Preclinical evaluation of novel BMI-1 inhibitors *in vivo* in intra-brainstem orthotopic xenograft mouse models

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Section 2. Executive Summary

Diffuse pontine glioma (DIPG) is a devastating pediatric malignancy with very poor prognosis. Virtually all patients with DIPG will die from their disease within1-2 years of diagnosis. Recent attempts to improve survival have been unsuccessful, and currently radiation is the only therapy offering limited benefit. One of the challenges in studying DIPG has been the lack of relevant animal models. The goal of this project is to evaluate a novel therapy in the treatment of DIPG by examining the anti-tumor activities of a series of BMI-1 inhibitors that can pass through the blood brain barriers in a panel of orthotopic xenograft models that have been established from autopsied DIPG materials. *(from the lab of Xiao-Nan Li, MD, PhD).* We hypothesize that i) Inhibiting BMI-1, a transcription repressor that plays an important role in stem cell renewal, with a series of novel small molecule inhibitors, will result in decreased cell proliferation both in vitro and in vivo in orthotopic xenograft mouse models of malignant pediatric brain tumors that over-express BMI-1. ii) Systemic analysis of known BMI-1 down stream genes/signaling pathways together with global gene expression will facilitate the understanding of mechanisms of action of these novel BMI-1 inhibitors. The evaluation of this series of small molecule inhibitors, developed by PTC therapeutics, will provide the pre-clinical rationale for clinical trials in the future. We will test this hypothesis with the following specific aims:

1. To determine if the BMI-1 inhibitor can kill primary cultured xenograft tumor cells, including those that express putative brain tumor stem cell markers (CD133) *in vitro;*
2. To determine if oral administration of the BMI-1 inhibitor can eliminate pre-established orthotopic xenograft tumors, leading to significantly prolonged animal survival times; and
3. To elucidate the mechanisms of BMI-1 inhibitors by examining the down stream targets of the BMI-1 pathway and whole genome gene expression profiling.

This proposed study would be carried out utilizing models derived from patient autopsy tissue, which has been transplanted into the brainstem of SCID mice. These models represent a unique preclinical testing platform, in that they resemble the pathology and the microenvironment of the original patient tumors. Initially, xenograft cells will be exposed to this novel agent *in vitro* and screened to determine the most responsive models, as well as the most effective compound. Both non-stem cells and cells which expressive putative stem cell markers will be evaluated, as BMI-1 is known to play a role in stem cell renewal. Subsequently, we will evaluate the efficacy of treating pre-established orthotopic xenograft tumors *in vivo* with the most effective compound. Finally, we will try to elucidate the method of BMI-1 induced killing by evaluating downstream targets of BMI-1 after treatment with this new agent.

This is the first preclinical study specifically designed to target therapy-resistant childhood DIPGs *in vivo* in clinically relevant animal models with a small molecule inhibitor for BMI-1. The utilization of this panel of novel patient tumor-derived orthotopic xenograft mouse models of DIPG, and the prospective examination of the therapeutic efficacy of a novel small molecule inhibitor of BMI-1 makes this an innovative approach. All the reagents and assays are well developed in our laboratory and we are uniquely positioned to accomplish the proposed study. The completion of our proposed study should provide strong preclinical rationale for the initiation of clinical trials in pediatric DIPGs in very near future.