CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170373

Project Title:
HTS for covalent GTP-competitive inhibitors of KRAS G12C

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

RAS mutations are some of the most common genetic abnormalities found in cancerous tumors with 30% of tumors showing RAS mutations, with even higher rates in deadly cancers such as lung, pancreatic and rectal. In normal cells RAS proteins direct cells to grow, divide and survive when appropriate. However, mutant RAS proteins cause cancer by signaling constantly and inappropriately. A number of labs have shown that cancer cells cannot survive after mutant RAS proteins are shut down, but their techniques are only applicable to laboratory settings and therefore cannot be used in patients. Efforts to develop drugs that specifically target RAS-driven cancers have been ongoing for several decades but no effective therapies exist. One of the cancer-causing effects of cigarette smoke is a specific genetic mutation in the KRAS gene which results in changes in the KRAS protein at amino acid position 12 from glycine to cysteine (G12C). KRAS G12C mutations are found in ~23,000 new cases of lung cancer per year. The Westover lab and collaborators previously developed 'tool' compounds such as SML-8-73-1 (SML) that, in a test tube, specifically and irreversibly attach to and inactivate KRAS G12C. This strategy is appealing because it exploits the very mutation that causes cancer. Therefore these compounds are unlikely to affect healthy normal cells which do not carry the KRAS G12C mutation. SML is not suitable for use as a drug because it cannot pass through the cell membrane of cancer cells. It should be noted that other groups are also targeting KRAS G12C using irreversible inhibitors, but their approaches are fundamentally different because their compounds do not bind to the enzymatic active site of KRAS G12C, as in our approach. We believe targeting the active site will have distinct advantages. This proposal aims to discover and further develop small molecules that act like SML, but are cell penetrant and can be used for clinical treatment of KRAS G12C-driven cancers.