Title of the Proposal:
EPIGENETIC ALTERATIONS AS THERAPEUTIC TARGETS IN PEDIATRIC BRAIN TUMORS

SECTION 2: EXECUTIVE SUMMARY

Brain tumors remain the leading cause of cancer-related deaths in children. Even among survivors, long-term neurocognitive and neuroendocrine sequelae of current therapies are often devastating. Hence, there is an urgent need to develop novel therapies that not only improve outcome, but mitigate long-term complications in children with brain tumors. Pediatric non-brainstem high-grade glioma (pNBS-HGG) and diffuse intrinsic pontine glioma (DIPG) are among the deadliest pediatric brain tumors. Epigenetic modulation of histones plays an important role in regulation of gene expression and oncogenic transformation in many cancer types. Among the most impactful findings to date has been the discovery in pNBS-HGG and DIPG of high prevalence mutations in chromatin remodeling genes *H3F3A* and *HIST1H3B* encoding histones H3.3 and H3.1, respectively. The consequence of these mutant histones relates to epigenetic modulation, mediated in large part by EZH2, a key component of the multi-protein histone methyltrasferase polycomb repressive complex 2 (PRC2). EZH2 catalyzes the trimethylation of histone H3 lysine 27 (H3K27me3), a repressive chromatin mark. H3.3K27M has been identified as a major driver mutation in pNBS-HGG and DIPG, and has been shown to be particularly prevalent in children. The presence of this mutation defines a clinically and biologically distinct subgroup of tumors and is associated with strikingly short survival. H3.3K27M is believed to target EZH2 activity to genes associated with tumorigenesis such as *p16Ink4A* and produces a repressive epigenetic alteration, thereby causing a decrease in the expression of these genes leading to tumor development. We hypothesize that EZH2 activity is critical for the establishment and the development of pNBS-HGG and DIPG and its specific inhibition will lead to the expression of tumor suppressor genes; thus, to the inhibition of tumor growth. We propose to evaluate the activity of a potent EZH2 inhibitor in DIPG and pNBS-HGG patient-derived cells and in mouse models of pNBS-HGG and DIPG.

The biology in pediatric HGG is poorly understood and understudied. There is a crucial need to identify targets to design new therapeutic agents. This pilot study will significantly contribute to the understanding of the biology of this devastating disease and may lead to the recognition of a targetable pathway and ultimately to a cure. This is the first study targeting EZH2 in pediatric brain tumors.

We request $100,000 to cover the cost of the above studies.