CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150032

Project Title:
Developing New Combinatory Therapies for Pediatric High Grade Glioma

Award Mechanism:
Individual Investigator Research Awards for Cancer in Children and Adolescents

Principal Investigator:
Li, Xiao-Nan

Entity:
Baylor College of Medicine

Lay Summary:

The five year survival in children with high grade glioma is still less than 10%. Recent advances of genomic sequencing methods have made it possible to discover nearly all gene mutations in pediatric gliomas. The objective of this application is therefore to develop new combinatory therapies that will selectively target those mutations critical for tumor cell survival. Since most of the tumors have many different mutated genes, we have designed a new “anchor-probe” strategy to selectively and efficiently target multiple abnormalities. Based on the genetic concept known as “synthetic lethality”, we hypothesize that simultaneous perturbation of two (or more) mutated genes can result in a deadly combination (i.e. kill the tumor cells). We plan to use “anchor” drugs to target recurring mutations found in pediatric gliomas and “probe” drugs, identified through high throughput screening from a large series of FDA-approved drugs and investigational agents, to launch a 2nd strike. We have established a large panel of patient-derived orthotopic xenograft (PDOX) models that replicate the pathologies and maintain gene mutations of this deadly disease. In this proposal, we will team up with the CPRIT-funded Texas Screening Alliance for Cancer Therapeutics to develop novel “anchor-probe” combinations for critical genetic mutations, confirm their therapeutic efficacy in our 16 PDOX models, the first and the largest panel in the world, and understand the mechanisms of cell killing and drug resistance in these tumors. Our goal is to establish strong preclinical rationale for these new combinatory therapies so that clinical trials can be initiated within 1-3 years. Completion of our studies will help to bridge the gap between cancer genomics findings and new effective therapies and will facilitate a paradigm shift from “one-size-fit-all” treatment to “customized” target therapies for children with high grade glioma.