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.

ISHR

International Society for Heart Research

The Janice Pfeffer Distinguished Lecture 2011

Janice M. Pfeffer, Ph.D.
1943-2001

Honored Speaker:

Thomas L. Force, M.D.

"Protein kinases old and new regulating novel pathways of injury and repair in the heart"

2011 Honored Speaker

Thomas L. Force, M.D. — Tokyo, Japan

Tom Force grew up in rural Illinois. He graduated from Harvard College where he was inducted into the Phi Beta Kappa Society. After taking a year off to be stage manager for rock concerts at Boston Garden and other venues in and around Boston, he went to Harvard Medical School. He did his residency at the University of Vermont and then his cardiology fellowship at West Roxbury VA Medical Center in Boston. In addition to his clinical responsibilities, he was one of the first of a small handful of investigators who helped develop the field of contrast echocardiography in the early 1980's. He moved to Massachusetts General Hospital in 1985 to run the Preventive Cardiology Program as well as being Director of the Stress Testing Laboratories, and it was at MGH that he met three scientists who radically changed his direction- John Kyriakis who was working in the Diabetes Unit under Joseph Avruch, and Joseph Bonventre. These three introduced him to basic science, specifically protein kinases, and this quickly became the focus of his work. After Kyriakis and Avruch cloned the JNKs, Force and Kyriakis set out to identify kinase pathways, initially focusing on Raf-1. They showed that Raf-1 was activated by various mitogens, and that it signaled to ERKs via a MAPKK (MEK1/2) which they purified and characterized, thus completing the first mammalian protein kinase cascade (JBC 1993; PNAS 1994). Then, working with Celia Pombo (Dr. Force's postdoctoral fellow) they identified and characterized mammalian members of the Sterile20-like kinase family (Mst family/MAP4Ks) including Germinal Center Kinase which is a key regulator of JNKs and p38 activation in systemic inflammation (*Nature* 1995) and SOK-1/STK25 (*EMBO J* 1996; *JBC* 1997) which is a cell death kinase activated by oxidant stress and ischemia. This kinase is mutated in patients with cerebral cavernous malformations, the most common cause of cerebral hemorrhage, and mechanisms potentially underlying this phenotype were later defined (*J Cell Sci*. 2010). Furthermore, this group was the first to report activation of JNKs by ischemia (*JBC* 1994).

Around this time, Force began to collaborate with a group of investigators at the Cardiovascular Research Center at MGH, including Tony Rosenzweig and Roger Hajjar, who helped change his direction toward more translational research focusing on the heart, specifically the role of kinases in ischemic injury and pathologic hypertrophy. Force was greatly aided by what would become a long-standing collaboration with James Woodgett at the University of Toronto. Woodgett had initially purified and cloned GSK-3 in Philip Cohen's lab, and Force and Woodgett began to actively collaborate. They reported the role of GSK-3β in regulating pathologic hypertrophy in The *Journal of Cell Biology* (2000) and implicated NF-ATs in the process. Force and Woodgett would go on to publish numerous papers exploring the role of GSK-3s in the adult and developing heart. These studies identified central roles of this family of kinases in everything from proliferation/differentiation of embryonic stem cells to cardiac development (deletion leading to double outlet right ventricle, VSD, and a hyperplastic myopathy that led to near obliteration of the LV cavity), post-MI and post-TAC remodeling, ventricular rupture, β–adrenergic responsiveness, and proliferation of cardiac stem/progenitor cells and immature cardiomyocytes (*JCI* 2008; *Circ Res* 2010; *JCI* 2010). During this period, Force also explored the role of Wnt signaling in the heart in the setting of TAC (*Mol Cell Biol* 2006) and first reported activation of Wnt pathways downstream of traditional GPCRs (*PNAS* 2003).

Most recently he has played a key role in highlighting the issue of cardiotoxicity of the so-called "targeted therapeutics" which largely inhibit various protein kinases that drive cancer progression. These agents had been predicted to be relatively free of cardiotoxicity, but Force dispelled that myth with the first report of cardiotoxicity with one of these agents (*Nat Med* 2006), and went on to identify the mechanism. This work increased scrutiny of these agents and culminated in the identification by Ming Hui Chen and Force of very significant cardiotoxicity with sunitinib, an agent widely used in various solid tumors (Lancet 2007). This, and work by a small group of others in 2006-2007 helped launch the concept of a medical sub-speciality called Cardio-Oncology, and also led to the development of guidelines for treating patients with these agents from the Heart Failure Association of the ESC and the U.S. National Cancer Institute, committees on which Force sat. Clearly, identifying potentially problematic agents before they are used in patients is a critical issue and most recently, Force has explored the use of zebrafish as a pre-clinical tool to attempt to do just that (*Circ Res* 2011).

Recently, Force was named incoming President of the Heart Failure Society of America. He also serves on numerous committees for the American Heart Association. Finally, Force would like to thank all the other collaborators and friends who have supported him, and most of all to thank the students, post-doctoral fellows, and technicians who actually performed the work. Without them, none of this work would have been possible. Force would also like to thank his wife and children for their support and encouragement.

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