Section 2: Executive Summary

The objective of this application is to examine if combining ionizing radiation with an oncolytic virus SVV-001 would lead to synergistically enhanced tumor cell killing and significantly improve therapeutic efficacy in vivo in patient-tumor-derived intra-brain stem xenograft mouse models of diffuse intrinsic pontine glioma (DIPG).

DIPG is the most lethal childhood cancer, and virtually all children with this disease die within 1-2 years of diagnosis. Traditional challenges for the development of new therapies include the lack of clinically relevant animal model systems, difficulties of drug delivery across the blood brain barrier (BBB) and limited options of targeting therapy-resistant tumor cells. Fortunately, we have established a panel of nine orthotopic xenograft mouse models of DIPG in the brain stems of SCID mice. Thanks to the generous support of the Cure Starts Now Foundation, we have completed a research project entitled “Eliminating therapy resistant DIPGs with oncolytic picornavirus SVV-001” and identified Seneca Valley Virus (SVV-001) as an attractive agent for DIPGs. Our data confirmed that SVV-001 can infect and effectively kill DIPG tumor cells in vitro, and pass through the BBB in vivo, leading to improved animal survival in a subset of intra-brain stem DIPG xenograft models. However, when compared with greater than 80% cell killing in vitro, the animal survival time was only prolonged ~ 10% ($P < 0.05$), indicating the limited efficiency of SVV-001 as a single agent.

To address such response discrepancies between the in vitro and in vivo activities and to seek new strategies to further improve therapeutic efficacy, we examined the cellular content of mitochondria, which is the recognized assembly station of many viruses. We found that mitochondria were very rich in the cultured DIPG cells, but scarce in many xenograft tumor cells derived from the same models. This has led us to hypothesize that the lack of mitochondria in the xenograft tumor cells in vivo impaired the intracellular replication of SVV-001 and subsequently weakened the oncolytic cell killing of the target tumor cells. Fortunately, we have found that ionizing radiation can activate robust mitochondrial biogenesis in vivo, converting mitochondria-depleted tumor cells to mitochondria-rich tumor cells. Indeed, our preliminary studies involving pediatric GBM have shown that combining fractionated radiation (2 Gy/day for 5 days) with single i.v. injection of SVV-001 led to significant improvement of animal survival times. Since many of the DIPG tumor cells were shown to be responsive to SVV-001 in vitro (they may therefore be inherently permissive to SVV-001), it is therefore our second hypothesis that radiation induced increase of mitochondria would provide SVV-001 the much needed replication “facilities”, thereby converting the “dormant” tumor cells into responsive tumor cells that can be killed. To test these hypotheses, we will utilize our established orthotopic xenograft mouse models to accomplish the following Specific Aims: 1) To prove that lack of mitochondria causes SVV-001 resistance in the permissive DIPG tumor cells in vivo; 2) To demonstrate that ionizing radiation activates mitochondrial biogenesis in previously mitochondria-deficient/depleted tumor cells and sensitizes them to SVV-001 induced cell death; 3) To demonstrate that combining ionizing radiation with intravenously injected SVV-001 can improve therapeutic efficacy in vivo, leading to significantly improved animal survival.

The innovations of our proposed studies are two fold. First, it lies in our novel use of a relatively large panel of intra-brain stem DIPG xenograft mouse models. These models were derived from terminal stage DIPG patients and represent the clinically proven therapy-resistant DIPGs that are in desperate need of new therapies. Our models 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. Secondly, it lies in our prospective examination of the therapeutic efficacy of a novel combined treatment that is rationally designed based on the molecular mechanisms that are complementary to each other. SVV-001 has many features that make it particularly attractive for brain tumors. Identifying the underlying mechanism of SVV-001 resistance and the subsequent development of a new strategy to overcome such resistance would prevent the premature drop-out of a potentially effective therapy. More importantly, since our approach is built on the top of radiotherapy, the standard treatment for DIPGs, our chances of rapid translation into clinical trials are therefore greatly improved.