EXECUTIVE SUMMARY

Responses of distinct cell populations to PDGFRA inhibitors in diffuse intrinsic pontine glioma

Diffuse intrinsic pontine glioma (DIPG) is an incurable childhood cancer and the leading cause of pediatric brain tumor death. Recent studies suggest that the tumor is heterogeneous—a combination of multiple, distinct cell types, the most prevalent being the oligodendrocyte precursor-like (OPC-like) cell driven by excessive plateletderived growth factor receptor-α (PDGFRA) signaling. Inhibition of PDGFRA signaling has anti-proliferative effects in vitro, but fails in the clinical setting, potentially because only a subset of tumor cells are sensitive.

Our central hypothesis is that the sensitivity of DIPG to PDGFRA inhibition is limited to a subpopulation of OPC-like cells. In this proposal, we are using low passage, autopsy-derived DIPG cell cultures to study the effects of PDGFRA inhibitors on the growth of OPC-like and other distinct cell populations. Our approach uses single-cell Western blotting to determine the proportions of OPC-like and other distinct cell populations predicted by previous single-cell RNA sequencing, in order to validate this data and correlate it with drug sensitivity. Our preliminary data have demonstrated that expertise of our team to execute the proposed studies, and the feasibility of the approach. If successful, this project is expected to provide the preliminary data for a future NIH R01 proposal in which we will study the interactions and drug sensitivity of each cell type in more advanced models, including biopsy specimens.