechanical rigidity of the matrix cells grew could control differentiation. As a graduate student I studied how the mechanical rigidity of synthetic gel materials influence differentiation of bone marrow stromal cells encapsulated within.

During the course of my PhD studies, I became very interested in understanding more of the molecular machinery that cells used to sense their mechanical environment. I realized I needed to have a stronger background in stem cell and molecular biology to do this, so I opted to pursue postdoctoral work in iPSC technology. My postdoctoral mentor, Bruce Conklin, uses iPSC and genome editing techniques to study inherited cardiomyopathies. While working with Bruce, I became interested in combining my interests in tissue engineering with these cells. Through a collaboration with Kevin Healy at Berkeley, I was able to leverage study my longstanding interest of mechanobiology toward questions about inherited heart disease.

Previous Page Images: (Left) Scanning electron micrograph of a micro-heart muscle formed on normal tissue culture plastic. (Right) Thin section of a self-organized human iPSC-derived micro-heart muscle. Cardiomyocyte structure is revealed by staining for Sarcomeric Alpha-Actinin (green) and cell nuceli (blue).

I do not think there was a singular "epiphany" that led me to pursue an academic career, but there were certainly people who encouraged me along the way. My PhD mentor, David Mooney, provided me with a strong foundation in using engineering approaches to study basic questions about cell biology, as did my postdoctoral mentors. I also had mentors and colleagues in the lab who supported me during my research training and career search.

Motivations

I have been very fortunate to work with passionate, driven students, which is motivating in itself. In terms of problems: we still do not understand exactly how cells sense their mechanical environment, in terms of the passive mechanics of the extracellular matrix, as well as active forces transmitted through the tissue. It is a basic question important to all tissues in our body including the heart. But it also has important implications for understanding how disease develops: protein-coding genetic mutations linked to sudden cardiac death most commonly occur in structures that generate mechanical contraction (sarcomeres) or maintain the integrity of cell-cell junctions under loading (desmosomes).

Important Achievements

As a PhD student, I led some of the first work showing that stromal cell differentiation could be controlled by the mechanics (rigidity) of a cell-encapsulating material, and that this could affect cell-mediated bone repair in vivo. These were some of the first studies showing that you could use physical properties of materials to elicit therapeutic behaviors from transplanted cells.

I also had the chance to be involved with the development of some material-based cancer vaccines. Although I didn't lead this work, I'm very proud to have contributed to it – in the time since I left grad school, these materials went on to be used to successfully treat cancer patients. It is very humbling to have been involved in work that went on to directly affect patients' lives.

Future Goals

Inherited heart disease is the most common cause of arrhythmias in children, but it's very hard to predict exactly who will be most at risk for arrythmias, even when we know patients' genetics. I'm interested in the possibility that mechanical loading on the heart – caused by patients' hemodynamics – could act as a non-genetic modifier of arrhythmia risk. In the next few years, I hope we can use these models we're developing to directly test this idea. I am also interested in developing ways to change cardiomyocyte signaling using peptide-conjugated polymers.

In terms of long-term goals, I want to create in vitro models that allow us to predict both genetic and non-genetic contributions to arrhythmia and heart failure. I want to leverage the same models to test new biomaterials-based regenerative therapies for the heart.

Being a Member of the CBAC

There is often a disconnect between basic research and clinical reality. Having the chance to meet clinicians and hear directly about the problems they face every day when treating patients is important for bridging that gap. I have also benefitted tremendously from the chance to collaborate with other CBAC members, particularly Jon Silva and Stacey Rentschler.

Hobbies

My wife and I have two young children and we spend our spare time doing things with them. There are many things we enjoy about St. Louis, but my kids' favorites are probably the zoo and the City Museum.

(Left to Right): The Huebsch Family - Nate, Jacob, Isabella and Grace at Galaxy's Edge in Disneyland, California

PhD STUDENT:
BRITTANY BRUMBACK

Department of Biomedical Engineering

Stacey Rentschler Laboratory

I am a 4th year BME PhD candidate in Dr. Stacey Rentschler's lab on the medical school campus. My thesis research is focused on studying left/right differences in gene expression that regulate electro-physiology in the context of development and disease in both mouse and human ventricles. My research spans across mouse models, adult human donor hearts, and human iPSC-derived cardiomyocytes. I am particularly interested in uncovering mechanisms underlying chamber-specific congenital heart diseases and arrhythmias.

So far, the PhD experience has been quite the adventure. Prior to joining Dr. Rentschler's lab, I had very little wet lab experience, so I have spent a significant amount of time continuously learning a wide range of techniques from optical mapping to Western blotting. In addition to my technical training, I have also had the privilege and opportunity to practice grant writing, present my research at WashU and beyond, form professional networks and collaborations, as well as teach and mentor several students.

As a first-generation student from a small town, I have always been motivated to push boundaries and explore the unknown. This passion to constantly learn new things has led me to study abroad in Australia, pursue a research internship in Brazil, and decide to embark on a PhD journey. In research, the excitement that comes with being the only

person in the world to know something (for a short bit!) drives me to design the next experiment to answer follow-up questions. I love solving complex, interdisciplinary problems and communicating my research with the global scientific community. In my career, I aim to help close the gap between basic science and clinical research of therapeutic design in the treatment of arrhythmias and cardiovascular disease.

During the summer before my senior year of undergrad, I completed a research internship in Dr. José Bassani's Cardiovascular Research Laboratory at the Center for Biomedical Engineering at the University of Campinas, Brazil. Under Dr. Bassani's guidance, I worked in collaboration with an electrical engineering graduate student to test a new circuit design for defibrillators that would be more effective and less dangerous. Ultimately, this experience taught me that clinicians can only treat patients to the extent that engineers can design therapeutics, which cannot be done effectively without understanding the problem's underlying mechanism.

