Project Title

Eliminating Therapy-Resistant Diffuse Intrinsic Pontine Gliomas with Oncolytic Picorna Virus SVV-001: an in vivo Study in Intra-brain Stem Xenograft Mouse Models

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Section 1

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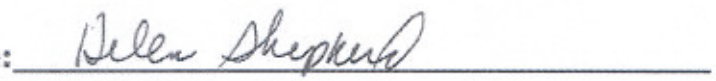
Signature: 

Section 2: Executive Summary

Diffuse intrinsic pontine glioma (DIPG) is the most lethal childhood cancer, and virtually all children with this disease die within 1-2 years of diagnosis. *Major challenges* for the development of new therapies include the lack of clinically relevant animal model system, difficulties of efficient drug delivery across the blood brain barrier (BBB) and limited options of targeting therapy-resistant tumor cells (cancer stem cells?). Fortunately, we have established a panel of five orthotopic xenograft mouse models of DIPG in the brain stems of SCID mice, and identified a novel oncolytic virus, the Seneca Valley Virus (SVV-001), that can pass through the BBB and effectively kill brain tumor cells (including brain tumor stem cells). The objective of this application is therefore to examine the *in vivo* anti-tumor activities of SVV-001 in the five intra-brain stem DIPG xenograft mouse models to establish preclinical rationale for the initiation of clinical trials in the near future.

Our **hypotheses** are: ***i***) therapy-resistant pediatric DIPG cells, including the cells that express cancer stem cell features and DIPG cell-of-origin markers, can be infected and killed by SVV-001 *in vitro*; ***ii***) systemic treatment of pre-established orthotopic xenograft tumors with SVV-001 would significantly prolong animal survival times in the DIPGs permissive to SVV-001; and ***iii***) the oncolysis of DIPG tumor cells is mediated by the activation of autophagy and/or apoptosis. To test these hypotheses, we will utilize our five newly developed orthotopic xenograft mouse models together with a recently established DIPG neurospheres by Dr. Monje et al (PNAS 2011) to accomplish the following **Specific Aims**: 1) To determine if SVV-001 can infect and kill DIPG cells in vitro, including primary cultured DIPG xenograft tumor cells, the tumor cells that express putative brain tumor stem cell markers (CD133 and CD15) and the cell-of-origin makers (Nestin, Vimentin and Oligo2) of DIPG; 2) To determine if intravenously administered SVV-001 can eliminate pre-formed intra-brain stem orthotopic xenografts, leading to significantly prolonged animal survival times; 3) To elucidate the mechanisms of SVV-001-induced cell killing by examining if activation of autophagy and induction of apoptosis play a role.

The innovations of our proposed studies are two folds. **First,** it lies in our novel use of a relatively large panel of intra-brain stem DIPG xenograft mouse models. These five models were derived from the terminal stage DIPG patients and represent the clinically proven therapy-resistant DIPGs that are in desperate need of new therapies. Since all the xenograft models were established through direct engraftment of autopsied human DIPG cells into the brain stems of SCID mice, and are shown to have replicated the histopathological and diffuse invasive phenotypes of DIPGs, they have provided us with unprecedented opportunities to study the biology and to test new therapies *in vivo* in a microenvironment that is the closest to human DIPGs. We have also optimized a protocol to establish primary cultures from these DIPG xenograft tumors to facilitate the *in vitro* screening of new therapeutic agents. **Secondly**, it lies in our prospective examination of the therapeutic efficacy of a novel oncolytic virus, the SVV-001, which can potentially kill the therapy-resistant DIPG cells. SVV-001 is a naturally occurring, non-pathogenic and replication-competent oncolytic virus. We have recently shown that SVV-001 is able to pass through the BBB after intravenous injection, and can effectively eliminate medulloblastoma and pediatric GBM cells, including the cancer stem cells, *in* vivo in mouse brains. Additionally, SVV-001 kills tumor cells through infection and intracellular replication, they may not be susceptible to the drug- and radiation-resistant mechanisms of DIPGs.

All the animal models, reagents and assays are well developed in our laboratory and we are uniquely positioned to accomplish the proposed study. Since SVV-001 is shown to be well tolerated in a recently completed Phase I trial in adult patients, and has entered phase I clinical trial in children with extra-cranial tumors, completion of our proposed study should provide strong preclinical rationale for the initiation of clinical trials of SVV-001 in pediatric DIPGs in the very near future (2-3 years).