CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130172

Project Title:
Exploiting synthetic lethality, drug synergy, and an animal model reproducing drug sensitivities in humans to identify small molecules to treat renal cancer

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Brugarolas, James

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Despite recent approval by the FDA of multiple drugs against kidney cancer, when metastatic, kidney cancer is rarely curable. To accelerate the process of drug discovery and development, we have created a unique pipeline which involves innovative assays for chemical library screening and an animal model that reproduces the treatment responsiveness of kidney cancer in patients. Kidney cancer is characterized by inactivation of the VHL gene, which is observed in 90% of tumors, and we have developed a powerful assay for the identification of chemicals that disable pathways required for the survival of cells that have lost VHL. We have completed a preliminary screen of 12,800/ 200,000 compounds and have established a proof-of-concept for the identification of such compounds. This smaller screen identified a drug previously evaluated in clinical trials against leukemia that preferentially killed VHL-deficient tumor cells. We seek to determine the potential of this drug against kidney cancer, but current models for drug testing are deficient and fewer than 10% of drugs that are successful in these models are eventually found to be effective in patients. To test chemicals emerging from the screen, we have developed a new model of kidney cancer. We have found that tumors from patients when implanted into the kidney of mice preserve the tumor characteristics and reproduce the sensitivity of kidney cancer to drugs in patients. To our knowledge this is the first therapeutically relevant model of kidney cancer. We plan to use this model to determine whether the drug we have found (as well as other compounds emerging from the screen) is active against kidney cancer. The integration of a sophisticated screening platform with an animal model that reproduces the sensitivity of kidney cancer to drugs in patients holds enormous potential for the discovery and development of new drugs for the treatment of kidney cancer.