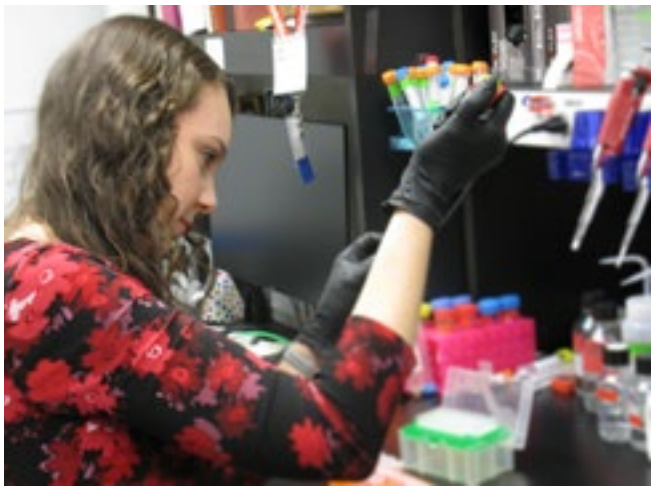
At a glance

Education:

- **2016** BS, Biomedical Engineering
  The George Washington University
- **2018** MS, Biomedical Engineering
  Washington University in St. Louis
- **x 2021** PhD, Biomedical Engineering
  Washington University in St. Louis

Research Interests:

The left/right differences in gene expression that regulate electrophysiology in the context of development and disease in both mouse and human ventricles.



(Left to Right): Stacey Rentschler, Brittany Brumback, Akshay Shekhar, and Glenn Fishman

Brittany Brumback receives her GRC Trainee Poster Award from Ursula Ravens (left) at the 2019 Gordon Research Conference on Cardiac Arrhythmia Mechanisms in Barga, Italy.

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In my senior year of undergrad at The George Washington University, I worked in Dr. Igor Efimov's cardiovascular engineering laboratory. That lab introduced me to panoramic optical mapping of the heart's conduction properties to study arrhythmogenic mechanisms. While working in the lab, I also realized that it was necessary to combine principles from my background in engineering and physiology with molecular biology to develop comprehensive understanding of the mechanisms underlying arrhythmias. From these experiences, I knew that interdisciplinary research was going to be a cornerstone of my future career as a biomedical scientist, and I chose to attend Washington University in St. Louis for my PhD studies due to the vast interdisciplinary cardiac research opportunities.

Before I arrived at WashU for my PhD, I met with Dr. Rentschler and became intrigued about how developmental signaling pathways could regulate crucial factors that can cause arrhythmias. My previous educational and research experiences were focused on medical device design for treatment of arrythmias, and I was looking for an opportunity to expand my graduate research to further understand biological mechanisms underlying cardiac disease. The Rentschler lab seemed to be an ideal place for me to become a part of, and after my rotation, I was hooked on both the interesting research and the amazing group of individuals working in the lab.

I am most proud of being awarded a National Science Foundation Graduate Research Fellowship and winning the best poster award at the Gordon Conference for Cardiac Arrythmia Mechanisms. Prior to graduate school, I had never had the chance to communicate my research, and these experiences early in my career have given me the confidence to continue presenting my research and pursuing professional development as an interdisciplinary scientist.

Since I have been in St. Louis, I have learned to embrace every opportunity to explore aspects of life outside of science and research to maintain a work-life blend. Taking time to further understand myself and my passions outside of lab has enabled me to grow personally and has ultimately made me a better scientist as well.

I am also proud that I have been able to overcome the barriers to becoming the first person in my family to not only graduate with a bachelor's but also a master's degree and soon a PhD, all while maintaining a 4-year international relationship with my now fiancé, Bruno. I would not have been able to make it through without the endless support of my family, friends, and Bruno.

My short-term goals are to publish manuscripts sharing my thesis research, defend my thesis, and ultimately finish my PhD training. While I have not quite resolved which career path lies beyond the PhD, my long-term goals are to remain connected to the research community and help advance translational research and therapeutic development for cardiovascular diseases.

When I'm not in lab, I enjoy spending time with my fiancé, Bruno, and exploring the events around St. Louis. We both are passionate about travelling and extreme sports such as bungee jumping, skydiving, glacier climbing, dog sledding, white water rafting, and more.

As a BME student working in a cardiology lab, the CBAC provides a home for interdisciplinary cardiac research that unites the Danforth and medical campuses. I enjoy attending the seminar series and constantly learning from scientists, physicians, and physician scientists that work on a huge range of topics related to cardiac health.

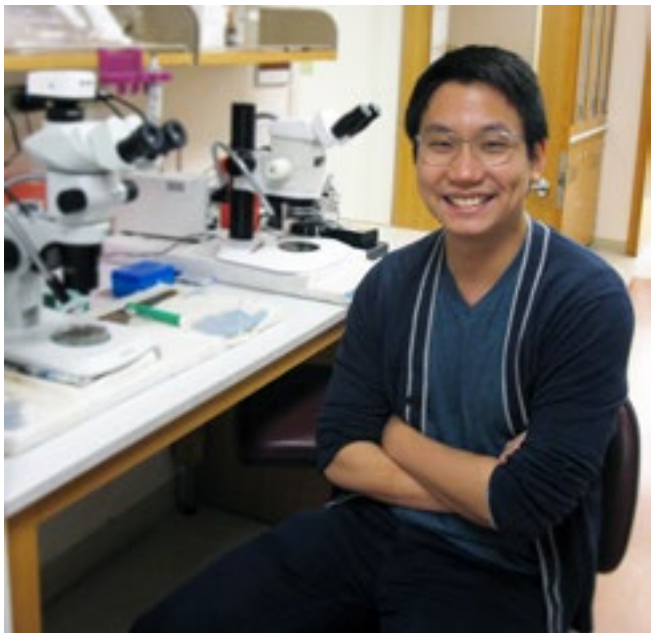
MD, PhD STUDENT:
POWEI (BILLY) KANG

Division of Biology & Biomedical Sciences

Jianmin Cui Laboratory

I enrolled as a MD/PhD student at WashU in 2015, and I am currently a third year PhD student in Dr. Jianmin Cui's lab working in the field of ion channel biophysics. I am particularly interested in the molecular aspect of cardiac electrophysiology. Normal heart function requires synchronized cellular electrical activity provided by proteins called voltage-gated ion channels. When these ion channels fail due to drug or inherited mutation, life-threatening arrhythmias can occur. My thesis work involves studying one such voltage-gated ion channel called KCNQ1. The lab's overall goal is to determine the molecular mechanism underlying how KCNQ1 opens to conduct ionic current in response to changes in the transmembrane potential of the cell. To this end, I perform experiments to record ionic current through KCNQ1 channels. I also measure KCNQ1 channel molecular movement and interaction with other protein partners through sensitive optical fluorescence experiments. These experiments ultimately allow us to understand how KCNQ1 channel normally function, how aberrant behavior of KCNQ1 may lead to disease, and how therapeutic strategies may be devised to restore abnormal KCNQ1 channels.

