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Synergistic Research between the Center of Arrhythmia Research and Michigan Biology of Cardiovascular Aging at The University of Michigan

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The Center for Arrhythmia Research (CAR) and the Michigan Biology of Cardiovascular Aging program (MBoCA) at The University of Michigan (UM) are performing synergistic research to examine how aging impacts arrhythmias, in particular atrial fibrillation (AF). This collaborative research endeavor has been driven by a very clear increasing clinical demand posed by the aging of our society. Specifically, by the year 2050 the number of older people over 65 years of age will exceed the number of younger people for the first time in history. Given this important trend, the growing health care needs of the aging population exacerbated by cardiovascular diseases will pose an ever-increasing burden on our health care resources. Cardiovascular diseases in the aging population have well surpassed other age-associated diseases such as susceptibility to infection, chronic lung disease and cancer as a cause of morbidity and mortality.[1] Investigation into the field of aging and cardiovascular diseases has tremendous potential to impact the health and quality of life of older people as no therapies exist that explicitly target aging-specific processes that enhance cardiovascular diseases such as AF.

Advanced age is the most critical factor for the development of AF; 10% of patients in their 8th decade have AF and 50% of patients with AF are 80 years of age or older. AF is largely a geriatric condition and older patients with AF have associated mortality and morbidity not only due to hemodynamic effects and thromboembolism but also to the side effects of therapy including an increased propensity for bleeding with anticoagulation and falls from heart rate controlling medications.[2] Not only does AF in older people pose a large health care morbidity and mortality burden, but AF with aging is costly. Thus, research is urgently needed to understand how aging predisposes to AF.

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The Center for Arrhythmia Research (http://www.med.umich.edu/arrhythmia_research/)

The UM Center for Arrhythmia Research (CAR) is a multi-disciplinary research facility that opened its doors on March 1, 2008. It is Co-Directed by José Jalife, M.D., Professor of Internal Medicine and the Cyrus and Jane Farrehi Professor of Cardiovascular Research, and Héctor Valdivia, M.D., Ph.D., the Frank Wilson Professor of Internal Medicine. The CAR's senior research staff is formed by a group of 8 cardiovascular investigators who hold tenured, tenure-track, and research faculty positions in the Department of Internal Medicine, with joint appointments in the Departments of Molecular & Integrative Physiology and Biomedical Engineering. They are supported by a staff of 40 individuals, including post-doctoral fellows, graduate students and technicians. The CAR is recognized as one of the leading centers worldwide in the study of cardiac electrophysiology, electromechanical coupling and arrhythmias. It is located within a 15,000 square feet area of state-of-the art research space of the North Campus Research Complex (NCRC) of the UM. The CAR strengthens what is already a leading research program in cardiovascular medicine at the UM and helps intensify our efforts at discovering new and effective approaches for the diagnosis and treatment of heart disease.

The history of the CAR began in December 2007 when 35 scientists and staff, under the leadership of Dr. Jalife, joined the UM Cardiovascular Center to form a new Center for Arrhythmia Research. While the CAR team brought with them more than $5 million a year in direct costs for research funding from federal agencies and foundations, and more than $2 million in research equipment, the move required major investment on the part of UM in terms of space, additional equipment and other resources. Thus, several major gifts to the Cardiovascular Center were crucial in making the recruitment of such a large group possible. They included the following: 1. Two endowed professorships. 2. A donor who pledged up to $50 million to the Cardiovascular Center in 2007. A portion of that gift helped support the creation of the CAR, which was an ideal example of the kinds of multidisciplinary programs the donor envisioned for the gift. 3. An anonymous donation that endowed the Bridges in Science Award, an annual one-time grant to foster innovative research that bridges the gap between scientific disciplines. Moreover, the purchase in 2009 of a land containing a 2.1 million square ft, 28-building complex from Pfizer, Inc., brought new and exciting opportunities for the members of the CAR. In November of 2011, they were among the first laboratory-based researchers who moved into the newly created NCRC, which gave CAR investigators additional ability to strengthen their collaborations with many other experts at the UM in fields that are relevant to cardiovascular research, and to create highly productive cooperative translational research programs of strong clinical significance.

