

James & Esther King Biomedical Research Program

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Molecular and Cellular Pharmacology
University of Miami

2010 Program
New Investigator Research
(3-year project)

Project Title: Understanding the Molecular Mechanisms of Troponin Mutations in Cardiac Muscle Dysfunction

Project Summary: Long-term tobacco use induces a ventricular hypertrophic response (increase in size) that compensates for damage to the myocardium (heart muscle) and can eventually result in heart failure. Hypertrophic cardiomyopathy (HCM) and Restrictive cardiomyopathy (RCM) are cardiovascular diseases that cause severe cardiac disability and heart failure. These diseases possess a genetic component that is an inherent risk factor for familial heart disease and are greatly affected by tobacco use. An urgent need exists for the development of therapeutic approaches that can tailor the myofilaments' (single functional unit that is responsible for the muscle contraction) contractile response. HCM is a common cardiac disorder and main cause of sudden death in the young. RCM is not well understood; however, it results in abnormal diastolic function and impaired ventricular filling. Mutations in Troponin, the protein that binds Ca^{2+} and regulates cardiac muscle contraction, have been linked to HCM and RCM, and both mutations induce sensitization of the myofilament to calcium. Calcium sensitization may contribute to the development of many overlapping features of both diseases. However, the clinical aspects of each disease are distinct. This project will explore the molecular mechanisms that underlie HCM and RCM mutations and will delineate specific *in vitro* and *in situ* observable differences in characteristics that arise from these inherited mutations.