

Janice M. Pfeffer, Ph.D.

1943-2001

The Janice M. Pfeffer Lectureship recognizes the scientific contributions of one of the pioneers in the field of cardiac remodeling. Born in Rockford, Illinois on October 31, 1943, Janice Marie Sikorski graduated with honors from Rockford College. There she studied with a lab partner named Marc Pfeffer, who shared her passion for integrative physiology. Janice and Marc became inseparable not only as husband and wife, but also as collaborators in integrative physiology. Janice M. Pfeffer was awarded her Ph.D. in Physiology and Biophysics from the University of Oklahoma, where she studied under Dr. Edward D. Frohlich. Her doctoral thesis, "Longitudinal Changes in Cardiac Function and Geometry During the Development of Left Ventricular Hypertrophy in the Spontaneously Hypertensive Rat," became a classic study on the role of cardiac hypertrophy and left ventricular remodeling. She continued her studies as a post-doctoral fellow in Dr. Eugene Braunwald's laboratory at the Peter Bent Brigham Hospital, Harvard Medical School. There she demonstrated that progressive ventricular enlargement, "ventricular remodeling", occurs following a myocardial infarction, and that this process continues long after the histologic resolution within the infarct zone. Her landmark study, "Influence of Chronic Captopril Therapy on the Infarcted Left Ventricle of the Rat", definitively demonstrated that ventricular enlargement was attenuated by angiotensin converting enzyme inhibitors, and that favorable alterations in ventricular remodeling in the animal model were associated with improved cardiac performance and prolonged survival. These pioneering animal studies introduced the concept of ventricular remodeling as a potential therapeutic target, and subsequently served as the basis for the landmark clinical trial, Survival and Ventricular Enlargement (SAVE), which showed that long-term treatment with an angiotensin converting enzyme inhibitor (captopril) prevented cardiac remodeling and resulted in improved clinical outcomes in humans. Based upon the results of this seminal translational study, angiotensin converting enzyme inhibitors have become one of the mainstays of therapy for the treatment of myocardial infarction.

In addition to being a meticulous and thoughtful scientist, Janice M. Pfeffer was a devoted mother and wife, who serves as a role model for countless women scientists. The intent of the Janice M. Pfeffer Lectureship is to acknowledge not only the latest insights and advances in the field of cardiac remodeling, but also to remember the remarkable personal and professional qualities that were emblematic of Dr. Janice M. Pfeffer.

About the Award...

Each year, the International Council selects a speaker to deliver the Pfeffer Distinguished Lecture at the World Congress or at the annual section meeting of one of the three largest ISHR Sections. The purpose of this lecture is to honor the memory of Dr. Pfeffer and to recognize her contributions to cardiovascular research. The topic of the lecture must be in the field of remodeling, heart failure and/or hypertrophy. The speaker receives a plaque and \$1,000. honorarium in addition to travel expenses.



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ISHR

International Society for Heart Research

The Janice Pfeffer Distinguished Lecture 2015



Janice M. Pfeffer, Ph.D.
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Honored Speaker:

Kinya Otsu, MD, PhD

“Mitochondrial quality control, sterile inflammation and heart failure”

2015 Honored Speaker

Kinya Otsu, M.D., Ph.D.

Kobe, Japan



Professor Kinya Otsu received his M.D. magna cum laude from Osaka University Medical School, Japan in 1983, and completed his clinical training in internal medicine at Osaka University Hospital. Since that time, his research and clinical interests have both focused on the treatment of heart failure. He began his scientific career at the National Institutes of Health, USA, with Dr. Jeffrey Froehlich, and then worked at the University of Toronto with Professor David MacLennan and at the University of Nice with Professor Jacques Pouyssegur. He moved back to Japan as a Senior Resident in Cardiology at the Osaka University Hospital and received his Ph.D. from Osaka University in 1992. He has led and managed an internationally competitive research team since then, initially in the Department of Pathophysiology (Professor Michihiko Tada). He was appointed as Assistant Professor in Cardiology in Professor Masatsugu Hori's Department at Osaka University Medical School in 1997 and promoted to Associate Professor in 2002. In 2012, he was recruited to London as Professor of Cardiology at King's College London and awarded a British Heart Foundation (BHF) Personal Chair of Cardiology.