The thrill of scientific discovery and unraveling fundamental knowledge of the natural world motivates me to do what I do. We devise new experiments and methodologies to answer these fundamental questions about how the world works. The answers we obtain



typically spawn questions that are even more interesting. This cycle of ever-changing questions excites me the most. I hope that my work can serve as research directions for others in the field, explain human diseases, and ultimately help advance human health.

I immigrated with my family to the U.S. from Taiwan when I was ten years old. I was drawn to engineering and science early on. Some of my best high school memories were of long nights spent with friends putting together engineering projects for Science Olympiad competitions. I distinctively remember an event in which we were tasked with building a car powered by gravitational energy. We took the heaviest pineapple can in the kitchen and rigged it to fall and send our car flying!

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Above: The microscopy setup that Powei (Billy) Kang uses to guide different colored laser beams into a fluorescence microscope to image ion channels in living cells.

These experiences drove me to pursue biomedical engineering at Johns Hopkins University. Even today in Dr. Cui's lab, I often find myself jerry-rigging parts for quick experiments. Unfortunately, I no longer use oversized pineapple cans for lab safety reasons.

During my undergraduate studies at Johns Hopkins University, I found myself leaning toward the electrical engineering and instrumentation courses. In my junior year, I was introduced to ion channel biophysics by Dr. David Yue. Dr. Yue gave riveting lectures on how ion channels function as biological transistors, analogous to how electronic transistors found in modern computers. I was fascinated by this intersection of biology and engineering. I later joined Dr. Yue's lab as an undergraduate student and eventually a master's student, where I studied voltage-gated sodium channels. I greatly enjoyed my work in the Yue lab and decided to continue pursuing the field of electrophysiology in my PhD studies.

I first met Dr. Cui when I interviewed for the combined MD/PhD program at WashU. The thirty-minute interview flew by as we both gushed about channel biophysics. My interviews with Dr. Cui and other faculty in the CBAC fully convinced me that WashU is an excellent place to train as an aspiring ion channel biophysicist. Given the strong training environment at WashU and the perfect match with my research interests, coming to WashU was an easy choice for me.

Lab Life and Hobbies

I have come to appreciate that every occasion for celebration should not be missed. Whether it is a birthday or a good manuscript peer review, life is significantly improved when small victories are celebrated.

My wife Lily and I enjoy spending the evening preparing a nice meal together.

Powei (Billy) Kang

Education:

- **2014** BS, Biomedical Engineering Johns Hopkins University
- **2015** MS, Biomedical Engineering Johns Hopkins University
- **x 2023** MD, PhD, Biomedical Engineering Washington University in St. Louis

Research Interests:

- Study the structure and function of the voltage-gated potassium channel KCNQ1
- How KCNQ1 works on the molecular level and how dysfunction in KCNQ1 can lead to human disease

We also enjoy playing co-operative video games, in which we work together (usually successfully), to complete objectives and puzzles.

What the Future Holds

After completing my doctoral thesis work, I plan to return to medical school to finish the remainder of the combined MD/PhD degrees. I expect to move on to residency training to solidify my clinical training. I plan to join a residency program with significant research or post-doc components such that I will continue to grow as a physician scientist.

CBAC Collaborations

CBAC is a strong community of electrophysiology researchers that fosters a highly collaborative research environment. I anticipate that I will participate in collaboration projects with other members of CBAC through the course of my thesis work. As another highlight, the CBAC seminars are easily among the best scientific talks at WashU.

NEWS & ANNOUNCEMENTS 2019-PRESENT

IN THE NEWS

Jon Silva, PhD, developed the first computational model that shows the molecular groundwork of a popular drug's effectiveness in a variety of ways. The findings were published in the Journal of the American College of Cardiology: Basic to Translational Science October 2019 issue.
Link: https://engineering.wustl.edu/news/Pages/New-model-of-irregular-heartbeat-could-boost-drug-efficacy.aspx

Clifford Robinson, MD, **Daniel Cooper**, MD, **Mitchell Faddis**, MD, PhD, **Timothy W. Smith**, D Phil, MD, **Pamela Woodard**, MD, **Yoram Rudy**, PhD, **Phillip Cuculich**, MD, et al. developed a noninvasive radiation therapy approach to treating ventricular tachycardia. A single high dose of radiation aimed at the heart significantly reduces episodes of a potentially deadly rapid heart rhythm, according to results of a phase one/two study. The research was reported on Sept. 15, 2019 at the American Society for Radiation Oncology (ASTRO) Annual Meeting in Chicago.
Link: https://medicine.wustl.edu/news/radiation-therapy-effective-against-deadly-heart-rhythm/

Phillip S. Cuculich, MD received the Skandy Award in Innovation from the Skandalaris Center for Interdisciplinary Innovation and Entrepreneurship, Washington University in St. Louis.

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NEWS & ANNOUNCEMENTS 2019-PRESENT (Continued)

CONGRATULATIONS TO

Yoram Rudy, PhD (right) received the Chancellor's Award for Innovation and Entrepreneurship on Nov. 8, 2019. Prior to that, he was inducted into the National Academy of Inventors (NAI) to the rank of Fellow.
Link: https://fuse.wustl.edu/two-faculty-members-named-national-academy-of-inventors-fellows/?_ga=2.7716786.1018925473.1546871913-1457637254.1545836855

Pamela Woodard, MD, recognized for her expertise in cardio-thoracic radiology has been named the inaugural Hugh Monroe Wilson Professor of Radiology.
Link: https://medicine.wustl.edu/news/woodard-named-wilson-professor-of-radiology/

Douglas Mann, MD received the Heart Failure Society of America Lifetime Achievement Award at the 23rd Annual Heart Failure Society of America Scientific Meeting in Philadelphia, PA.
Link: https://www.hfsa.org/douglas-l-mann-md-fhfsa-to-receive-2019-hfsa-lifetime-achievement-award/

Clifford Robinson, MD received the James T. Willerson Award In Clinical Science for paper "Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia," recognizing "the best clinical paper published in Circulation in the preceding twelve months." Paper: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331281/

Yoram Rudy, PhD gave two keynote lectures, "Noninvasive Mapping of Ventricular Arrhythmic Substrates and Arrhythmias in the Intact Human Heart" Universitat Politecnica de Valencia, Ciudad Politecnica de la Innovacion, CARBIOyTEC 2019 in Valencia, Spain and "The Story of ECG-Imaging from Concepts to Clinical Application" UCL & Barts Heart Centre Translational Electrophysiology Symposium in London, UK

Rajan Sah, MD and **Chao Zhou**, PhD received the Leadership and Entrepreneurial Acceleration Program (LEAP) Award from Washington University in St. Louis.
Link: https://fuse.wustl.edu/washu-fall-2019-leap-challenge-winners/

Jennifer N. Avari Silva, MD received the World Zoroastrian Chamber of Commerce Outstanding Zarathushti Entrepreneur and the Skandy Award in Innovation from the Skandalaris Center for Interdisciplinary Innovation and Entrepreneurship, Washington University in St. Louis.

