SECTION 1: CONTACT INFORMATION

Institute: Cincinnati Children's Hospital Medical Center

Title: Establishment of a pre-clinical model for pediatric glioblastoma

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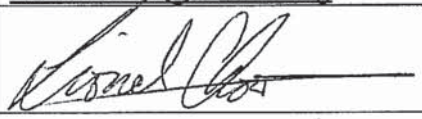
Signature:	

2. Institutional Authority

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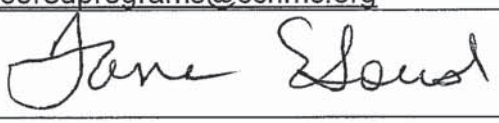
Signature:	

Grant Title
Establishment of a pre-clinical model for pediatric glioblastoma

SECTION 2: EXECUTIVE SUMMARY

Glioblastoma is a highly aggressive astrocytoma affecting thousands of adults and children each year in the United States. Current treatments are ineffective and as a consequence, overall survival is dismal. Moreover, there have been few clinical gains achieved in the last three decades. Accumulating evidence obtained through the study of primary high-grade astrocytomas (HGAs) suggests that pediatric and adult tumors have different molecular pathologies that may underlie differences in the clinical behavior of these patients. Interestingly, there is recent evidence that diffuse intrinsic pontine gliomas (DIPGs) may share some molecular pathological features with pediatric HGAs but not adult tumors. This suggests that effective molecularly targeted therapies for adults may be ineffective or minimally effective in pediatric patients. However, major gaps in our understanding of pediatric HGA biology remain and one hurdle is the lack of animal models that faithfully recapitulate these tumors.

We have generated a mouse model for HGA by using inducible Cre-loxP mice to target brain-specific inactivation of the tumor suppressors *Pten*, *p53* and the Rb pocket family members *Rb1* and *Rbl1* (which encodes p107). These genes regulate core pathways that are frequently dysregulated in pediatric HGA. Preliminary data indicates that this model gives rise to highly penetrant, spontaneously occurring brain tumors that bear a striking histopathological resemblance to pediatric HGA. We hypothesize that a comparative analysis of secondary mutations occurring in mouse tumors and those occurring in pediatric HGA will lead to the identification of critical genes and pathways governing tumor growth and survival. Moreover, we propose that the use of this model in pre-clinical multi-agent trials will accelerate the investigation of combined targeted agents in clinical trials.

The specific aims of the proposal are three-fold. 1) We will perform a comprehensive and comparative molecular pathological characterization of mouse and pediatric HGAs in order to identify mutations and pathways contributing to tumor growth and survival. This will involve the interrogation of tumors with microarray technology (array comparative genomic hybridization, gene expression microarray and microRNA expression array) coupled with an integrative analysis of the data and independent validation of potential targets. 2) We will demonstrate proof-of-concept for the use of this mouse model in preclinical studies by comparing the effect on *in vivo* HGA growth in mice treated with “standard of care” (cranial irradiation) to targeted therapy against a core pathway in glioblastoma, the PI3K/Akt/mTor pathway (rapamycin or BEZ-235). Treatment with these targeted agents is expected to result in delayed growth but not eradication of HGA. 3) To identify the most promising targets for combination therapy, we will perform gene expression profiling on HGA treated *in vivo* with rapamycin or BEZ-235. The comparison of gene expression profiles between untreated and treated tumors will highlight growth and survival pathways that allow tumors to escape single agent therapies, which have been uniformly disappointing in clinical trials to date. Targeted agents against these pathways will be used in combination with rapamycin or BEZ-235 for *in vivo* treatment of mice to test for synergy against HGA growth. This scheme will be applied iteratively to build a multi-agent treatment protocol.

Our goal is to harness the power of genetically engineered mouse models for cancer, which have been found to replicate human tumors more faithfully than cell lines or xenografts, and the growing library of molecularly-targeted small molecule inhibitors in order to rapidly develop rational protocols of treatment for this devastating disease that can be tested in clinical trials. In addition to the principal investigator’s expertise in clinical neuro-oncology and in the design, handling and analyses of mouse models for brain tumors, this project will also draw on the expertise of a clinical neuropathologist familiar with the histology of mouse tumors (Dr. Lili Miles) and a bioinformatician who has developed novel pathway analysis tools using gene expression data (Dr. Zhandong Liu). This project will also provide the preliminary data required to secure external funding for further pre-clinical studies.