

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 3 largest 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.



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ISHR

International Society for Heart Research

The President's Lecture 2013



Honored Speaker

**Richard N. Kitsis,
M.D.**

“Understanding Cell
Death in the Heart”

Richard N. Kitsis, M.D.

2013 Honored Speaker
San Diego, CA, USA

Dr. Rick Kitsis is Professor of Medicine and Cell Biology, The Dr. Gerald and Myra Dorros Chair in Cardiovascular Disease, and Director of the Wilf Family Cardiovascular Research Institute at the Albert Einstein College of Medicine in New York City. Dr. Kitsis is one of the pioneers of the cardiac cell death field and has been at its cutting edge for the past 25 years. His laboratory has made seminal contributions to our understanding of both the fundamental biology of how and why cells die, and the roles of cell death in heart disease and other human conditions. His work is known for its novelty, rigor, and depth.

It is now widely accepted that cell death is important in the pathogenesis of multiple cardiac diseases, but this was not always the case. The field was once rife with controversy – with some researchers insisting that actively-mediated forms of cell death do not exist in the heart, while others reporting unrealistically high rates. Using a combination of molecular and cellular biology, biochemistry, genetics, and physiology, the Kitsis lab provided the first compelling data that programmed cell death plays critical roles in the pathogenesis of the most common and lethal cardiac syndromes: myocardial infarction and heart failure.

In the case of myocardial infarction, the issue was not whether cell death occurs, but whether it is actively carried out by the cell itself. Dr. Kitsis showed that mice harboring independent loss of function mutations in an array of cell death genes manifest the same phenotype following myocardial ischemia/reperfusion: less cell death, smaller infarcts, and preserved cardiac function. This demonstrated for the first time that programmed cell death is crucial in the pathogenesis of myocardial infarction. Heart failure was a much more difficult problem to address because, in contrast to the massive, short-lived burst of cell

death in myocardial infarction, the increased loss of cardiomyocytes during heart failure occurs at a low rate and over a protracted time course. By creating a genetic model of inducible caspase dimerization/activation *in vivo*, the Kitsis lab provided the first mechanistic evidence that the cumulative loss of small numbers of cardiomyocytes mediates cardiac remodeling and lethal cardiomyopathy. These studies established cell death as a critical mechanism in the pathogenesis of heart disease, and suggested that inhibition of this process may provide a novel therapeutic target for these disorders.

Another phase of investigations by the Kitsis lab focused on the cell death inhibitor ARC. ARC was an attractive subject for study because it is highly expressed in the heart. As importantly, the wide spectrum of death stimuli against which ARC appeared to be cytoprotective suggested to Dr. Kitsis that ARC blocks multiple cell death pathways. This proved correct and contrasts with the actions of most cell death inhibitors which antagonize a single pathway. The Kitsis lab went on to delineate biochemical mechanisms by which ARC inhibits central pathways that lead to apoptosis and necrosis. In the course of this work, a new type of protein-protein interaction was identified. In terms of the role of ARC in heart disease, Dr. Kitsis and associates observed that loss of ARC by proteasomal degradation is an essential trigger for infarction in response to ischemia/reperfusion. In addition, ARC is a critical regulator of post-infarct remodeling. Unexpectedly, they also discovered that the roles of ARC go beyond the heart. ARC functions as an oncogene that drives breast tumorigenesis and metastasis, and as a critical survival factor in pancreatic β -cells during type 2 diabetes. These latter studies have engendered intense interest in ARC across multiple fields.

Current research in the Kitsis lab is focused on two goals: The first is to understand the fundamental question of how cells decide whether to die by necrosis versus apoptosis. This work began with the lab's discovery that Bax, a classic regulator of apoptosis, also regulates necrosis during myocardial infarction. The decision of cells to die by necrosis versus apoptosis is important in diseases such as myocardial infarction and stroke, where both forms of cell death are prominent and have markedly different consequences with respect to tissue damage.

The second goal of the current research is to create a small molecule drug to block cardiomyocyte death. This

project, a collaboration with Dr. Evripidis Gavathiotis, combines chemistry, biology, and molecular structure. Both unbiased high-throughput chemical screening and target-based approaches are being employed. One objective of this work is to reduce heart damage during myocardial infarction and/or to slow the kinetics of cell death sufficiently so as to widen the time window for successful reperfusion therapy using angioplasty/stenting. A second objective is to inhibit the deaths of cardiac progenitors during engraftment to the myocardium.

Training is also an important part of Dr. Kitsis' activities. This has included serving as mentor to 10 Ph.D. or M.D./Ph.D. students and numerous postdocs who have gone on to independent positions in academia or pharma. A significant number of these trainees have been from minorities that are under-represented in biomedical science.

Dr. Kitsis has also devoted time to the larger cardiovascular community. He has served as Chair of the AHA BCVS Council and the ISHR Signaling Interest Group. He is on the editorial boards of JCI, Circulation Research, JMCC, and Cardiovascular Research, and associate editor of Circulation Heart Failure. He is currently Chair of the NIH MIM Cardiovascular Study Section, and has organized Keystone and AHA research meetings.

Previous Award Winners.....

Steven Houser, PhD: Fukuoka, Japan 2012

Sian Harding, PhD: Haifa, Israel, 2011

Issei Komuro, MD, PhD: Kyoto, Japan, 2010

R. John Solaro, PhD: Baltimore, MD, 2009

Gerd Hasenfuss, MD: Yokohama, 2008