



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100846

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

Award Mechanism:
Individual Investigator

Principal Investigator:
Gardner, Kevin

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Hypoxia Inducible Factors (HIFs) are the basis of the mammalian response to low cellular oxygen levels, a condition known as hypoxia. In response to this state, HIFs control the transcription of over 100 genes that help cells adapt to this challenge and improve local oxygenation to relieve it. While this response is critical under nonpathological conditions, constitutively increased levels of HIFs are highly correlated with several forms of human cancer. As such, there is significant interest in the development of artificial compounds to regulate HIF function, both to provide reagents for study of HIF signaling pathways and as lead compounds for therapeutic development. To this end, we have recently used a combination of biophysical, biochemical and chemical approaches to study the structure and function of the Per-ARNT-Sim (PAS) domains of human HIFs, which serve as critical protein/protein interaction modules in assembling the functional complex of the two HIF subunits, HIF α and ARNT. These studies have identified several artificial compounds that potently bind one of the HIF PAS domains, triggering structural changes that dissociate the dimeric HIF α /ARNT complex and thus block its function. Here, we propose three aims to extend this research: 1). Optimize pharmacokinetic and biochemical properties of the artificial HIF-regulating compounds we have identified to date; 2). Screen natural product libraries for alternative compounds with favorable properties; 3). Screen libraries from human cells to identify metabolites that may naturally regulate HIF function. Taken together, these studies will provide further insight into HIF function, chemical tools for further studies, and lead compounds for therapeutic evaluation.