TITLE CHANGES

R. Martin Arthur, PhD is now the Newton R. & Sarah Louisa Glasgow Wilson Emeritus Professor.

Daniel Cooper, MD, has been promoted to Associate Professor of Internal Medicine, Cardiovascular Division. He is also the Director of Electrophysiology Fellowship.

TITLE CHANGES (CONTINUED)

Patrick Jay, MD, PhD, is currently a Director at Alnylam Pharmaceuticals in Boston.

R. Gilbert Jost, MD is now the Professor Emeritus of Radiology.

Amit Noheria, MBBS, SM, is now an Associate Professor in the Department of Cardiovascular Medicine at Kansas University Medical Center, the University of Kansas.

Daniel Ory, MD, is now also a Senior Vice President of Translationational Medicine, Casma Therapeutics.

Jean Schaffer, MD, is currently the Associate Research Director, Joslin Diabetes, and a Member, Faculty of Medicine, Harvard Medical School.

Jon Silva, PhD, has been promoted to Associate Professor of Biomedical Engineering, Department of Biomedical Engineering.

Gautam Singh, MD is now a Professor of Pediatrics at Central Michigan University.

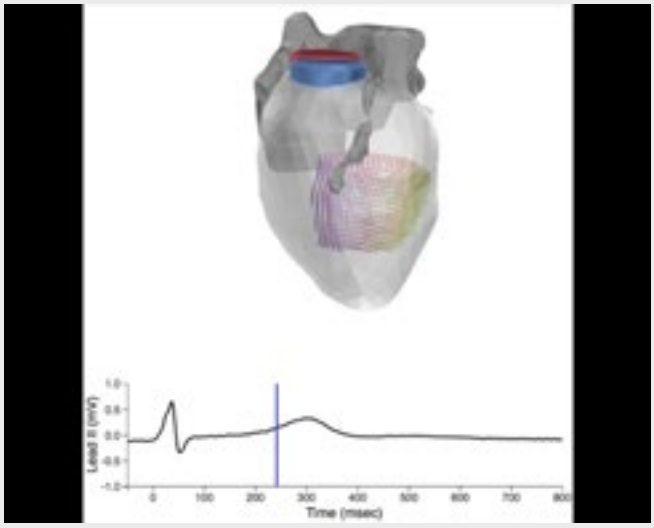
George Van Hare, MD is now also a part-time Medical Officer in the FDA's Implantable Electrophysiology Devices Branch in the Cardiac Devices division of CDRH.

FOCUS ON A SPECIAL REPORT

ELECTROMECHANICS OF THE NORMAL HUMAN HEART IN SITU

The Yoram Rudy laboratory conducts first study of electromechanics of healthy, living human hearts.

Link: https://engineering.wustl.edu/news/Pages/Rudy-lab-conducts-first-study-of-electromechanics-of-healthy,-living-human-hearts.aspx



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January 2019 - June 2020

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PAMELA K. WOODARD, MD

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PAMELA K. WOODARD, MD (Cont.'d)

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LECTURES & PRESENTATIONS

January 2019 - June 2020

DANIEL H. COOPER, MD

2019 Cooper DH. "Approach to PVC and VT ablation.'' EP Core Curriculum Conference, Washington University School of Medicine, St. Louis, MO (January).
2019 Cooper DH. "Chair/Master of Ceremony: Ask the EP Experts." ACC Scientific Sessions, New Orleans, LA (March).
2019 Cooper DH. "Live Case: LV Summit PVC Ablation for PVC-induced Cardiomyopathy." ARCH EP St. Louis, MO (April).
2019 Cooper DH. "Moderator: Real-World Case Presentations." ARCH EP, St. Louis, MO (April).
2019 Cooper DH. "Painless Defibrillation." ARCH EP, St. Louis, MO (April).
2019 Cooper DH. "Novel PVC Mapping & Navigation with Robotic EP." Robotic EP Pro Talks at HRS 2019, San Francisco, CA (May).
2019 Cooper DH. "SA Node, AV node, His-Purkinje System" EP 101: A Program for Incoming EP Fellows, Boston, MA (May).
2019 Cooper DH. "Workshop: Cardiac Conduction System" EP 101: A Program for Incoming EP Fellows, Boston, MA (May).
2019 Cooper DH. "Proof and Probability: Approach to Narrow Complex Tachycardia." EP Core Curriculum Conference, Washington University School of Medicine, St. Louis, MO (August).
2019 Cooper DH. "'Brady' and Blocks: Who should make me nervous" Cardiology and Primary Care Update, Yosemite National Park, CA (August).
2019 Cooper DH. "Corralling the Racing Heart: Approach to SVT." Cardiology and Primary Care Update, Yosemite National Park, CA (August).
2019 Cooper DH. "Sorting Through the Headlines: Anticoagulation in Atrial Fibrillation." Cardiology and Primary Care Update, Yosemite National Park, CA (August).
2019 Cooper DH. "Beyond Beta Blockers: Modern Day Management of PVCs." Cardiology and Primary Care Update, Yosemite National Park, CA (August).
2019 Cooper DH. "Sorting out Syncope: Benign to Deadly." Cardiology and Primary Care Update, Yosemite National Park, CA (August).
2019 Cooper DH. "Finding and Fighting the Enemy: Sudden Cardiac Death." Cardiology and Primary Care Update, Yosemite National Park, CA (August).

