

THE JANICE PFEFFER
DISTINGUISHED LECTURE 2010

REGULATION OF MYOCARDIAL GROWTH
AND DEATH BY OXIDATIVE STRESS

HONORED SPEAKER: DR JUNICHI SADOSHIMA
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JUNICHI SADOSHIMA, M.D., Ph.D. holds the position of Professor and Vice Chair in the Department of Cell Biology and Molecular Medicine at the University of Medicine and Dentistry of New Jersey, New Jersey Medical School. He also serves as the Associate Director of the Cardiovascular Research Institute, within the Department of Cell Biology and Molecular Medicine. Dr. Sadoshima received his M.D. and Ph.D. from Kyushu University in Fukuoka, Japan, and completed his postdoctoral training at Harvard Medical School. Dr. Sadoshima was awarded the American Heart Association's Louis N. and Arnold M. Katz Basic Science Research Prize (1995) and Cardiovascular Research Prize (2001). He is a Fellow of the American Heart Association and the International Society of Heart Research, and is a member of the American Society for Clinical Investigation. Dr. Sadoshima sits on the editorial board of 10 journals, including *Circulation Research*, *Journal of Molecular and Cellular Cardiology*, *Autophagy*, and *Journal of Clinical Investigation*. Dr

Sadoshima serves on grant review panels for the NIH and the AHA. Dr. Sadoshima's research has been supported by the NIH, the AHA and the Leducq Foundation. Dr. Sadoshima has mentored 6 PhD students and 24 postdoctoral fellows, two of whom were also awarded AHA prizes: the Melvin L. Marcus Young Investigator Award in Basic Cardiovascular Sciences (2003) and the Louis N. and Arnold M. Katz Basic Science Research Prize (2008).

Dr. Sadoshima is a recognized world leader in the field of cardiac growth and survival signaling. His landmark study, reported in *Cell* over 16 years ago, first established the importance of myocyte-generated angiotensin and auto-activation of AT1 receptor signaling and hypertrophy in response to mechanical stretch. Over the past two decades, his laboratory has continued to conduct seminal research on the regulators of cell death, survival and growth, which have included major studies of the roles of glycogen synthase kinase 3, the mammalian Hippo pathway thioredoxin and sirtuins.



One thrust of his recent research has been the role of reactive oxygen species and oxidative stress on both survival and hypertrophic stimulation. His laboratory was the first to establish a central role of the key reductive protein, thioredoxin-1, in growth and death of cardiomyocytes, and again led the field by showing the mechanisms of its control.

Most recently, Dr. Sadoshima demonstrated a novel mechanism whereby thioredoxin-1 regulates the oxidation of transcription factors (class II histone deacetylases), providing the first direct link between oxidative stress and a mechanism for cardiac hypertrophy. His extremely creative work has identified many new and important pathways that have become subsequent targets of research worldwide. ■

His recent experiments have established the importance of mutations in the intermediate filament protein desmin and the chaperone, alpha B crystalline, as causative for a class of cardiomyopathies, which has recently led to the startling observation that intracellular pre-amyloids appear to play an important, and possibly generalized role in cardiovascular diseases of various etiologies. In addition, recognizing the limits of the

murine models for studying critical therapeutic avenues as well as certain aspects of human cardiovascular disease, Dr. Robbins developed the ability to carry out cardiac specific transgenesis in the rabbit. This has already led to fundamental discoveries in hypertrophic cardiomyopathy, and allows the extension of cardiovascular gain-of-function to an animal whose cardiovascular system more closely resembles that of the human.

Dr. Robbins' recent work has focused on integrating the changes observed in contractile behavior with altered cardiomyocyte protein homeostasis and misfolding. Understanding the critical pathogenic pathways that link altered contractility with generalized deficits in protein folding may allow for the identification of novel therapeutic targets for the treatment of cardiovascular disease. ■