

# Wallace H. Coulter Foundation Lecture Series

## Systems Approach to Target Discovery for Cardiometabolic Disease



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Lecture: Friday, February 9, 2018  
9:00AM-10:00AM  
Room EC 2300  
10555 West Flagler Street  
Miami, FL 33174

### Biography

Dr. Masanori Aikawa is Yoshihiro Miwa Associate Chair and Founding Director of the Center for Interdisciplinary Cardiovascular Sciences and a principal investigator at the Center for Excellence in Vascular Biology of Brigham and Women's Hospital (BWH) and Associate Professor of Medicine at Harvard Medical School (HMS). He received his MD and PhD degrees from Juntendo University, Japan. Dr. Aikawa's initial research at the University of Tokyo demonstrated the diversity of smooth muscle cell phenotype in developing and diseased human arteries through the cloning and characterization of myosin heavy chain isoforms. As Research Fellow at BWH/HMS, he pioneered the "plaque stabilization" theory by lipid lowering. As a faculty member, Dr. Aikawa provided the first in vivo evidence for the impact of MMP-collagenases on collagen in atherosclerosis and aneurysms. He published early reports of in vivo molecular imaging of atherosclerotic plaque macrophages. In the past decade, his laboratory has explored new signaling mechanisms for macrophage activation. A series of his studies demonstrated the pro-inflammatory role of Dll4-Notch signaling in vascular and metabolic disorders. More recently, Dr. Aikawa's systems approach to target discovery for vascular diseases has used cutting-edge technologies including multi-omics, original bioinformatic programs, network analyses, and machine learning-assisted complex data analyses.

### Abstract

Despite the impact of macrophage activation in vascular and metabolic diseases, such as coronary atherosclerosis, peripheral artery disease, vein graft failure, and type 2 diabetes and fatty liver, the underlying mechanisms remain obscure. Clinical evidence suggests that modern therapies for modifiable cardiovascular risks, including potent statins, cannot save all the patients. To tackle such residual risks, we have explored the novel mechanisms for pro-inflammatory activation of macrophages. We established that Delta-like ligand 4 (Dll4) of the Notch pathway promotes macrophage activation and promotes various cardiometabolic disorders. We have also found a novel mechanism by which the Dll4-Notch axis promotes inflammation in chronic kidney disease. More recently, we have taken more holistic approaches, involving multi-omics and systems biology, to speed target discovery. Global omics of macrophages have identified several pathways (e.g., the interplay of ADP-ribosylation enzymes PARP9 and PARP14) and long-noncoding RNAs including lnc-FAM164A1 as possible molecular switches of macrophage activation. A similar approach also re-profiled old molecules such as PPAR in new disease contexts. Key pathways for macrophage activation may provide molecular bases for the development of new therapies for cardiometabolic diseases.