RALPH J. DAMIANO, Jr, MD

2019 Damiano, Jr, MD. "Optimizing Results of the Maze IV Procedure; Lessons Learned from the ABLATPAS Post Market Approval Trial and An Update on Recent Research and Clinical Papers." The Society of Thoracic Surgeons Annual Meeting, San Diego, CA (January).
2019 Damiano, Jr, MD. "Cox-Maze IV." 1st Annual St. Louis Cardiac Surgery Symposium, St. Louis, MO (February).
2019 Damiano, Jr, MD. "Patients with Advanced Atrial Fibrotic Myopath Should be Surgically Ablated." Western Atrial Fibrillation Symposium, Park City, UT (February).
2019 Damiano, Jr, MD. "Case Presentations - Houston, We have a Problem! " Afib. Re-Evolution Summit, Houston, TX (April).
2019 Damiano, Jr, MD. "Persistent AF: PVI Plus What? Lessons from Surgical Maze Experience. ARCH, St. Louis, MO (April).
2019 Damiano, Jr, MD. "How to Deal with the Appendage." American Association for Thoracic Surgery Annual Meeting Mitral Conclave, New York, NY (May).
2019 Damiano, Jr, MD. "Maximizing Bipolar Ablation Performance." New Research. American Association for Thoracic Surgery Annual Meeting Mitral Conclave, New York, New York (May).
2019 Damiano, Jr, MD. "Second Conduit for CABG in a 75-Year-Old: Vein." American Association for Thoracic Surgery Annual Meeting, Toronto, Canada (May).
2019 Damiano, Jr, MD. "Indications for Atrial Fibriallation Surgery and Open Chest/Concomitant Maze." Get in Rhythm. Stay in Rhythm. Atrial Fibrillation Patient Conference, Dallas, TX (August).
2019 Damiano, Jr, MD. "How I do it: Maze-IV Procedure." The Catheter and Surgical Therapies for Atrial Fibrillation Conference, Chicago, IL (August 16).

RALPH J. DAMIANO, Jr, MD (Cont.'d)

2019 Damiano, Jr, MD. "Long-term Results of the Maze Procedure for Atrial Fibrillation." The Catheter and Surgical Therapies for Atrial Fibrillation Conference, Chicago, IL (August).
2019 Damiano, Jr, MD. "Surgical Treatment of Atiral Fibrillation: Current State of the Art." 2019 Annual Meeting, Northern New England Chapter, ACC. New Castle, NH (October).
2019 Damiano, Jr, MD. "Surgical Treatment of Current Atrial Fibrillation: State-of-the-Art." University of Missouri School of Medicine, Columbia, MO (October).
2019 Damiano, Jr, MD. "Minimally Invasive A-Fib Ablation and LAA Closure." Course Director: The Heart Team Summit, Chicago, IL (October).
2019 Damiano, Jr, MD. "ECGI and Advanced in Atrial Fibrillation Surgery." Asia Pacific Heart Rhythm Society Scientific Session, Bangkok, Thailand (October).
2019 Damiano, Jr, MD. Moderator: "Surgical Ablation of Atrial Fibrillation: Joint sessions between STST and APHRS." Asia Pacific Heart Rhythm Society Scientific Session, Bangkok, Thailand(October).
2019 Damiano, Jr, MD. "Minimally Invasive Septal Myectomy for HCM." Asia Pacific Heart Rhythm Society Scientific Session, Bangkok, Thailand (October).
2019 Damiano, Jr, MD. "Surgical Treatment of Atrial Fibrillation: Current State of the Art." Grand Rounds, Johns Hopkins University School of Medicine. Baltimore, MD (November).
2019 Damiano, Jr, MD. "Mechanisms of Atrial Fibrillation: New Insights and Their Implications for Surgical Ablation." China Heart Congress, Beijing, China (November).
2019 Damiano, Jr, MD. "The Scienfific Basis of Surgical Ablation." China Heart Congress, Beijing, China. (November).
2019 Damiano, Jr, MD. "Live Operation – Maze IV procedure in Atrial Fibrillation Concomitant Mitral Valve Surgery." China Heart Congress, Beijing, China (November).
2019 Damiano, Jr, MD. "The Evolution of Current Role of the Cox Maze IV Procedure." Keynote Speaker. China Heart Congress, Beijing, China (November)..

MICHAEL J. GREENBERG, PhD

2019 Greenberg, PhD. "Dissecting the Mechanism of Familial Cardiomyopathies from the Ground Up." Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, MO (May).
2019 Greenberg, PhD. Keynote Lecture - Department of Physiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
2019 Greenberg, PhD. "Understanding Familial Cardiomyopathies from the Ground Up." Cardiac Bioelectricity and Arrhythmia Center, Washington University, St. Louis, MO (December).
2020 Greenberg, PhD. "Disrupted Mechanobiology in Familial Cardiomyopathies." Department of Genetics, Washington University, St. Louis, MO (February).

NATHANIEL HUEBSCH, PhD

2019 Huebsch, PhD. "Metabolic Cues Enhance Maturation of Human iPSC-derived Cardiomyocytes in a Cardiac Microphysiological System." SelectBio Biofabrication & Biomanufacturing Europe Conference, Rotterdam, The Netherlands (June).
2019 Huebsch, PhD. "*In vitro* studies of the synergy between mechanical loading and genetics within human induced stem cell derived micro-scale engineered heart tissues." Keynote Speaker. 56th Annual Technical Meeting of the Society for Engineering Science, St. Louis, MO (October).

DOUGLAS L. MANN, MD

2019 Mann, MD. "Myocardial Recovery and the Failing Heart: The Audacity of Hope." Frontiers in Cardiovascular Medicine, University of Michigan, Ann Arbor, MI (April).
2019 Mann, MD. "Myocardial Remission in Heart Failure: The End of the Beginning or the Beginning of the End." University of Missouri Biomedical Science, Columbia, MO (April).
2019 Mann, MD. "Myocardial Remission in Heart Failure: The End of the Beginning or the Beginning of the End," Northwestern University, Chicago, IL (June).
2019 Mann, MD. "Medical Device-Based Therapies for Heart Failure with Reduced Ejection Fraction." Gordon Research Conference on Assisted Circulation, Castelldefels, Spain (June).
2019 Mann, MD. "Mechanisms of Reverse Remodeling." Gordon Research Conference on Assisted Circulation Castelldefels, Spain (June).

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LECTURES & PRESENTATIONS

January 2019 - June 2020 (continued)

JEANNE M. NERBONNE, PhD

2019 Nerbonne, PhD. "Advances in Cardiac Ion Channel Structure." Gordon Research Conference entitled: Cardiac Arrhythmia Mechanisms: Addressing Multiscale Challenges in Arrhythmia Biology by Integrating Molecular, Genomic, Computational and Translational Approaches, Lucca, Italy. Discussion Leader (April).

COLIN NICHOLS, PhD

2020 Nichols PhD. "K Channels and Diseases." Function journal inaugural symposium. Duke University, Durham, NC (January).

