

Bankhead-Coley Cancer Research Program

Radhakrishnan, Rangasudhagar

*Molecular Oncology
H. Lee Moffitt Cancer Center & Research Institute*

*2010 Program
Postdoctoral Research Fellowship
(2-year project)*

Project Title: Role of Histone Deacetylases in DNA Mismatch Repair

Project Summary: Colon cancer is one of the leading causes of death among the elderly population, and various risk factors have been identified to be associated with this increased incidence. Among the risk factors, two genetic elements have been identified as potential causes for colon cancer genesis. They are the germ line mutations in genes that are involved in either Adenomatous Polyposis Coli (APC) or DNA Mismatch repair pathways (MMR). This project focuses on the gene that is involved in the DNA mismatch repair pathway. A functional MMR is not only required for the cells to maintain the genomic integrity in the event of DNA replication errors, but also for initiating cellular response to certain chemotherapeutic drugs that give rise to mismatches. The net results are either correction of the mismatch and promotion of cell survival in case of DNA replication errors, or mounting an apoptotic response to kill the cancer cells in case of chemotherapy. Failure of this system because of mutations in the genes that are involved in DNA mismatch repair leads to accumulation of errors in DNA and cells' loss of sensitivity to chemotherapeutic agents. This research attempts to identify the role of acetylation of MSH2, a critical gene that is involved in colon cancer etiology, in DNA mismatch repair, and colon cancers. (Since acetylation of proteins has been shown to alter their function, the present study is highly significant.) The results of this study will also identify the role of histone deacetylases, the proteins that regulate these acetylation changes, in DNA mismatch repair and colon cancers.