Like for almost everyone else in biomedical research, NIH funding has been a challenge. In addition, CAR membership has undergone substantial turnover in its faculty roster since it was established in 2008, Nevertheless, CAR has maintained its critical mass. Its members continue to be productive basic and translational researchers who bring modern molecular, biochemical, biophysical and mathematical concepts to increase the understanding of the mechanisms of life-threatening cardiac arrhythmias, from the molecule to the bedside.

Together, they study the role of ion channels and signaling pathways in mechanisms of cardiac excitation, intercellular communication and impulse propagation and the underlying bases of acquired and inheritable cardiac arrhythmias. Importantly, CAR faculty members have secured more than $20 million (direct costs; 27 million in total costs) of research funding from the National Institutes of Health, the Leducq Foundation, the American Heart Association and industry. The major reason for CAR´s success is the research productivity of its members, which has been outstanding during the past 9 years. It has resulted in more than 150 publications in top journals such as Circulation Research, Circulation, Journal of Clinical Investigation, Proceedings of the National Academy of Sciences of the United States of America, and others. CAR members were first to investigate mechanisms of cardiac fibrillation using optical mapping techniques and to demonstrate the relevance of high-frequency rotors in the mechanisms of both AF and ventricular tachycardia/fibrillation.[3] One major topic of their research is the study of mechanisms of the transition from paroxysmal to persistent AF, including electrical remodeling, structural remodeling and fibrotic remodeling of epicardial fat.[4] CAR members recently developed a clinically relevant sheep model of long-term persistent AF that enables preclinical genomic and proteomic determination of electrical and structural remodeling associated with AF. Their studies in collaboration with clinical electrophysiologists at the UM have demonstrated for the first time that the pro-inflammatory protein galectin-3 is elevated in patients with persistent atrial fibrillation and that upstream therapy with a galectin-3 inhibitor significantly delays the progression to the persistent or permanent forms of AF in a sheep model.[5] Importantly, CAR´s recently established partnership with the UM MBoCA program has opened new and exciting avenues for research on the relationship between aging, inflammation and AF and should significantly increase research productivity and ability to secure funding in years to come. CAR members are also leading experts in the molecular mechanisms of excitation-contraction coupling, intracellular Ca^{2+} signaling and mechanisms of operation of ligand-gated Ca^{2+} channels, with strong interests in inheritable arrhythmogenic diseases related to intracellular calcium dysfunction like hypertrophic cardiomyopathy and catecholaminergic polymorphic ventricular tachycardia.[6, 7] Moreover, CAR members use state-of-the-art single-cell, 2D and 3D human induced pluripotent stem cell-derived cardiomyocyte platforms to investigate patient specific cardiac arrhythmia mechanisms, including inheritable channelopathies, hypertrophic cardiomyopathy, age related arrhythmias and drug cardiotoxicity.[8]

Finally, CAR offers interdisciplinary training and support programs for graduate students, medical students, postdoctoral fellows and clinical scientists. Since its inception CAR students have come from more than 20 countries. Many are physicians-in-training - cardiology fellows, who have completed medical school and residency, and intend to practice cardiology - but want to learn basic cardiac electrophysiology. Other students include scientists with PhDs seeking postdoctoral training and graduate students pursuing PhDs. This training has resulted in many publications. Our faculty members teach laboratory research, computational research and elective courses in cardiovascular science. Students meet regularly to discuss research papers to CAR faculty and prepare presentations of their work at scientific meetings. Graduates of the CAR go on to highly-coveted positions and many of our formal trainees now hold leadership positions in academy and industry.

