

James & Esther King Biomedical Research Program

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

Project Title: Mechanisms by Which HDAC6 Confers Chemoresistance in Lung Cancer

Project Summary: With 1.2 million new cases diagnosed every year, lung cancer is the leading cause of cancer-related mortality in both men and women. Two first line regimens of lung cancer treatment are platinum with taxane and platinum with gemcitabine. One of the major obstacles of these treatments is that patients often develop resistance to platinum. Histone deacetylases (HDACs), are enzymes involved in a wide variety of biological processes including transcription regulation, cell growth/differentiation, cell death, etc., and are thought to play a role in developing platinum resistance. HDAC inhibitors now hold great promise in cancer treatment in that they could restore the chemo-sensitivity in tumor cells, including lung cancer cells. However, the role of these enzymes in chemo-resistance is largely unknown. Our preliminary data show that one of the HDACs, termed HDAC6, interacts with and modifies the DNA mismatch proteins, which play critical roles in the recognition of DNA-cisplatin complex and trigger programmed cell death. Cisplatin is one of the most widely used platinum compounds in lung cancer treatment, and we will use it as a representative drug to study platinum-resistance. Therefore, in this grant, we will investigate the mechanisms by which HDAC6 confers cisplatin-resistance via modification of DNA mismatch repair proteins in lung cancer. The results of our research will identify HDAC6 as a novel therapeutic target in lung cancer and suggest the application of clinically relevant HDAC6-selective inhibitors as agents to enhance the efficacy of chemotherapy drugs.