Large scale sequencing studies have implicated increasing numbers of transcription factors (TFs), chromatin regulators (CRs) and histones as direct targets of mutations and rearrangements in cancer. These genetic alterations are now recognized to play critical roles in cellular transformation by altering key transcriptional programs involved in cellular differentiation, plasticity and proliferation. Aberrant epigenetic programs and hierarchies of cellular differentiation are concepts particularly relevant to the biology of gliomas, complex infiltrating brain tumor affecting both adults and children that remain incurable.

Glioma cells display unique dependencies on programs of neural development, maintaining distinctive transcriptional circuits that reflect their differentiation status. There are strong evidences that these epigenetic programs have a major influence on glioma cell properties, with stem-like cells driving tumor-propagation and recurrence, while more differentiated cells lack these capabilities. These programs are dictated and sustained by master TFs, CRs and associated cellular networks that direct activation or repression of cis-regulatory elements. Our laboratory establishes genetically and epigenetically relevant cellular models from patient tumors, and utilizes epigenomic profiling, genome-editing technologies, cellular reprogramming and single-cell RNA sequencing to reconstruct cellular circuits and uncover novel dependencies in gliomas.

Targeting neurodevelopmental programs in primary human glioblastoma stem cells.

We have integrated large scale epigenomics with functional experiments and cellular reprogramming in primary glioblastoma, the most common genetic variant of the disease. With this approach, we have demonstrated that a core set of four neurodevelopmental TFs (SOX2, POU3F2, SALL2 and OLIG2) code the unique properties of glioblastoma stem-like cells, including their \textit{in vivo} tumor-propagating potential. We have shown that this core combination of TFs is expressed by subsets of stem cells in patient tumors and have begun to dissect their transcriptional program. We suggest that these programs are either pre-existing epigenetic states hijacked by genetic mutations or aberrant states.

The Suvà laboratory is focused on the biology of brain tumors, in particular glioblastoma and oligodendroglioma. We dissect how cellular heterogeneity and plasticity contribute to tumor cells properties. We study primary human samples up to the single-cell level and establish genetically and epigenetically relevant cellular models from patient tumors. We model how brain cancer cells exploit their plasticity to establish phenotypically distinct populations of cells, with a focus on programs governing glioma stem cells. Additionally, the laboratory investigates how mutations affecting genes involved in chromatin regulation contribute to cellular transformation. Given the tremendous heterogeneity of genetic aberrations in brain tumors, we seek to identify common programs integrated at the chromatin level that would offer novel therapeutic options in these dismal diseases.
generated during cellular transformation. Our working hypothesis is that aberrant neurodevelopmental programs could represent key targets that can be therapeutically exploited not only to eliminate existing stem-like populations, but potentially to prevent their generation through bi-directional plasticity. Our lab is currently utilizing novel genome-editing technologies to generate functional knock-out of critical nodes in the network to identify novel dependencies in glioblastoma and assess novel therapeutic options.

**Annotation of functional genomic elements in secondary glioblastoma, pediatric glioblastoma and oligodendroglioma.**

At least two additional genetic routes lead to glioblastoma development, namely secondary glioblastoma bearing signature IDH mutations and pediatric glioblastoma with H3F3A mutations. These mutually exclusive mutations are of particular interest, as they are both thought to impact on the epigenome of cells, possibly through shared mechanisms. In collaboration with groups in the MGH Brain Tumor Center, we are applying deep chromatin profiling to genetically defined cultures of secondary glioblastoma and H3F3A mutant pediatric glioblastoma. As additional model, our group is mapping the epigenome of oligodendrogliomas, another type of glioma. Our goal is to identify the regulatory elements and their associated networks that control cellular state across the spectrum of human gliomas.

**Gliomas heterogeneity assessed at single-cell level.**

Tumor heterogeneity poses a major challenge to cancer diagnosis and treatment. It can manifest as variability between tumors, or within cells from the same tumor, that may harbor different mutations or exhibit distinct phenotypic or epigenetic states. Such intratumoral heterogeneity is increasingly appreciated as a determinant of treatment failure and disease recurrence. In a collaboration between the neurosurgery department at MGH, the Bernstein Lab at MGH and the Regev Lab at the Broad Institute, we are pursuing our previous efforts in single-cell transcriptional profiling. We are currently investigating single cells from many different types of gliomas to assess tumor heterogeneity at an unprecedented depth.