ISHR Outstanding Investigator Prize

The purpose of this Prize is to recognize an outstanding scientist who (i) is making major and independent contributions to the advancement of cardiovascular science, and (ii) is likely to further develop his/her research in the future. The main criteria for selecting awardees are scientific excellence, independence, and potential for future research contributions. While the Peter Harris Award recognizes lifelong accomplishments and the Richard Bing Award recognizes young investigators, the Outstanding Investigator Prize is similar to the Research Achievement Award; the major difference between the two is that the latter is presented during the ISHR World Congress while the former is given at Section meetings. To avoid overlap with the Research Achievement Award, the Outstanding Investigator Prize is not given in the years when the World Congress convenes.

The Outstanding Investigator Prize is presented at the meeting of the ISHR Section to which the winner belongs. The winner receives free registration, reimbursement for travel expenses, $3,000 honorarium and a plaque. An announcement of this Prize, along with a photograph and a biosketch, is published in the *Journal of Molecular and Cellular Cardiology* and in *Heart News and Views*, and posted on the ISHR website.

Nominations for the Outstanding Investigator Prize are sought by the Secretary General from members of the International Council, members of the Editorial Board of the *Journal of Molecular and Cellular Cardiology*, and the Councils of ISHR Sections. In addition, the Secretary General publishes an open invitation in *JMCC*, in *Heart News and Views*, and on the ISHR Website for members to submit nominations.

This award is funded by a generous contribution from ***Aventis Pharmaceuticals***.

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International Society for Heart Research

The Outstanding Investigator Prize 2005

Prize Winner

Dr. Eric Olson

Eric Olson, Ph.D.

2005 Prize Winner
New Orleans, LA

Eric Olson was born on September 27, 1955 and grew up in North Carolina. He received a B.A. in chemistry and biology from Wake Forest University in 1977 and a Ph.D. in biochemistry at Bowman Gray School of Medicine of Wake Forest University in 1981. After a postdoctoral fellowship at Washington University School of Medicine, Dr. Olson joined the Department of Biochemistry and Molecular Biology at The University of Texas M. D. Anderson Cancer Center in 1984 as an Assistant Professor where he rose to the rank of Professor and Chairman in 1991. In 1995, he moved to The University of Texas Southwestern Medical Center at Dallas, where he is Professor and Chairman of the Department of Molecular Biology and Associate Director of the D. W. Reynolds Center for Clinical Cardiovascular Research. He holds the Robert A. Welch Distinguished Chair.

Dr. Olson has dedicated his career to understanding the mechanisms that control muscle gene expression. Dr. Olson has used a sophisticated combination of biochemistry and genetics to discover many of the key transcription factors known to be important for cell fate determination, differentiation, growth, and patterning of cardiac, vascular and skeletal muscle cells. His work exposed a cascade of cardiac transcription factors that function in organisms as diverse as mice and fruit flies, and his demonstration that developmental control genes are redeployed in the adult heart to drive pathologic cardiac enlargement leading to heart failure has provided new therapeutic targets and directions for cardiovascular medicine.

Beginning in the early 1980's, Dr. Olson laid much of the groundwork of our current understanding of muscle gene regulation through the discovery of the basic helix-loop-helix (bHLH) transcription factor myogenin and the MEF2 transcription factor, which he showed to be essential coregulators of skeletal muscle development. Using a combination of Drosophila and mouse genetics, buttressed by biochemistry, Dr. Olson demonstrated that MEF2 was required not only for skeletal muscle differentiation, but also for differentiation of all muscle cell types. It is therefore the most fundamental of the myogenic transcription factors. Dr. Olson also discovered the bHLH transcription factors MyoR, capsulin, and paraxis, which he showed to be required for patterning of different skeletal muscles. Dr. Olson's work on skeletal muscle development served as the template for subsequent studies by his laboratory and others into the mechanisms of cardiac and smooth muscle development.

Based on the central role of bHLH proteins in skeletal muscle development, Dr. Olson and his colleagues searched for and discovered the cardiac bHLH proteins HAND1 and HAND2, the first transcription factors found in different cardiac chambers. Expression of HAND2 is confined to the right ventricular chamber, and knockout mice showed that HAND2 controls the formation of this specific cardiac compartment. This was a landmark discovery that provided the first evidence that a single gene defect could result in ablation of a specific region of the heart. Dr. Olson also found that HAND2 controls limb growth and development, providing mechanistic insights into the basis for the frequent association of heart and hand defects in humans. He showed that HAND1 expression is confined to the left ventricular chamber and is essential for ventricular growth, as well as development of the cardiac valves.

Dr. Olson's laboratory showed that MEF2C is required for cardiac and vascular development whereas MEF2A is required for postnatal growth of the heart. His group also discovered the hairy-related transcription factor (HRT) family, which mediates the action of the notch receptor on cardiovascular development, and he demonstrated that the GATA4 transcription factor is required for the formation of the embryonic heart tube.

