

James & Esther King Biomedical Research Program

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*Molecular Medicine
University of South Florida*

*2008 Program
Bridge (1-year project)*

Project Title: Regulation of the Endothelial Citrulline-Nitric Oxide Cycle

Project Summary: Impairment of vascular wall (endothelial cell) function has been suggested to be an early, causative event in smoking, diabetes, and hypertension leading to atherosclerosis. In this grant, we will investigate the cellular mechanisms by which physiologic and pathogenic stimuli affect vascular wall health through the regulation of a critical enzyme named argininosuccinate synthase (AS).

Based on our evidence that insulin regulates vascular wall health, in part, through a modification process of AS, the first specific aim of this grant is designed to explore the mechanisms and biological significance of this insulin-mediated modification as it relates to vascular wall function. We are also exploring the mechanisms that impair the action of insulin in mediating this type of regulation by examining alterations under inflammatory pathogenic conditions reflected in smoking, diabetes, and obesity. The second aim is based on our work demonstrating that components of the gene encoding AS in the vascular wall also produce an alternative small protein we named Argininosuccinate Synthase Regulatory Protein (ARP). We are examining the mechanism by which ARP represses the synthesis of AS in the vascular wall in response to pathogenic stimuli found in diabetes, hypertension, or smoking. In the third specific aim, we are examining the molecular mechanisms underlying cardiovascular actions of insulin on AS production utilizing an animal model of diabetes that is known to demonstrate vascular wall (endothelial) dysfunction. The use of this animal system will permit the process of confirming our understanding defined in tissue culture and in vitro systems into whole animals. Overall, we believe examination of the function and regulation of this critical enzyme is essential to understanding vascular wall function and will potentially distinguish new therapeutic strategies for the treatment of diabetes, hypertension, and smoking-related cardiovascular disease.