Project Title: Gain of function mutant p53 and MDM2 in lung oncogenesis

Lay Description.

Lung cancer is the deadliest of all cancers in the United States and the world, with more than 1.5 million deaths per year worldwide. p53 is the most frequently mutated "driver" gene in lung cancer; the majority of these p53 mutations have gain-of-function (GOF) properties (i.e., acquired growth enhancing and oncogenic functions). A majority of lung cancer cells are "addicted" to mutant p53 expression, inhibition of which eliminates tumorigenesis, raising the possibility of a novel approach to therapeutically target lung cancer. Human homolog of double minute 2 (MDM2) is an oncogene that is also deregulated in a significantly large number of lung cancers along with p53 mutations. Further, deregulation of epidermal growth factor receptor (EGFR) signaling pathways by overexpression of the receptor or its downstream mediator EPS8 (EGFR receptor pathway substrate 8) is frequent in lung cancer. The **objectives** of the project are to: (1) determine the mechanism of “addiction” to GOF p53 in human lung cancer cells; (2) determine the mechanism by which EPS8, a gene whose expression is induced by GOF p53 mutants in lung cancer, is activated and takes part in lung oncogenesis; (3) determine the mechanism by which GOF p53 protein is stabilized, resulting in massive accumulation in cancer cells, by its interplay with MDM2; and (4) determine the mechanism of lung cancer induction by MDM2 with its interplay with GOF p53 using mouse models.

The long-term goal of this program is to determine the molecular mechanism(s) of the mutant p53 pathway of lung oncogenesis and how MDM2 functionally interacts with it. Successful completion and continuation of the described work will lead to a new line of personalized therapy for a large number of lung cancer patients.