CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180590

Project Title:
Development of an engineered & pharmacologically optimized human methionine-gamma-lyase drug candidate for the treatment of prostate cancer and glioblastoma

Award Mechanism:
Individual Investigator

Principal Investigator:
Stone, Everett

Entity:
The University of Texas at Austin

Lay Summary:

This proposal outlines the development of a novel biologic drug and an understanding of its mechanism of action that exploits a key defect observed in prostate cancer (PCa) and glioblastoma (GBM) metabolism; namely the extreme appetite that these cancers have for the amino acid methionine which fuels their growth. This demand is so great that radiolabeled methionine can be used to selectively image these tumors. The therapeutic we are developing depletes methionine from the blood and is selectively toxic to cancer cells as normal tissue does not have the same requirement for methionine. There is further evidence that methionine depletion keeps cancers from resisting the effects of standard of care chemotherapies; a major obstacle that leaves cancer patients with fewer treatment options. For example about 1 in 39 PCa patients will die as their tumors become unresponsive to therapy and in GBM patients it is even worse, with current drugs providing a median survival of only 15 months. Safe effective therapeutics that target cancer by unique mechanisms and can be used with current treatments are sorely needed to provide more choices. In an effort to take advantage of the methionine dependence observed in malignancies like prostate cancer our team at University of Texas at Austin developed a unique prototype therapeutic (an engineered human enzyme called hMGL) that depletes methionine from circulation. We found hMGL was highly effective in killing both drug sensitive and resistant GBM cells and using a mouse PCa model we found that our prototype hMGL halted tumor growth without any apparent toxicities, loss of weight, or loss of appetite even after several weeks of treatment indicating that our proposed mode of treatment is likely to be well tolerated. The objective of this proposal is to make further improvements in the potency of this drug, understand the mechanism of action and identify biomarkers for selecting patients most likely to benefit from this therapy.