

**James & Esther King Biomedical Research Program**

***Rai, Priyamvada***

*Medicine  
University of Miami*

*2009 Program  
New Investigator (3-year project)*

**Project Title:** Exploring a Role for Oxidative Stress and Oxidative DNA Damage in Limiting the Progression of Non-Small Cell Lung Carcinomas (NSCLCs)

**Project Summary:** Exposure to tobacco smoke is the leading cause of non-small cell lung carcinoma (NSCLC), a commonly occurring malignant and chemotherapy-resistant form of lung cancer. Many NSCLC's express mutated forms of a protein called Ras that predisposes cells to becoming cancerous. Mutant Ras expression leads to increased cellular reactive oxygen species (ROS) and DNA damage, stresses that usually kill cells or prevent their proliferation. Yet NSCLC cells are able to tolerate Ras despite having impaired processes for repairing oxidative DNA damage. We hypothesize that NSCLCs require compensatory protective processes in order to avoid these cell-toxic and tumor-suppressive effects.

It has been reported that NSCLC tumors have elevated levels of an enzyme, human MutT homolog1 (MTH1), which detoxifies oxidant-damaged building blocks of DNA, thus reducing the need for DNA repair. Our preliminary results show that reduction of MTH1 protein protect cells from Ras-induced oxidative DNA damage and that reduction of MTH1 levels in an NSCLC-derived human cell line impairs its tumor formation ability in mice. Thus, using cellular and mouse NSCLC models, the objective of our grant is to assess if inhibiting MTH1 expression limits tumor growth and can sensitize NSCLC cells to certain forms of chemotherapy. Our studies are likely to provide information for the development of novel chemotherapeutic regimens via use of pharmacological MTH1 inhibitors to halt NSCLC tumor progression.