CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150242

Project Title:
Functional and structural characterization of a small chemical compound that arrests glioma stem cell growth with high activity and specificity

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Glioblastoma multiforme (GBM) is the most common type of malignant brain cancer and is incurable. Therefore, there is a critical need to identify new ways of investigating and attacking this disease. The Cancer Genome Atlas Project, a multi-institutional effort to study the DNA of cancers in the hopes of finding common mutations that may indicate new targets for developing therapies identified mutation combinations of a dozen or so genes previously associated with cancer in GBM. Of these, three cancer associated genes: p53, NF1 and Pten were among the five most frequently mutated GBM associated genes. We have constructed genetically engineered mice that harbor the above three mutations and they develop GBM with 100% efficiency. These mouse GBMs are similar to human GBM by all commonly used pathological and molecular criteria and can be used to better understand GBM and to discover treatments. Detailed study of the tumors in our mice has led us to conclude that a limited number of cells within the tumor (termed cancer stem cells, CSCs) have the unique property of reinitiating tumor growth after chemotherapy. These CSCs retain general properties of stem cells and we can readily culture them. We have used these CSCs to screen 200,000 molecules for compounds that might neutralize the ability of these brain tumor CSCs to grow. The focus of the current application is one such compound, 12M11 that has powerful action on mouse GBM and human GBM cells, and on experimental mouse tumors. We aim to optimize the antitumor properties of 12M11 and to identify specifically the mode of action of this compound in cancer cells. A key feature is the fact that this compound has strong effects on GBM cancer cells and other types of cancer cells but not on normally dividing cells, therefore the pathways involved are important to the ability of a tumor to grow but not of a normal cell to grow.