CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170169

Project Title:
High throughput combinatory drug screening for pediatric medulloblastomas with a dysregulated EZH2 pathway

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

Principal Investigator:
Li, Xiao-Nan

Entity:
Baylor College of Medicine

Lay Summary:

Medulloblastoma (MB) is the most common malignant brain tumor that occurs in children. Among the four distinct molecular subgroups, group 3 and 4 MBs often have the poorest prognosis. New therapies are needed. Fortunately, recent studies have found a gene, EZH2, that is frequently activated in the most difficult to treat MBs. While many new EZH2 inhibitors have been developed, the bad news is that they only have limited efficacy as single agent. Our objective is therefore to develop new combinatory therapies that will target EZH2 together with a 2nd gene critical for tumor survival. Based on a genetic concept known as “synthetic lethality”, we hypothesize that simultaneous targeting of two (or more) tumor genes can result in a deadly combination (i.e. kill the tumor cells). Since MBs may depend on different mechanisms to survive, we have designed a new “anchor-probe” strategy to efficiently target multiple abnormalities. We will use EZH2 inhibitors as “anchor” drug and apply “probe” drug, identified through high throughput screening from <7,000 FDA-approved drugs and investigational agents, to launch a 2nd strike. In this proposal, we will team up with the CPRIT-funded Texas Screening Alliance for Cancer Therapeutics to develop novel “anchor-probe” combinations for EZH2 activation in our 16 patient-derived orthotopic xenograft (PDOX) models, the first and the largest panel in the world, which not only replicate group 3 and 4 subtypes of MB but also maintain EZH2 over-expression. We will demonstrate the therapeutic efficacy, understand the mechanisms of cell killing and drug resistance. Our goal is to establish strong preclinical rationale for the new combinatory therapies so that clinical trials can be initiated within 1-3 years. Completion of our studies will bridge the gap between cancer biological discoveries and new effective therapies to facilitate a paradigm shift from “one-size-fit-all” treatment to “customized” target therapies for highly malignant MB.