Many congenital heart defects in humans affect only specific regions of the heart. Dr. Olson's analysis of the phenotypes of mouse mutants lacking cardiac transcription factors revealed that the heart is assembled in a modular fashion, with each compartment governed by a distinct genetic program. Based on Dr. Olson's work, the process of heart development can now be viewed as a pathway with discreet steps controlled by distinct transcription factors.

Dr. Olson discovered the cardiovascular transcription factor myocardin, which regulates both cardiac and smooth muscle genes by associating with serum response factor (SRF), a MADS-box transcription factor related to MEF2. This finding extended Olson's original model, that muscle development is controlled by combinatorial interactions between myogenic factors, such as MyoD or myogenin, and MADS-box factors, like MEF2. The activity of myocardin/SRF is repressed by an unusual homeodomain transcription factor, called HOP, which Dr. Olson discovered as a modulator of cardiomyocyte proliferation and differentiation.

Dr. Olson's contributions have also directly impacted on understanding the pathophysiology of heart failure. His work has shown that many of the same transcription factors and regulatory mechanisms that control heart formation are called into play in the adult heart as a consequence of pathological stress. Dr. Olson discovered two stress-response pathways that connect abnormalities in myocyte function to maladaptive changes in cardiac gene expression. His laboratory was the first to recognize the importance of the calcium-sensitive phosphatase, calcineurin, in cardiac hypertrophy and failure. His work showed that calcineurin induces hypertrophy via a biochemical cascade that targets the NFAT and GATA transcription factors and that calcineurin inhibition prevents hypertrophy. In addition, Dr. Olson and his colleagues identified a key role for class II histone deacetylases (HDACs) as negative regulators of cardiac growth. Histone acetyltransferases (HATs) activate gene expression by relaxing chromatin structure while HDACs tighten coiling to inhibit transcription. Dr. Olson showed that hypertrophic stimuli cause phosphorylation of HDACs leading to dissociation from MEF2 and nuclear export, thereby allowing MEF2 to associate with HATs and activate genes involved in cardiac stress. Thus, a major determinant of heart size and function is the balance between activating HAT and deactivating HDAC interactions with MEF2. Dr. Olson's discovery of stress signaling pathways mediated by calcium-dependent signaling molecules, recipient transcription factors and chromatin remodeling enzymes has spawned new areas of investigation and has provided novel therapeutic targets for treatments of hypertrophic and atherosclerotic heart failure.

Dr. Olson's prior awards include the Edgar Haber Cardiovascular Research Award (1998), the Basic Research Prize (1999), and the Founding Distinguished Scientist Award (2003) from the American Heart Association, the Gill Heart Institute Award for Outstanding Contributions to Cardiovascular Medicine (1999), the Pasarow Award in Cardiovascular Medicine (2000), the Louis and Artur Lucian Award for Research in Cardiovascular Diseases (2003), and a MERIT Award from the National Institutes of Health (2000). In 2003, he received an honorary doctorate from his *alma mater*. He is a member of The National Academy of Sciences, the American Academy of Arts and Sciences, and the Institute of Medicine. Dr. Olson is the Editor-in-Chief of *Developmental Biology* and a member of numerous editorial boards including *Science, Molecular and Cellular Biology, Circulation Research, Circulation,* and *The Proceedings of the National Academy of Sciences.* He also serves as a member of the Scientific Review Board of the Howard Hughes Medical Institute.

2003 Prize Winner
Issei Komuro, M.D., Ph.D. Tokyo, Japan

Dr. Komuro is Professor and Chairman of Cardiovascular Medicine at Chiba University where he leads over 100 doctors in clinical work as well as research.

Dr. Komuro has published over 200 original articles, many of which have appeared in leading journals. He has also published 40 book chapters/review articles, is a regular speaker at national and international meetings, and serves as an associate editor of the *Journal of Molecular Cellular Cardiology* and on the editorial boards of *Circulation* and *Circulation Research.*

2002 Prize Winner
Peter Carmeliet, M.D., Ph.D. Szeged, Hungary

Dr. Carmeliet is Professor of Medicine at the University of Leuven, vice-director of the Center of Transgene Technology and Gene Therapy, and Professor of Medicine at CARIM, University of Maastricht, Netherlands.

Dr Carmeliet has published numerous original articles, reviews and editorials in leading journals. He is the recipient of the Liliane Bettencourt Award Life Sciences (2003), Francqui Prize (2002), and Bristol Myers Squibb Grant (2001), and has served on the Editorial Boards of *Cancer Cell, Circulation Research, Trends in Cardiovascular Medicine,* and as Guest Editor of *Cardiovascular Research.*