Section 2: Executive Summary

Scientific Merit

Recent genetic analyses have revealed specific and unique K27M mutations in the histone 3.3 side chain in more than 90% of DIPG cases. Post-translational modifications of this histone 3.3 side chain are normally used as a "histone code" for fine-tuning gene expression across the whole genome. *I hypothesize that K27M mutations induce an aberrant epigenetic and transcriptional programs, rendering tumor cells uniquely sensitive to further epigenetic perturbations. I further hypothesize that these tumor-specific alterations of the DIPG epigenome are sustained by epigenetic modifiers and master transcription factors, and as such, are potentially targetable.* I expect that I will reveal key contributors that underlie DIPG epigenetic programs by applying two new technologies: **1)** The CRISPR/Cas9 system, which allows the knock-out of epigenetic modifiers to identify novel tumor vulnerabilities and dependencies; and **2)** Large-scale chromatin profiling, which permits a genome-wide look at DNA activation/repression states, in combination with RNA-seq to identify master transcriptional regulators.

Disease Impact

Applying these new technologies to patient-derived tumor samples will shed unprecedented light on unique tumor vulnerabilities and dependencies that are not identifiable by genetic studies alone. The proposed research will provide an unparalleled view of the epigenetically mediated networks underlying DIPG biology and reveal novel tumor vulnerabilities that could rapidly enter pre-clinical and clinical trials - ultimately leading to a cure.

Innovation

The proposed study is the first ever to systematically study epigenetic dependencies in DIPG and map the DIPG epigenome in a cell-, location- and differentiation-specific context. By using cutting-edge technologies and computational analysis available at our institutions and at the Broad Institute, the two distinct but complementary approaches will provide a novel view of the molecular pathways driving DIPGs.

Feasibility

Both research methods proposed have already been established in collaboration with the Broad Institute. Drs. Filbin and Suva have privileged access to the Genomic Pertubation Platform, where pilot studies on CRISPR/Cas9 screens for various pediatric cancer cell lines have already been successfully completed. A close collaboration with computational scientists 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 a unique and complementary combination of 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 high-grade gliomas. Dr. Suva is a faculty scientist at MGH and the Broad Institute and has led ground-breaking research on the underlying epigenomic and transcriptional networks in adult glioblastoma.

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