SECTION 2 – EXECUTIVE SUMMARY

Malignant brain tumors are the leading cause of cancer-related mortality in children (1), and diffuse intrinsic pontine glioma (DIPG) is one of the most devastating, with a median survival of <1 year following treatment with radiation therapy (2). Despite more than 250 clinical trials over the past 30 years (3), not a single chemotherapeutic agent has demonstrated survival benefit. There is thus an urgent need for novel treatments for this disease. Our data and two recent high profile studies have implicated the protein EZH2 (enhancer of zeste homologue 2) as a specific therapeutic target in DIPG (4,5). Although EZH2 inhibitors exist and have shown very promising results in phase I clinical trials in other cancers, all the currently available EZH2 inhibitors *do not cross the blood brain barrier and thus cannot be effectively employed in brain tumor patients.*

We have generated novel brain penetrant inhibitors of EZH2 in conjunction with the drug development institute at MSKCC (Tri-Institutional Therapeutics Development Institute), and the major goal of this project is to validate the in vivo efficacy of these inhibitors using pre-clinical models of DIPG.

We hypothesize that brain penetrant inhibitors of EZH2 will represent effective therapeutics for DIPG based on our data, and recent studies* (4,5) *which show genetic knockdown of EZH2 has an anti-tumor effect in DIPG.

The primary objectives of this project are:
1) Validate the *in vivo* efficacy of novel brain penetrant EZH2 inhibitors we have generated, using pre-clinical models of DIPG
2) Characterize critical epigenetic effects of histone mutations (found in DIPG) on self-renewal and differentiation, to gain understanding of how these mutations promote tumors

Impact and Innovation: Aim 1 is directly translational, and our aim is to have a small molecule to enter IND (investigational new drug) studies in preparation for phase 1 clinical trials in patients with DIPG. EZH2 has been strongly implicated as a target in other brain tumors e.g. CNS atypical teratoid rhabdoid tumors, and various types of brain metastases; thus successful development of a brain penetrant EZH2 inhibitor will also be beneficial for this group of patients. Aim 2 is *directly mechanistic*; and we anticipate that the proposed experiments will reveal insights into how H3K27M mutations promotes the formation of tumors.

Feasibility: All the techniques outlined in this proposal, are already well established in the Allis Laboratory and will allow prompt initiation and completion of the project. It is anticipated that further optimization of the novel brain penetrant EZH2 inhibitors will be required, and further chemical biology support for continued optimization of the already generated brain penetrant inhibitors will be provided by the Tri-Institutional Therapeutics Discovery Institute (Tri-I-TDI). The ultimate goal will be to have a small molecule to enter IND (investigational new drug) studies within a period of 12-18 months in preparation for phase 1 clinical clinical trials in DIPG patients.

Expertise: This project is a collaboration between Dr. Richard Phillips is a brain tumor specialist and physician-scientist at MSKCC and Dr. David Allis a world-leader in the study of epigenetics at Rockefeller. The Allis Lab has been a leader in dissecting the mechanisms by which the H3K27M mutation promote DIPG (6,7). Dr. Richard Phillips MD PhD has spear-headed a collaboration with chemical biology experts at the MSKCC drug development core (Tri-I-TDI) which has led to the development of two novel brain penetrant inhibitors of EZH2 which will be further characterized in this study. The combination of these expertise will facilitate the successful completion of this project.

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