CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170640

Project Title:
Capitalizing on Therapeutic Liabilities in RAS-Mutant Cancers With a Rational Combination Therapy With PARP and MEK Inhibitors

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Mills, Gordon B

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

Lay Summary:

Background Mutant RAS, one of the most common aberrations in cancer, is present in 11% of all cancers and at higher frequencies in pancreatic (90%), colorectal (50%), lung (30%), and endometrial cancers (21%) and melanoma (30%). Unfortunately, few effective therapeutic options are available for patients with mutant RAS tumors. Improved patient benefit will require development of rational approaches to identify effective combination therapies. MEK inhibitors (MEKi) target mutant RAS tumors but are ineffective as monotherapy. Poly ADP ribose polymerase inhibitors (PARPi) are effective in patients with mutations in the breast cancer 1 and 2 genes (BRCA1/2). Similarly immune-oncology “checkpoint inhibitors” have demonstrated remarkable activity in some cancer patients. Unfortunately, as with most targeted agents, responses to PARPi and MEKi are short and, similar to immune-oncology agents, restricted to a subpopulation of patients. Preliminary data Based on a rational approach designed to identify effective drug combinations, we demonstrated in vitro synergy of PARP and MEK inhibitors in 32 of 45 pancreas, lung, melanoma, ovarian, and endometrial mutant lines. In preliminary in vivo studies, PARPi/MEKi combinations induced regressions and markedly prolonged survival in three KRAS mutant models. Again based on our rational approach, we demonstrated that PARPi and immune-oncology agents demonstrate marked synergy in vivo. Significance and High Impact/High Yield Rationale: PARPi/MEKi combinations, if translated to the clinic, could benefit a large number of patients with no other therapeutic opportunities. Unfortunately, PARPi/MEKi combinations have entered the “valley of death” where additional in vivo data is required to justify clinical trials. Our proposed studies are designed to provide the critical data demonstrating that PARPi/MEKi combinations with or without immune-oncology agents warrant investigation in patients with RAS mutant tumors.