CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130513

Project Title:
Discovery and optimization of natural and artificial ligands regulating Hypoxia Inducible Factor

Award Mechanism:
Individual Investigator

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

Lay Summary:

Human cells must monitor and respond to changes in their environment to survive. Oxygen, critical for many cellular functions, is among the most important external signals. In humans, oxygen is detected by a protein called Hypoxia Inducible Factor (HIF), which cells use to control hundreds of genes as oxygen levels change. Normally, these genes give cells the ability to adapt and survive under stress conditions. Unfortunately, this same response is exploited by cancer cells that hijack HIF to enable their own survival and proliferation. Given that this aberrant HIF function contributes to the growth of tumors and the aggressive nature of cancers, drugs that inactivate HIF could provide the basis of new anti-cancer therapies. Humans have three similar versions of HIF, called HIF-1, HIF-2 and HIF-3. Given that different cancers rely on different members of this group, and that each member has its own unique shape, we need to target each HIF individually. We recently developed compounds that bind HIF-2 in a region that controls its function, tightly binding the protein and blocking its ability to promote cell survival. These findings reveal a promising therapeutic route for renal cell carcinoma, a cancer where HIF-2 is known to play a critical role. However, as HIF-1 is the central player in numerous other cancer types, we need compounds designed to block its function as well. To this end, we aim to identify compounds targeting HIF-1 using the strategy we previously used to successfully develop HIF-2 inhibitors. In addition, we propose to investigate the mechanism of a recently discovered protein that inactivates HIF-1 in human cells, but acts through an unknown mechanism. Taken together, these insights into artificial and natural ways to inhibit HIF will pave the way for both powerful new tools and strategies to target this key controller of cancer progression.