STACEY RENTSCHLER, MD, PhD

2019 Rentschler, MD, PhD. "Notch-Mediated Transcriptional and Epigenetic Regulation of Cardiac Ion Channels." Gordon Conference on Cardiac Arrhythmia Mechanisms, Lucca, Italy (April).
2019 Rentschler, MD, PhD. Weinstein Cardiovascular Development Conference, Cardiac Conduction System, Indianapolis, IN. Session Chair (May).
2019 Rentschler, MD, PhD. "Transcriptional and Epigenetic Regulation of Cardiac Electrophysiology." Baylor College of Medicine, Cardiovascular Research Institute, Houston, TX (November).
2019 Rentschler, MD, PhD. Cincinnati Children's Heart Institute, Cody Lecture Series, Cincinnati, OH
2019 Rentschler, MD, PhD. American Heart Association Scientific Sessions Arrhythmia Research Summit, Philadelphia, PA (November).
2020 Rentschler, MD, PhD. Duke University, CVRC Mandel Seminar Series, Durham, NC (February).

CLIFFORD G. ROBINSON, MD

2019 Robinson, MD. "ENCORE-VT for Ventricular Tachycardia." George Washington University Combined Cardiology and Radiation Oncology Grands Rounds and Visiting Professorship, Washington, D.C. (February).
2019 Robinson, MD. "ENCORE-VT for Ventricular Tachycardia." University of Miami Combined Cardiology and Radiation Oncology Grands Rounds and Visiting Professorship, Miami, FL (March)
2019 Robinson, MD. "Live Case – Noninvasive Cardiac Radioablation." ARCH Symposium, St. Louis, MO (April).
2019 Robinson, MD. "Radiotherapy as a Last Resort." Heart Rhythm Society Annual Meeting, EHRA/HRS Joint Session, San Francisco, CA (May).
2019 Robinson, MD. "Role of Immunotherapy and SBRT for Inoperable Early Stage NSCLC" IASLC Chicago Meeting, Chicago, IL (October).
2019 Robinson, MD. "ENCORE-VT for Ventricular Tachycardia." SABR Symposium Plenary Session (November).
2019 Robinson, MD. "ENCORE-VT for Ventricular Tachycardia." Cedars-Sinai Combined Cardiology and Radiation Oncology Grands Rounds and Visiting Professorship, Los Angeles, CA (November).
2019 Robinson, MD. "ENCORE-VT for Ventricular Tachycardia." University of Pittsburgh Combined Cardiology and Radiation Oncology Grands Rounds and Visiting Professorship, Pittsburgh, PA (December).
2020 Robinson, MD. "Noninvasive Cardiac Radioablation for Ventricular Tachycardia." 25th annual kukuna-o-ka-la Radiation Oncology Conference, Kapolei, HI (January).
2020 Robinson, MD. "ENCORE-VT for Ventricular Tachycardia." Lehigh Valley Health Network Combined Cardiology and Radiation Oncology Grands Rounds and Visiting Professorship, Allentown, PA (March).
2020 Robinson, MD. "Noninvasive Cardiac Radioablation for Ventricular Tachycardia." ESTRO Annual Meeting Plenary Session, Milan, Italy (April).

YORAM RUDY, PhD, FAHA, FHRS

2019 Rudy, PhD, FAHA, FHRS, "Non-invasive Electrocardiographic Imaging (ECGI): Methods and Examples of Clinical Applications."University College London (UCL) Institute of Healthcare Engineering (March).
2019 Rudy, PhD, FAHA, FHRS. "Relating Ion Channel Structural Dynamics to Physiological Function – The IKs Paradigm." Gordon Research Conference on Cardiac Arrhythmia Mechanisms, Il Ciocco, Italy (April).
2019 Rudy, PhD, FAHA, FHRS. University of Florence School of Medicine, Firenze, Italy (April).
2019 Rudy, PhD, FAHA, FHRS. Imperial Centre for Translational and Experimental Medicine, Imperial College London, London, United Kingdom (May).
2019 Rudy, PhD, FAHA, FHRS. "Noninvasive Mapping of Ventricular Arrhythmic Substrates and Arrhythmias in the Intact Human Heart." Keynote Lecture. Universitat Politecnica de Valencia, Ciudad Politecnica de la Innovacion, CARBIOyTEC 2019, Valencia, Spain (May).
2019 Rudy, PhD, FAHA, FHRS. Universitat Politecnica de Valencia, Institute for Research and Innovation in Bioengineering, Valencia, Spain (May).
2019 Rudy, PhD, FAHA, FHRS. University College London (UCL) Institute of Cardiovascular Science Distinguished Speaker Seminar, London, United Kingdom (June).
2019 Rudy, PhD, FAHA, FHRS. "The Story of ECG-Imaging from Concepts to Clinical Application." Kenote Lecture. UCL & Barts Heart Centre Translational Electrophysiology Symposium, London, United Kingdom (June).
2019 Rudy, PhD, FAHA, FHRS. University of Bern School of Medicine Seminar in Cardiology, Bern, Switzerland (June).
2019 Rudy, PhD, FAHA, FHRS. University of Bern Department of Physiology, Bern, Switzerland (June).
2019 Rudy, PhD, FAHA, FHRS. University of Amsterdam, Grand Rounds in Cardiology, Amsterdam, The Netherlands (July).
2019 Rudy, PhD, FAHA, FHRS. University of Amsterdam, Department of Clinical and Experimental Cardiology Seminar, Amsterdam, The Netherlands (July).
2019 Rudy, PhD, FAHA, FHRS. University of Amsterdam, Department of Clinical and Experimental Cardiology, Master Class on ECGI, Amsterdam, The Netherlands (July).
2020 Rudy, PhD, FAHA, FHRS. 6th UC Davis Cardiovascular Symposium, Davis, CA (February).

