CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

Award ID:
RP100941

Project Title:
Mapping Inhibitor Interactions and Conformational Space of the MAP3K TAO2, a New Protein Kinase Cancer Drug Target

Award Mechanism:
Individual Investigator

Principal Investigator:
Goldsmith, Elizabeth J

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

The problem addressed here is to find potent and cancer-selective inhibitors of pre-validated cancer drug targets. We have chosen to find inhibitors of the MAP3K TAO2 because its elimination in a NSCLC (non-small-cell lung carcinoma) cell line killed the cells. TAO2 has been shown to participate in the DNA damage induced cell-cycle arrest, further validating it as a cancer target. We will find specific inhibitors of TAO2 by screening for non-ATP competitive kinase inhibitors in direct binding assays to multiple distinct conformers of TAO2. Inhibitors will be identified at the UT Southwestern High Throughput Screening Laboratory, and validated by reacquisition and assay. Protein kinases are an excepted family of drug targets, and targeting enzymes involved in the G2/M checkpoint is an established strategy in cancer drug discovery. TAO2 is a newly-identified enzyme in this pathway. Inhibitors to other members in this pathway, the checkpoint kinases 1 and 2, have so far not been selective. The concept of finding non-ATP competitive inhibitors is known, but so far those identified have been obtained serendipitously. We will find more selective inhibitors of TAO2 by binding inactive conformers, which tend to be more diverse among protein kinases than the active forms. If successful, our experiment will change the way that inhibitors are found, both for protein kinases and other drug targets possessing multiple conformers.