CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100782

Project Title:
Genetic mouse models of glioma: translational tools for therapeutic development

Award Mechanism:
Individual Investigator

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

Lay Summary:

Malignant astrocytomas are incurable, locally infiltrative brain tumors. Conventional anticancer therapy has failed in making meaningful improvement in treatment. Although the full spectrum of molecular events that drives tumor initiation and progression has yet to be defined, recent data from The Cancer Genome Atlas has revealed frequent mutation in several tumor-relevant genes. We developed mouse models of glioma that have conditional inactivation of three of the five most frequently mutated genes in glioma: p53, Nf1, and Pten. 100% of these mice develop tumors that histologically and molecularly resemble human astrocytomas. These tumors arise from a population of neural stem/progenitor cells that can be propagated and expanded in culture. Importantly, the primary tumor cell cultures plate at high efficiency without evidence of undergoing crisis or massive selection. Our research design employs these primary tumor-derived cells for unbiased, large-scale small molecule and genomic screening. We have devised a series of progressive assays to determine the specificity (cell death, differentiation, arrest) and efficacy of our screens. Interesting candidates will be functionally analyzed in mouse and human cancer cells, and in vivo. Our glioma mouse models are clinically relevant, powerful tools that provide a uniquely advantageous cell population for these comprehensive large-scale screens, and we believe that these screens will identify novel compounds and genes that may be therapeutically tractable in human glioma.