Dr. Herbert and Nicole Wertheim Leadership in Healthcare and Medicine Lectureship

GRK2 Inhibition for Heart Failure: A 20-Year Translational Journey

Walter J. Koch, Ph.D., F.A.H.A.
W.W. Smith Chair in Cardiovascular Medicine
Professor & Chairman, Department of Pharmacology
Director, Center for Translational Medicine
Temple University School of Medicine

Date: 10/21/15
Time: 1pm - 2pm
Venue: AHC2-170

Biography

Professor Koch (Ph.D., Pharmacology and Cell Biophysics, University of Cincinnati College of Medicine, 1990) began his career at Duke University Medical Center and Howard Hughes Medical Institute as a postdoctoral fellow (1990-95) in the lab of Dr. Robert Lefkowitz (Nobel Prize, Chemistry, 2012) and advanced to tenured Professor of Surgery before moving to Thomas Jefferson University in 2003 to build a Center for Translational Medicine. He became the Chairman, Dept. of Pharmacology and Director of the Center for Translational Medicine at Temple University in 2012. As principal investigator and project leader of several multimillion dollar NIH grants, he has overseen numerous advances in cardiac research. His work revealed the novel roles G protein-coupled receptor kinases (GRKs) play in cardiac injury and repair. Manipulating these GRKs and targeting them with therapeutics could lead to new treatments for heart failure patients. Inhibition of GRK2 in the heart has led to the reversal of heart failure in several animal models. This has been shown to occur by using a gene therapy approach in pre-clinical studies in small and larger animal models. This methodology is one step away from human clinical trials. Further, small molecule inhibitors of GRK2 are now emerging. Numerous awards and honors have recognized Koch's research, including the International Society for Heart Research 2011 Outstanding Investigator Award, the American Heart Association Thomas Smith Memorial Lecture and Award for Cardiovascular Signaling in 2009, and a National Institutes of Health 10-year MERIT award through 2019. He published >350 peer-reviewed articles and served on NIH study sections as a reviewer and Chair. He has just won the Temple University Paul W. Eberman Faculty Research Award.

Abstract

We have spent the last two decades investigating novel molecular targets for correcting ventricular dysfunction in heart failure. We have identified the G protein-coupled receptor (GPCR) kinase-2 (GRK2) as such a target. We have shown that inhibiting the activity of this kinase or genetic deleting this kinase in the heart can prevent and reverse heart failure in mouse models. Moreover, a gene therapy approach with a peptide inhibitor of GRK2 (βARKct) has been used in several small and large animal models to rescue heart failure. This includes a recent study in a pre-clinical pig model of heart failure and βARKct gene delivery reversed ventricular dysfunction and caused reverse remodeling. A clinical trial is being planned and these studies will be presented. In addition to a gene therapy approach for GRK2 inhibition we are pursuing small molecule pharmacological inhibition and recent studies have shown the FDA approved anti-depressant drug paroxetine is a specific GRK2 target outside its actions to prevent serotonin re-uptake. We have recently published results that will be presented showing that paroxetine can reverse heart failure in an animal model and this therapeutic effect is independent to its CNS effects. This paves the way for paroxetine derivatives and other small molecules to target GRK2 for future heart failure therapy.

Co-sponsor information.

Cellular Biology and Pharmacology
Lisa Riolo | p.305-348-1474 | f. 305-348-1577
lriolo@fiu.edu

FIU Herbert Wertheim College of Medicine