RAJAN SAH, MD, PhD

2019 Sah, MD, PhD. "SWELL1/LRRC8a (VRAC) channel signaling." Ion Channel Symposium, University of Copenhagen, Copenhagen, Denmark (May).
2019 Sah, MD, PhD. "SWELL1/LRRC8a mediated nutrient sensing." 30th Ion Channel Meeting, Association Canaux Ionique, Setes, France (September).
2019 Sah, MD, PhD. "SWELL1-LRRC8 regulation of glucose homeostasis." Department of Biochemistry & Molecular Medicine School of Medicine & Health Sciences, The George Washington University, Washington, DC (September-October)
2019 Sah, MD, PhD. "Targeting dysfunctional ion channel signaling to treat cardio-metabolic disease." Cardiology Grand Rounds, Cardiovascular Division, Washington University in St. Louis, St. Louis, MO (October).
2019 Sah, MD, PhD. "Targeting dysfunctional ion channel signaling to treat NAFLD." NAFLD Interest Group, (October).
2019 Sah, MD, PhD. "Dysfunctional adipose ion channel mechano-signaling induces NAFLD and T2D." Digestive Diseases Research Center Seminar Series, Division of Gastroenterology, Washington University in St. Louis, St. Louis, MO (November).
2020 Sah, MD, PhD. "Pharmacological SWELL1-LRRC8 induction improves systemic glycemia and non-alcoholic fatty liver disease in murine Type 2 diabetes." NASH-TAG Conference, Park City, UT (January).

JENNIFER N. AVARI SILVA, MD

2019 Silva, MD. "From Unmet Need to Clinical Tool: Through the Eyes of an EP." Division of Cardiology Grand Rounds, University of Minnesota, Minneapolis, MN (January).
2019 Silva, MD. "Where Would You Ablate?" Women in Electrophysiology, San Diego, CA (February).
2019 Silva, MD. "What It Takes To Get A FDA Cleared Solution On The Market." VR in Healthcare, Tuscon, AZ (March).
2019 Silva, MD. "Wearable Technology And Cardiac Application." American College of Cardiology, New Orleans, LA (March).
2019 Silva, MD. "Novel Approaches to Ventricular Tachycardia Ablation." American College of Cardiology, New Orleans, LA (March).

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LECTURES & PRESENTATIONS

January 2019 - June 2020 (continued)

JENNIFER N. AVARI SILVA, MD (Cont.'d)

2019 Silva, MD. "Is VR and AR Ready for Clinical Medicine?" American College of Cardiology, New Orleans, LA (March).
2019 Silva, MD. "Navigating in 3D—What IR Can learn from other spaces?" Society for Interventional Radiology, Austin, TX (March).
2019 Silva, MD. "Avoiding Secondary Prevention ICDs." Heart Rhythm Scientific Sessions, San Francisco, CA (May).
2019 Silva, MD. "Social Media and Advocacy: Pipe Dream or Reality?" Heart Rhythm Scientific Sessions, San Francisco, CA (May).
2019 Silva, MD. "From Unmet Need to Practical Solution." Department of Anesthesiology Grand Rounds, Washington University School of Medicine,St Louis, MO (June).

JONATHAN R. SILVA, PhD

2019 Silva, PhD. "Precision Antiarrhythmic Medicine: The Devil is in the Molecular Details." Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine,St Louis, MO (February).
2019 Silva, PhD. "Understanding Emerging and Disruptive Technologies." Skandalaris Center for Interdisciplinary Innovation and Entrepreneurship, Washington University in St. Louis, St Louis, MO (February).
2019 Silva, PhD. "Precision Antiarrhythmic Medicine." Department of Biomedical Engineering, Ohio State University, Columbus, OH (November).
2020 Silva, PhD. "Modeling studies." Na+ Channels and Transporters Section, UC Davis Cardiovascular Symposium, Davis, CA (February).
2020 Silva, PhD. "Predicting Long QT Type 3 Patient Response to Class I Antiarrhythmics: The Devil is in the Molecular Details." Channelopathy 2020, Quebec City, Canada (June).

GEORGE VAN HARE, MD

2019 Van Hare, MD. "Challenging accessory pathways: Difficult supraventricular tachycardia - How to survive in the lab." European Heart Rhythm Association meeting, Lisbon, Portugal (March).
2019 Van Hare, MD. "Pay It Forward: Tips For Teaching Ablation." Heart Rhythm 2019, 40th Annual Heart Rhythm Scientific Sessions, San Francisco, CA (May).
2019 Van Hare, MD. "What's New in congenital AV block management?" European Cardiac Arrhythmia Society: 15th Annual Congress, Marseille, France (June).
2019 Van Hare, MD. "Have Rhythm management Randomized Clinical Trials Died: Who killed them and where are the alternatives?" FDA Viewpoint, 14th Global Cardiovascular Clinical Trialists Forum, Washington, DC (December).
2019 Van Hare, MD. "Risk Stratification for Sudden Arrhythmic Death: Is there a role for machine learning, big data or other options?" FDA Viewpoint, 14th Global Cardiovascular Clinical Trialists Forum, Washington, DC (December).

PAMELA K. WOODARD, MD

2019 Woodard MD. "Imaging the Biology of Atherosclerosis.' Hugh Monroe Wilson Professor of Radiology, Inaugural Installation, Eric P. Newman Center, Washington University School of Medicine, St. Louis, MO (January).
2019 Woodard MD. "Recent Advances and The Future of Cardiovascular CT: The Editors Speak!" Circulation Journals: Circulation/Circulation Cardiovascular Imaging, Society of Cardiovascular Computed Tomography (SCCT), Baltimore, MD (July).
2019 Woodard MD. "The Year-in-Review: Editor's Picks." Circulation Cardiovascular Imaging (as Associate Editor), North American Society for Cardiovascular Imaging, Seattle, WA (September).
2019 Woodard MD. "Cardiac PET/MRI perfusion imaging in Ischemic Heart Disease – New Frontiers." North American Society for Cardiovascular Imaging, Seattle, WA (September).

PAMELA K. WOODARD, MD (Cont.'d)

2019 Woodard MD. "Research in medical school and residency." Radiology Interest Group (RIG), Howard University College of Medicine, Washington, DC (September).

