Section 2: Executive Summary

Scientific Merit
Single-cell genomic profiling is revolutionizing our understanding of tumor biology, as it enables for the first time a genome-wide interrogation of tumor programs at cellular resolution, offering unprecedented insights into tumor cells and their micro-environment at a depth that was unthinkable even a few years ago. I expect that defining the genetic and cellular programs of DIPG with these techniques directly deployed in patient samples will reveal the key programs that underlie DIPG biology. By additionally leveraging the CRISPR/cas9 system to perform targeted and specific genetic knock-outs, we will functionally test candidate regulators and expect to identify novel tumor vulnerabilities and dependencies.

Disease Impact
Applying single-cell genomic technologies to precious patient-derived tumor samples at biopsy as well as autopsy will shed unprecedented light on unique tumor vulnerabilities and dependencies that are not identifiable by bulk genetic studies alone. The proposed research will provide an unparalleled view of the cellular architecture and transcriptional networks underlying DIPG biology, and moreover, reveal novel tumor vulnerabilities that could rapidly enter pre-clinical and clinical trials.

Innovation
The proposed study is the first ever to systematically study DIPG at cellular resolution, and is expected to reveal the interplay between genetically and developmentally driven programs in DIPG. By using the combination of cutting-edge single cell genomic technologies, genome editing tools and computational analysis available at our institutions and at the Broad Institute, these novel and complementary approaches will shed light on the molecular pathways driving DIPGs.

Feasibility
Single-cell RNA sequencing as well as genome editing technologies have been established in the laboratory of Dr. Suva. A close collaboration with computational scientists at the Broad Institute is also already in place. The novel findings contributed by this study will provide a rational basis for renewed attempts at improving clinical care of DIPG patients.

Expertise
Dr. Suva and Dr. Filbin have unique and complementary expertise that makes them the ideal investigators to complete the proposed research. Dr. Filbin is a pediatric neuro-oncologist at Dana-Farber Cancer Institute and research fellow in Dr. Suva's laboratory at Massachusetts General Hospital (MGH) and the Broad Institute. Her previous work includes the discovery of a novel combinatorial targeted treatment for glioblastoma, which led directly to clinical trials in adults and pediatric patients with gliomas. Dr. Suva is a faculty scientist and neuropathologist at MGH and the Broad Institute and has led ground-breaking research deploying single-cell genomics in adult gliomas.

Total Grant amount requested: $100,000