Dr. Otsu's work has made major contributions to our knowledge of the pathophysiology of heart failure, including the delineation of new cardiac pathogenic pathways amenable to therapeutic targeting. Dr. Otsu cloned the cDNA encoding the calcium release channel of rabbit cardiac muscle sarcoplasmic reticulum for the first time, an important discovery in understanding the molecular mechanisms underlying muscle contraction. He also found that a single nucleotide mutation in the

skeletal isoform was the cause of malignant hyperthermia, enabling prediction of the propensity to develop this life-threatening problem. Cardiomyocyte death plays an important role in the progression of adverse cardiac remodeling. He has worked on the roles of each of three types of cardiomyocyte death: apoptosis, necrosis and autophagy. Working initially on the pathways driving cardiomyocyte apoptosis, he identified a novel intracellular signal transduction pathway in which neurohumoral factors induced by mechanical stress activate a Pyk2-Rac1-reactive oxygen species-apoptosis signal regulating kinase 1 (ASK1)-p38/JNK-NF- κ B cascade. He used a combination of *in vitro* and *in vivo* studies, including numerous novel gene-modified models, to define the roles of each of these molecules. His results show that ASK1-JNK activation is involved in promoting apoptosis whereas p38 and NF- κ B activation protect cells against stress. The balance between the two signaling pathways determines cell fate. Turning to programmed necrosis, he made the major finding that the mitochondrial permeability transition pore is the key molecule responsible for the execution of cardiomyocyte necrosis. When the necrotic pathway is adequately controlled, it is possible to avoid necrotic cardiomyocyte death in the setting of ischemia-reperfusion injury. He then investigated the role of autophagy, a mechanism through which cells degrade cytosolic proteins and organelles. He discovered that autophagy does not contribute to cardiomyocyte cell death during stress but is instead a mechanism that protects cells against lethal stress by maintaining the quality of proteins and organelles. This seminal report demonstrated the protective *in vivo* role of autophagy in response to chronic disease stress and has transformed paradigms in autophagy research. Most recently, he has identified a key molecular mechanism underlying so-called sterile inflammation, which is believed to play a pivotal role in many non-infective chronic diseases including heart failure. He discovered that mitochondrial DNA that escapes from autophagy-mediated degradation activates TLR9-mediated inflammatory responses in car-

diomyocytes and in heart failure, a finding that identifies another novel potential therapeutic target. Damaged mitochondria in failing hearts are degraded by a specific form of autophagy known as mitophagy. No mammalian mitophagy receptor has previously been identified. He discovered that Bcl2-like protein 13 is the mitophagy receptor in mammalian cells. His findings offer novel insights into mitochondrial quality control.

Dr. Otsu's research findings have led to many publications in high impact journals such as Nature, Nat Med, PNAS and J Clin Invest. Dr. Otsu's international standing and leadership are evidenced by numerous invitations to participate in international specialist and generalist scientific conferences such as World Congress of ISHR, the Annual Scientific Sessions of AHA, Cell Symposium, Keystone symposium and he has had significant organisational involvement in such activities. In addition, his accomplishments have been reported to the lay public in newspapers, journals and on the Web. His work is highly relevant to the development of new therapies for heart failure, a condition with increasing prevalence and major public health relevance.

Dr. Otsu is an open-minded, generous collaborator and has shared his insights with the research community. He is an excellent mentor and has trained and mentored numerous graduate students and postdoctoral fellows, many of whom have gone on to establish highly successful careers in both academia and medicine. Dr. Otsu is an outstanding role-model for clinician scientists and a very good communicator with the lay public.

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