Bankhead-Coley Cancer Research Program

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Chemistry and Biochemistry
Florida State University

2010 Program
Postdoctoral Research Fellowship
(3-year project)

Project Title: Structural Dynamics of Human MDM2 and MDMX Interactions with p53 and Antagonistic Ligands by Multidimensional NMR Spectroscopy

Project Summary: The protein p53 plays a key role in many cellular processes, including tumor suppression, DNA repair, and aging. p53's function can be disabled by specific interactions with other proteins, in particular MDM2 and MDMX. Therefore, disruption of these interactions by peptides and small molecules (drugs) is of considerable pharmaceutical interest. However, only a few peptides and small molecules developed so far have been found to have in vivo activity. MDM2 and p53 interact, and the complex formation involves a significant conformational change to MDM2 and global conformational change in p53. Thus, a series of complex structural dynamic events play a key role in the function of MDM2/MDMX, whose characterization evades traditional structural biology approaches. The goal of this project is to understand these processes at an atomic level and to determine how they can be disrupted by small molecules using state-of-the-art Nuclear Magnetic Resonance Spectroscopy available through the Department of Chemistry and Biochemistry at Florida State University and the National High Magnetic Field Laboratory. The knowledge gained in this research is crucial for the development of new chemotherapeutic agents for the treatment of p53-related diseases.