CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180700

Project Title:
Mechanisms of Drug Resistance in Lung Cancer

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Alto, Neal

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

The future of cancer research lies in a personalization of medicine, where each patient's treatment regime is tailored to the unique genetic makeup of their tumor. However, tumor resistance to chemotherapy continues to be a major threat to personalized medicine as the underlying mechanisms of drug resistance are often unclear. In addition, the identification of biomarkers that predict drug resistance in patients remains a major future challenge. This proposal investigates a potentially new mechanism of cancer cell resistance to a promising new class of chemotherapeutics, collectively termed "Smac-mimetics". These small molecules kill tumor cells by initiating an inflammatory type of cell death program. Despite the promise of SMAC-mimetic compounds, many tumors are highly resistant to their mechanism of action, which remains a major obstacle for their broad use in the clinic. Here, we will identify and functionally characterize a potentially broad mechanism for SMAC-mimetic resistance in models of Non Small Cell Lung Cancer (NSCLC), the leading cause of cancer related death in the United States. Specifically, our preliminary studies revealed that two developmentally regulated genes, called Sine oculis (SIX1 and SIX2), can inhibit SMAC-mimetic induced cell death. The proposed work will determine if indeed SIX-protein reactivation is a major driver of NSCLC resistance to this important chemotherapeutic paradigm (Goal 1). A data driven analysis will identify the genetic basis of SMAC-mimetic resistance, which may reveal biomarkers that can predict SIX-dependent drug resistance phenotypes (Goal 2). Lastly, we will test if aberrant SIX-protein expression is responsible for NSCLC resistance to SMAC-mimetics in preclinical models of therapy (Goal 3). Together, these studies may lead to new therapeutic options aimed at eliminating SMAC-mimetic resistant cancer cell populations.