CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140469

Project Title:
Novel Small Molecule Probes Targeting IDH Mutated Glioma

Award Mechanism:
Individual Investigator

Principal Investigator:
Song, Yongcheng

Entity:
Baylor College of Medicine

Lay Summary:

Glioma is the most common form of brain tumors and can be classified into four grades at diagnosis. Grade I is a type of benign tumor. However, grades II and III gliomas are invasive, which can often progress to highly malignant, grade IV disease, i.e., secondary glioblastoma multiforme (GBM). Secondary GBM is a lethal disease with a median survival of 3.8 year as well as less than 10% 5-year survival rate for the patients. There is therefore a pressing need to find new therapeutics to treat gliomas. Isocitrate dehydrogenase (IDH) is one of the key enzymes in human metabolism. DNA sequencing of more than 1,000 human giloma samples has revealed that 75% of low-medium grade gliomas and secondary GBM carry IDH mutations. Growing evidence strongly supports IDH mutation is a target for intervention. Small-molecule inhibitors of mutant IDH could represent novel therapeutics to treat IDH mutated glioma and be used as probes to investigate the biological functions of this mutation. However, few potent inhibitors mutant IDH have been developed and none tested in clinically relevant glioma mouse models. Given the low success rate in drug discovery, more inhibitors with distinct chemotypes are needed. For Aim 1, we will use medicinal chemistry to develop two series of inhibitors of mutant IDH. X-ray protein crystallography and structure activity relationship will be explored to design inhibitors with improved potency. For Aim 2, the enzyme and cell activity of these compounds will be tested. Pharmacokinetic and toxicological properties of promising compounds will be evaluated to find if they are good drug candidates. For Aim 3, we will use our mouse models of human GBM with IDH mutation to test the in vivo activities of selected inhibitors and perform molecular and cell biology methods to investigate their possible mechanisms of action. The success of this work could open up a new avenue to the first targeted therapy of gliomas with IDH mutations.