DukeNUS Medical School

Signature Seminar Series

Therapeutic Targeting of Proteotoxicity in Heart Failure: New Concepts in an Old Disease

ABOUT THE LECTURE

We recently created and phenotyped the first mouse model of cardiac-specific human BAG3 P209L, which develop a progressive systolic and diastolic heart failure. In parallel, an increase in pre-amyloid oligomer (PAO) are seen at 12 months, which have been demonstrated to directly mediate heat failure via proteotoxicity, paralleling the pathobiology underlying Alzheimer's disease. Based on studies in Alzheimer's disease linking PAO-mediated proteotoxicity to p38 activation, we identified that cardiac PAO-mediated heart failure in cardiac Bag3 P209L is mechanistically linked to p38 activation. Bag3 P209L Tg+ mice, phenotypically normal at birth, exhibit a progressive systolic and diastolic heart failure and parallel p38 activation starting at 8 months. Treatment of Bag3 P209L Tg+-associated cardiomyopathy with the p38 inhibitor durably resolves established systolic dysfunction. These findings parallel both the therapeutic attenuation of the PAO-induced cytotoxicity in Alzheimer's disease models. The mechanistic gap remaining is understanding how PAO's activate p38 to cause heart failure in vivo, which may offer potential therapeutic targets previously unrecognized.

Speaker: ***Associate Prof Monte Willis***
Vice-Chair of Pathology & Lab Med,
Assoc. Professor/PI McAllister Heart Institute
University of NC Chapel Hill

Host: ***Prof Shirish Shenolikar***
Professor, Cardiovascular & Metabolic Disorders Programme
Professor, Neuroscience & Behavioural Disorders Programme
Duke-NUS Medical School

Date: Tuesday, 12 April 2016

Time: 12:00 PM - 1:00 PM
(Light refreshments will be served at 11:30 AM)

Venue: Duke-NUS Medical School
Amphitheatre, Level 2

Contact Person: Ms Cynthia Lim, Duke-NUS Research Affairs Department
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ABOUT THE SPEAKER

Dr. Willis received his MD/PhD at the University of Nebraska Medical Center, did his residency in Clinical Pathology and Post-Doctoral fellowship in Cardiac Pathophysiology at the Univ of Texas Southwestern, and is currently an Assoc Professor at the Univ of North Carolina. He is a practicing physician with a research program studying the role of the ubiquitin proteasome system and proteotoxicity in heart failure, supported by NIH and the Leducq Foundation TransAtlantic Network of Excellence.



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