CBAC NEW MEMBERS:

AARTI DALAL, DO

Assistant Professor, Department of Pediatrics, Cardiology

Research Interests:
Pediatric heart rhythm disorders, electrophysiology studies, catheter ablation and pacemaker/defibrillator implantation

Education:
2002 BA, cum laude, Boston University
2007 DO, Rowan University, School of Osteopathic Medicine (formerly University of Medicine and Dentistry, School of Osteopathic Medicine)

MICHAEL J. GREENBERG, PhD

Assistant Professor of Biochemistry & Molecular Biophysics

Research Interests:
Understanding the regulation of cardiac power output in both health and disease

Education:
- 2004 BS, Brandeis University, Waltham, MA
- 2010 PhD, Boston University Medical School, Boston, MA

NATHANIEL HUEBSCH, PhD

Assistant Professor, Department of Biomedical Engineering

Research Interests:
- Pluripotent-stem cell derived cardiac micro-tissues for modeling cardiac development, drug toxicity and cardiomyopathy
- Synthetic Extracellular Matrix Mimetics with defined presentation of adhesion ligands and growth factors

Education:
- 2003 BS, Bioengineering, University of California, Berkeley, CA
- 2010 PhD, Engineering Science and Medical Engineering Harvard University, MA

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CBAC NEW MEMBERS
(CONTINUED)

RAJAN SAH, MD, PhD
Associate Professor of Medicine, Cardiovascular Division

Research Interests:
- Ion channel signaling in the adipocyte
- Ion channel regulation of pancreatic ß-cell function
- Modulators of calcium signaling in skeletal muscle
- Novel ion channel signaling in myocardium
- Ion channel signaling in endothelium

Education:
1996 BS, Physiology: University of Toronto, Ontario, Canada
2001 PhD, Institute of Medical Sciences, University of Toronto, Ontario, Canada
2004 MD, Institute of Medical Sciences, University of Toronto, Ontario, Canada

CHAO ZHOU, PhD
Associate Professor, Department of Biomedical Engineering

Research Interests:
- Space-division multiplexing optical coherence tomography (SDM-OCT)
- Molecular-targeted OCT and OCM for cancer detection
- OCT and OCM Imaging in Developmental Biology
- 3D OCT imaging of Brain Functions
- OCT (OCM) combined with deep learning
- Optogenetic pacing in Drosophila melanogaster using integrated OCM imaging and red light stimulation system

Education:
2001 BS, Department of Physics Peking University, Beijing, P.R. China
2003 MS, Department of Physics and Astronomy University of Pennsylvania, Philadelphia, PA
2007 PhD, Department of Physics and Astronomy University of Pennsylvania, Philadelphia, PA

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DIRECTOR YORAM RUDY, PhD, FAHA, FHRS

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DANIEL H. COOPER, MD

Associate Professor of Medicine
Cardiovascular Division
Director, Electrophysiology Fellowship
Washington University School of Medicine

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The Cardiac Bioelectricity & Arrhythmia Center (CBAC) presents:

CBAC 2019 Fall Seminar Schedule

Mondays @ 5:15 pm | Whitaker Hall, Room 218

Mon. 9/16

"Unravelling the Mechanisms of Fight or Flight: It's All About the Neighborhood"

Steven O. Marx, M.D. - Herbert and Florence Irving Professor of Cardiology; Professor of Medicine (Pharmacology), Columbia University College of Physicians and Surgeons; Director, Cardiovascular Fellowship Program, Columbia University Irving Medical Center

Mon. 10/28

"From Biological Pacemakers to Cancer Therapy"

Ira S. Cohen, M.D., Ph.D. - Distinguished Professor, Department of Physiology and Biophysics, Renaissance School of Medicine
Stony Brook University

Mon. 11/4

"Structural Mechanisms of Selectivity & Gating of the Mitochondrial Calcium Uniporter"

Youxing Jiang, Ph.D.- W.W. Caruth, Jr. Scholar in Biomedical Research
Rosewood Corporation Chair in Biomedical Science
UT Southwestern Medical Center, HHMI Investigator

Mon. 11/25

"ECGI AI in 2019: The Power to See the Invisible"

David E. Albert, M.D. - Founder & Chief Medical Officer
AliveCor Inc.

Mon. 12/2

"Understanding Familial Cardiomyopathies from the Ground Up"

Michael Greenberg, Ph.D. - Assistant Professor
Department of Biochemistry and Molecular Biophysics
Washington University in St. Louis School of Medicine

The Cardiac Bioelectricity & Arrhythmia Center (CBAC) presents:

CBAC 2020 Spring Seminars

MONDAYS @ 5:15 PM | WHITAKER HALL, ROOM 218

MON. 1/27

"FROM PACING THE HEART TO THE PACE OF EVOLUTION"

DENIS NOBLE, C.B.E., PH.D., F.R.S.
EMERITUS PROFESSOR OF CARDIOVASCULAR PHYSIOLOGY,
UNIVERSITY OF OXFORD, UNITED KINGDOM

MON. 2/10

"AN INTEGRATED HIGH-SPEED IMAGING AND OPTOGENETIC PACING SYSTEM TO STUDY THE DROSOPHILA HEART"

CHAO ZHOU, PH.D.
ASSOCIATE PROFESSOR, DEPARTMENT OF BIOMEDICAL ENGINEERING
WASHINGTON UNIVERSITY IN ST. LOUIS

MON. 3/23 TO BE RESCHEDULED

"ARRHYTHMIAS AFTER MYOCARDIAL INFARCTION - OF MYOCYTES AND FIBROBLASTS"

KARIN R. SIPIDO, M.D., PH.D.
PROFESSOR AND HEAD OF EXPERIMENTAL CARDIOLOGY DIVISION OF EXPERIMENTAL CARDIOLOGY,
DEPARTMENT OF CARDIOVASCULAR SCIENCES, KU LEUVEN, UNIVERSITY OF LEUVEN, BELGIUM

MON. 4/27 TO BE RESCHEDULED

"ABNORMALITIES IN SODIUM CURRENT AND CALCIUM HOMEOSTASIS AS DRIVERS OF ARRHYTHMOGENESIS IN HYPERTROPHIC CARDIOMYOPATHY"

ELISABETTA CERBAI, PH.D.
PROFESSOR OF PHARMACOLOGY, DEPARTMENT OF NEUROSCIENCES, PSYCHOLOGY, DRUG RESEARCH AND CHILD HEALTH, DIRECTOR, CENTER FOR MOLECULAR MEDICINE, SCHOOL OF MEDICINE AND SURGERY, UNIVERSITY OF FLORENCE, ITALY

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The CBAC Seminar Series was established in 2005 and has provided a steady platform for scientific exchange and discussion in the fields of cardiac electrophysiology and arrhythmia. The seminar speakers are leaders in these fields, from the US and abroad, both in the basic science and clinical aspects of cardiac electrophysiology. The archive of more than 150 seminar videos is an invaluable resource, available to all both on the CBAC website (cbac.wustl.edu) and on YouTube (**just type "cbac seminars" in the youtube.com search bar** or go to this link: https://www.youtube.com/channel/UCYz22ssMTrCTSva0n9uGfsA/).

We hope that the cardiac electrophysiology community will take advantage of this treasure.

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

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