EXECUTIVE SUMMARY

i. Scientific Merit

In the past decade, we have witnessed exciting discoveries in the DIPG field, with the discovery of the unique genetic alterations found in human DIPGs such as the H3K27M mutations as well as other unique genetic alterations such as ACVR1. In particular, these have demonstrated conclusively that DIPGs, are a unique developmental disease that differs from adult gliomas as well as pediatric high-grade gliomas that arises in other parts of the brain. Now the challenge is to develop DIPG models that can be more predictive of clinical activity in the clinic. We have all heard of novel therapies that cure cancer in mouse models but that do not translate when evaluated in patients with the respective disease.

Therefore, we hypothesize that developing a DIPG that recapitulates the genetic alterations of the human disease in the correct cell-of-origin (spatiotemporally) will provide an important tool to the DIPG community for interrogation of the pathogenesis of DIPG and the evaluation of novel therapeutics.

ii. Disease Impact

DIPG is an incurable brain tumor that arises in children. The standard of care today in 2018 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 develop an improved DIPG model that arises in the most likely cell-of-origin for DIPG, an oligodendroglial progenitor cell or OPC. We will then apply this model to identify targets of the histone mutation as well as evaluate how radiation alters DIPG tumor characteristics in an immunocompetent mouse model.

iii. Innovation

It is earlier from studies in other cancer models that a key component of a good model for any cancer is initiation of that cancer in the correct cell(s)-of-origin. The combined

work from Michelle Monje, Mario Suva, and Arturo Alvarez-Buylla strongly suggest that the oligodendroglial progenitor cell (OPC) is the most likely cell-of-origin. Therefore, it is important to develop murine models of DIPG that arise in OPCs and compare the transcriptome to the human disease as well as assess response to therapy to credential this novel model.

iv. Feasibility

We have all the appropriate mice strains in our lab and have established feasibility of this project by generating preliminary data that murine DIPGs can be initiated in Olig2 progenitors of the neonatal brainstem (see figures 1 and 2).

v. Expertise

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

treatment and follow-up that will improve patient outcome in addition to maximizing quality of life.