Department of Molecular Genetics, Biochemistry, and Microbiology
COLLEGE OF MEDICINE

SUMMER RESEARCH OPPORTUNITIES
FOR UNDERGRADUATE WOMEN

APPLICATION DEADLINE: March 1, 2012

The Department Molecular Genetics, Biochemistry, and Microbiology is pleased to offer the following research project for the summer of 2012. Interested students are urged to contact the faculty member(s) directing the project that most interests them. By contacting the faculty member, you can discover more about the project, learn what your responsibilities will be and, if possible, develop a timetable for the twelve-week research period.

PROJECT TITLE: Understanding Structure in the Regulatory Region of Cardiac Myosin Binding Protein-C: Toward a Treatment of Heart Failure

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Project Description

Our research interests focus on protein structure/function relationships in cardiovascular proteins. Studies are designed to fill critical gaps in our knowledge of heart regulation and provide new avenues for drug therapy in the treatment of heart disease. We are interested in the structural consequences of phosphorylation and mutation of sarcomeric proteins leading to specific disease states such as familial hypertropic cardiomyopathy, myocardial infarction, ischemia, atrial fibrillation, and heart failure. We are currently studying structure/function relationships in two sarcomeric proteins, cardiac troponin and cardiac myosin binding protein-C, that play key roles in regulating heart contraction. Cardiac troponin consists of three subunits; troponin C (cTnC), troponin I (cTnI), and troponin T (cTnT) and is the Ca^{2+} -sensitive switch responsible for initiating each heart contraction. Unique isoforms of cardiac TnC, TnI, and TnT allow modulation of heart contraction via phosphorylation during development and disease. Understanding modulation of the Ca^{2+} -sensitivity of heart contraction will aid in the design of pharmacological agents capable of modulating contraction through alterations in thin filament protein-protein interactions. Cardiac MyBP-C (cMyBP-C) interacts with both myosin and actin where it provides an additional allosteric mechanism for regulation of cardiac contractility. Phosphorylation of cMyBP-C is cardioprotective, protecting against ischemic-induced proteolysis. In addition, mutations in cMyBP-C are inherited by an estimated 60 million people worldwide with 90% of older individuals carrying these mutations developing cardiac complications. Thus, understanding the molecular consequences of cMyBP-C phosphorylation and mutation are critical to the design of new agents to protect the heart and improve cardiac function after ischemic-reperfusion injury.

Our laboratory uses a synergistic blend of structural biology, biochemistry, and physiology to elucidate protein structure and protein-protein interactions utilized by these

dynamic protein machines to modulate cardiac contraction. We utilize high-resolution structural techniques (NMR) in conjunction with lower resolution methods (small-angle x-ray and neutron scattering) to elucidate changes in thin filament molecular interactions resulting from phosphorylation or mutation. NMR can provide structural and dynamic information at the atomic level on both folded and natively disordered proteins. NMR is especially effective for measuring short-range interactions in proteins and protein complexes in solution. Small angle-scattering of x-rays or neutrons complements NMR by providing long-range distance information that reveal the overall shapes of proteins in solution. Neutrons have the additional advantage that by using selective deuteration, the shapes and relative dispositions of protein subunits within complexes can be determined. Higher resolution information obtained from NMR and crystallographic studies of individual proteins or protein modules can be assembled into complete structures using shape and domain orientation information provided by small-angle scattering.