ISHR

International Society for Heart Research

The President's Lecture 2021 "Calcium Cycling Circuits in Cardiac Function and Survival"

Evangelia Kranias, PhD

2021 Honored Speaker
ISHR-ES Virtual Meeting

Dr Evangelia (Litsa) G. Kranias is currently The Hanna Professor, Distinguished University Research Professor and Director of Cardiovascular Biology in the Department of Pharmacology & Systems Physiology at the University of Cincinnati College of Medicine. She received her BS degree from the University of Chicago and her Masters and Ph.D. degrees under L.R. Dumas from Northwestern University, Chicago. She served as a postdoctoral fellow under R.A. Jungmann at Northwestern University Medical School, Chicago and started her faculty career at the University of Cincinnati Medical Center in 1978.

Dr Kranias' internationally recognized research program has provided fundamental insights into the regulatory mechanisms and signaling pathways underlying calcium homeostasis in cardiac physiology and pathophysiology with special emphasis in heart failure and arrhythmia. Dr Kranias has also extended her basic research findings to the clinical arena and has elucidated the functional significance of Ca-handling in the deteriorated function of human failing hearts. She was the first to identify human mutations in calcium cycling genes and show that these may predispose to arrhythmias and heart failure. The overall goal of Dr Kranias' research program has been to build a comprehensive understanding on the role of calcium cycling in cardiac contractility and cell survival.

Early in her scientific career, Dr Kranias recognized the importance of a small molecule, phospholamban (PLN), in the regulation of calcium cycling through the sarcoplasmic reticulum and the overall regulation of cardiac function. Her biochemical work showed that phospholamban regulates specific steps in the calcium ATPase enzymatic process, implicating this molecule as a regulator of cardiac function. Subsequently, Litsa Kranias with John Solaro were the first to demonstrate (Nature: 1982) that phospholamban is phosphorylated in the heart on a beat- to-beat basis. This was the first evidence of the physiological importance of this protein and its significance in "flight or fight" responses. In parallel studies, the Kranias lab pioneered studies on isolation and characterization of the sarcoplasmic reticulum protein kinases and phosphatases that regulate calcium transport and thus, cardiac relaxation. This provided evidence of a multimeric compartmentalized complex, which reversibly regulates calcium cycling in the cardiomyocyte.

Dr Kranias' in vitro, biochemical studies were then extended to in vivo settings and she provided the first evidence that controlling the levels of phospholamban alone, it is possible to fix the heart's pumping action. Dr Kranias has also extended her basic research findings to the clinical arena and showed that the phospholamban levels, relative to the sarcoplasmic reticulum calcium ATPase (SERCA), are higher in failing hearts and this may contribute to the impaired calcium handling and cardiac function. In addition,hospholamban is dephosphorylated in human and experimental heart failure, which may result in further inhibition of SERCA. Indeed, inhibition of protein phosphatase 1 by a constitutively active inhibitor 1 (AA 1-65 with T35D) resulted in increased phos-

phorylation of phospholamban, signicant improvement of function and prevention of remodeling in small and large animal models with heart failure. These preclinical studies in collaboration with Roger Hajjar have led to a clinical trial that started in January, 2020.

Over the last decade, Dr Kranias continued to identify novel regulators of calcium cycling and cell death. One of them is HAX-1, the anti-apoptotic protein, which interacts with PLN and serves as an additional regulator of sarcoplasmic reticulum calcium cycling and apoptosis. The other one is the small heat shock protein 20 (Hsp20), which along with inhibitor-1 attenuates the phospholamban phosphatase activity and protects the heart from apoptosis and remodeling under stress conditions. Finally, the SR intraluminal histidine-rich Ca-binding protein (HRC) was found to interact with the calcium-ATPase (SERCA) and regulate the enzyme's maximal Ca-transport velocity. Recent studies indicate that this multimeric SERCA/PLN-ensemble is involved in heart failure and arrhythmias, as well as apoptosis and cell death. In support of this concept, human mutations and variants in the SR calcium cycling genes have been linked to aberrant Ca-handling and increased cell death, suggesting that their selective targeting may hold promise in heart failure and arrhythmias. Notably, a mutation in the PLN gene (deletion of arginine 14), which associates with dilated cardiomyopathy and death by middle age in heterozygotes, appears to be prevalent in the Netherlands and a group of mutant gene carriers created the PLN Genetic Heart Disease Foundation. This foundation sponsors international collaborative research on the deadly condition.

Dr Kranias' research has been funded by the National Institutes of Health (NIH), the American Heart Association and the Leducq Foundation. She received both a NIH Research Career Development Award (RCDA) and a Method of Extension in Time (MERIT) Award. Her scientific investigations have been published in over 255 original manuscripts and 80 invited reviews. Dr Kranias has been invited to organize, chair and speak at numerous National and International scientific meetings. She has also been a dedicated mentor for young scientists: she has graduated 23 Ph.D. students and mentored 48 post-doctoral fellows/research associates. Dr Kranias has received many National and International awards and honors. These include the Daniel Drake Medal, which is the highest honor of the UC Medical Center, the American Heart Association Samuel Kaplan award, the Janice Pfeffer award from the ISHR and an Honorary Doctorate degree from the University of Athens. In 2009, Dr Kranias was named an AHA Distinguished Scientist and in 2012, she was elected as a corresponding member of the Academy of Athens. She received the ISHR award that combined the Research Achievement Award and the Peter Harris award (2014) and was selected by the American Heart Association Basic Cardiovascular Sciences to deliver the George E. Brown Memorial Lecture (2016). In 2018, she received the Basic Research Prize from the American Heart Association.

Dr Kranias served on several councils and committees including the National Council of the Biophysical Society, the Council of the ISHR (International and NA-section), the AHA Research Committee and the AHA BCVS Leadership and Nominating committees. She has also served as Associate Editor or an Editorial Board member of several journals and a member of numerous review committees.

The President's Lecture

In October 2004, the International Council created a new distinguished lecture, named The President's Lecture, which is a highlight of ISHR World Congresses and Section meetings.

The President's Lecture is held at each World Congress of the ISHR and, in non-Congress years, at the annual meeting of one of the ISHR Sections on a rotating basis. This lecture is intended to be a high profile event and is scheduled as a keynote plenary lecture. The International Council selects the speaker. **The topic of the lecture is in the field of molecular biology, genetics, genomics or proteomics, but the content should be chosen to be of broad interest to the cardiovascular community.** The speaker is reimbursed for travel expenses, and receives a plaque and a $1,000 honorarium. A photograph and biosketch of the speaker is published in *Heart News and Views*, and is posted in the ISHR website.

The President's Lecture enhances the content of the ISHR scientific meetings by providing a high-quality presentation in a topical area that is not covered by other distinguished lecture awards, and reflects the continuing growth of the ISHR as a professional Society. This award is funded by a generous donation from Roberto Bolli, MD, winner of the ISHR 2004 Research Achievement Award, who declined to collect the monetary prize associated with the Award and requested that it be used for this purpose.