CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170233

Project Title:
K-ras Spatiotemporal Dynamics: Novel Therapeutic Targets

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Ras is a protein that operates as a molecular switch, toggling between an active “on-state” and an inactive “off-state” in response to growth signals received by the cell. When Ras is in the “on-state” it activates a signaling network that instructs the cell to divide. Unfortunately 15-20% of all human tumors acquire mutations that lock the Ras switch in the “on-state”. Cells with a mutant Ras switch therefore receive a constant signal to undergo cell division, resulting in the outgrowth of a tumor. The major clinical problem is with a form of Ras called K-Ras that is mutated in more than 90% of pancreatic cancers, approximately 50% of colon cancers and 25% of non-small cell lung cancers. We have known for over 25 years that Ras proteins are anchored to the inner surface of the cell limiting membrane, called the plasma membrane. Whilst there are currently no drugs that directly target mutant Ras, there is a wealth of experimental data to show that K-Ras must be localized to the plasma membrane and then organized into small clusters in order to activate its signaling network and drive tumor growth. Our study is therefore looking for new ways of interfering with the mechanism whereby K-Ras binds to the plasma membrane. We have already identified drugs and small molecules that prevent the normal association of K-Ras with the plasma membrane and shown that these compounds selectively kill tumor cells transformed by mutant K-Ras. In this study we will figure out how these drugs work and determine whether they have clinical utility as new anti-K-Ras cancer agents. One especially exciting aspect of the proposal is that some of these drugs are already being used in the clinic to treat other diseases, what we will therefore investigate is whether these drugs can be repurposed in novel combinations to treat K-Ras cancers.