**Section 2: Executive Summary**

i. Scientific Merit

We and others co-discovered the presence of activating mutations in ACVR1 in 25% of human DIPGs in 2014. Subsequently, my laboratory has developed a murine DIPG model incorporating R206H ACVR1 and observed that R206H ACVR1 significantly accelerates brainstem gliomagenesis. In addition, short-term treatment with a bone morphogenetic protein pathway inhibitor (LDN-212854), significantly reduced proliferation in this model. Furthermore, we have preliminary data that the MAPK pathway is upregulated in human DIPGs with ACVR1 mutations and that the MAPK pathway remains activated in our murine DIPG model despite BMP pathway inhibition.

Therefore, we hypothesize that inhibiting both the BMP pathway and the MAPK pathway will significantly prolong survival of ACVR1 mutant DIPG-bearing mice. Here are proposing to test two treatment strategies: 1) LDN-212854 (a BMP pathway inhibitor) in combination with a MEK inhibitor (PD-0325901), and 2) E6201, a small molecule inhibitor that inhibits both the BMP pathway and the MAPK pathway. Of note, both PD-0325901 and E6201 are already in clinical trials in adult cancers.

ii. Disease Impact

DIPG is an incurable brain tumor that arises in children. The standard of care today in 2017 is the same as it was in the 1960s. This is due, in part, to the frequent "recycling" of adult brain tumor treatment approaches, which is becoming less common due to the discovery of significant genetic differences between adult and pediatric gliomas, including DIPG. In this proposal, we seek to change this. Here we are proposing to evaluate the in vivo efficacy of a bone morphogenetic protein (BMP) pathway inhibitor in combination with a MEK (MAPK/ERK Kinase) inhibitor in our murine DIPG model that harbors the R206H ACVR1 and H3.1K27M mutations. We will evaluate two treatment regimens; one treatment regimen will be a combination of two drugs (LDN-212854 and PD-0325901) and another will be one drug that inhibits both the BMP and MAPK pathways (E6201). Of note, we will evaluate both treatment regimens in combination with radiation, the standard of care for children with DIPG. Results from this proposal will guide future preclinical work as well as guide the development of a clinical trial for children with DIPG through the PBTC.

iii. Innovation

We have developed a murine DIPG model that incorporates mutant ACVR1 (R206H) and H3.1K27M (two genetic alterations that often co-occur in human DIPG specimens). Using this model, we have observed that R206H ACVR1 accelerates brainstem gliomagenesis and that H3.1K27M accelerates brainstem gliomagenesis only in the presence of ACVR1 R206H. We propose to evaluate inhibitors of the BMP and MAPK pathways in this genetic mouse model to help prioritize therapies for clinical trials in children with DIPG. Furthermore, we will also investigate mechanisms of resistance by comparing the RNAseq of treated and untreated tumors.

iv. Feasibility

We have developed this murine DIPG model and have already started making these tumors at Northwestern. With regards to LDN-212854, we have an ongoing collaboration with Paul Yu (a researcher who studies FOP at Harvard) who provides drug to our lab for preclinical testing. We will purchase PD-0325901 from Selleck Chemicals and will receive E6201 from Strategia Therapeutics (See letter of Support).

v. Expertise

My laboratory has developed these murine models of DIPG and we are experienced in preclinical testing of targeted therapies using this model.

vi. Total Grant Amount Requested

$100,000