



## CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:  
RP100773

Project Title:  
Discovery and Validation of Novel Cancer Drug Targets through Synthetic Lethal Screening

Award Mechanism:  
Individual Investigator

Principal Investigator:  
Mills, Gordon B

Entity:  
The University of Texas M.D. Anderson Cancer Center

### Lay Summary:

The goal of this project is to discover novel strategies to attack cancer cells. Unfortunately, many of the cancer drugs used today have strong toxic side effects because they do not target cancer cells specifically. Ideally, cancer drugs would target molecules whose disruption specifically kills cancer cells but does not harm normal cells. In the proposed research project, we aim to discover such 'ideal' drug targets. To do this, we performed a series of genome wide, high-throughput RNAi screens in human and *Drosophila* cultured cells to discover such drug targets referred to as "synthetic lethals." We screened for genes whose knock-down specifically kills cells with hyperactivation of the Akt/PI3Kinase pathway, a signaling pathway which is deregulated in a majority of human cancers. This cross species approach using both human and *Drosophila* screens identified a set of 27 genes that show highly specific synthetic lethal interaction with hyperactivation of the Akt/PI3Kinase pathway. We propose to determine the mechanism underlying the synthetic lethal interactions using a systems biological approach that can detect changes in the signaling status of hundreds of proteins. We will also evaluate the potential of these genes as targets for novel cancer therapeutics and their normal functions through *in vivo* studies. These genes may be excellent drug targets because they may attack cancer cells with precision, potentially providing optimal therapeutic effect with no negative side effects.