CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140233

Project Title:
Structure-Guided Kinase Inhibitor Design for Cancer Therapy

Award Mechanism:
Individual Investigator

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

Lay Summary:

Small molecule inhibitors are powerful tools for understanding cell physiology and validating drug targets for the treatment of a variety of diseases, especially cancer. Modern drug discovery often begins with the identification of cellular targets followed by chemical compound development. Translation of hypothetical drug targets into pharmacological proof-of-concept studies is a major bottleneck because production of new classes of small molecule inhibitors requires many lines of expertise including chemistry, enzymology, structural biology, cell biology and disease modeling in animals. Large collaborations enable the needed progress. We belong to a collaborative group with a track record of producing first-in-class compounds which have contributed to understanding many biological processes and have the potential to become new therapeutic cancer drugs. Within our collaborative group we provide biochemistry and structural biology expertise. Specifically we do x-ray crystallography which reveals the 3 dimensional details of how chemical ligands bind to drug targets and thereby informs design choices during compound optimization for potency and other ‘drug-like’ properties such as solubility, bioavailability and metabolic stability. Numerous examples illustrate the value of the structure-based design approach including the development of many atypical antipsychotics, selective COX-2 inhibitors, HIV medications and kinases inhibitors. Indeed, the structure-based design paradigm is dominant in the field of kinase inhibitor development. In this application we propose studies, including the commitment to solve co-crystal x-ray structures of three different cancer-related kinases (HER3, TAK1 and CDK8) bound to promising lead compounds, to facilitate development of new classes of cancer drugs. These drugs would potentially apply to a range of cancer types including breast cancer, gastrointestinal cancer, skin cancer and blood cancers.