MBoCA (https://mboca.medicine.umich.edu)

The Michigan Biology of Cardiovascular Aging Program (MBoCA) was initiated in 2016 and is led by Dr. Daniel R. Goldstein, The Eliza Maria Mosher Professor of Internal Medicine, who was recruited from Yale University. Dr. Goldstein is a physician scientist and transplant cardiologist whose research interests are in the area of aging and inflammation.[9] The goals of MBoCA are i) to catalyze synergistic research endeavors at the UM as to how aging impacts cardiovascular diseases; ii) provide enhanced mentoring to trainees and provide seed grants to young investigators who have an interest in the field of aging and cardiovascular diseases; and iii) provide educational forums on the topic of cardiovascular aging. MBoCA is supported by a leadership award from the National Institute on Aging to Dr. Goldstein and by an anonymous donor to the UM. Within its first year, MBoCA provided two seed grants to junior faculty. Partnering with the Claude D. Pepper Center at the UM, MBoCA presented two awards, each of $40,000, to Dr. Durga Singa and Dr. Adam Stein. Dr. Singer will investigate gender differences in a murine diet induced obesity model, and Dr. Stein will investigate novel epigenetic mechanisms as to how aging leads to heart failure in mice.

As part of the MBoCA educational initiative, we held an inaugural research symposium in June 2017 and invited Dr. James Kirkland from The Mayo Clinic to present his group's research on senescence, senolytics and cardiovascular function. Other presentations from UM investigators included: Dr. David Lombard (Novel functions of Sirtuins in Aging); Dr. Sharlene Day (Intersection of Cardiovascular Aging and Disease); Dr. Cary Lumeng (Metabolic Inflammation in Adipose Tissue); and Dr. Richard Mortensen (Immune Cell Phenotype Affecting Cardiovascular Diseases).

To initiate research collaborations among investigators at UM, MBoCA has been hosting monthly meetings across the medical school. We have heard from experts in longevity (Dr. Richard Miller), hemostasis and platelet function (Dr. Michael Holinstat), diastolic dysfunction and heart failure (Dr. Scott Hummel), and vascular mechanics (Dr. Daniel Beard). On top of this, Dr. Goldstein has been sharing reagents and strategizing with members of The CAR group, notably Drs. Jalife, Valdivia and Justus Anumonwo to understand the intersection between aging, inflammation and arrhythmias. Given the clinical importance of AF as essentially a disease of cardiovascular aging, elucidating the mechanisms by which inflammation and aging enhance AF has become a priority for synergistic endeavors of MBoCA and CAR.

Strategic Plans for the Future: AF, Aging and Inflammation

AF has been associated with inflammation[10]. Clinical studies have associated several circulating inflammatory mediators, including C-reactive protein (CRP), interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, immune complement activation and galectin-3 with AF.[5, 11] Macrophages and neutrophils may contribute to AF by infiltrating atrial tissue, releasing reactive oxygen species (ROS), producing inflammatory cytokines, metalloproteinases or myeloperoxidases.[12] Aging is associated with increased inflammation, evidenced by increased presence of circulating inflammatory cytokines., although the

mechanisms underlying this phenomenon are not clear.[13] Inflammatory cytokines, produced by a specific pathological condition enhanced by aging may lead to Ca^{2+} channel dysfunction, which increases action potential prolongation and triggered activity predisposing to AF.[12] Although there is substantial circumstantial evidence linking inflammation and aging to AF, cause and effect relationships have been difficult to ascertain experimentally due to the limitations in specific experimental models.[14] Large animal models, such as the sheep, pig or dog, are clinically relevant models to study phenotypic alterations leading to AF but are not practical to study aging and genetic manipulations, such as knock out, and transgenic animals are not readily available.[14] Murine models of AF are often associated with ventricular dysfunction such as dilated or hypertrophic cardiomyopathy.[14] Transgenic expression of pro-fibrotic factors, such as TGF-β, can lead to AF in the absence of ventricular dysfunction[15] but mouse models rarely lead to sustained AF, which is the most relevant clinical phenotype. However, murine models are more practical than large animals to study aging given that mice typically live to 25–30 months of age. Clearly, an approach which combines murine models with large animal models and human cells will be the optimal approach to understand how aging impacts inflammation to predispose to AF. This is one of the high priority areas of the CAR - MBoCA partnership at UM. It is the goal of CAR and MBoCA to conduct multi-disciplinary research between arrhythmia experts, cellular immunologists, gerontologists and bioengineers to unravel how aging may impact inflammation to lead to AF. With such an approach, new therapies could be unraveled to reduce the morbid complications of AF in older people.

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