Mario L. Suvà, MD, PhD

Suvà Laboratory

Lilly Bussema, BS
Nick Gonzalez-Castro, MD, PhD
Simon Gritsch, MD, PhD
Toshiro Hara, PhD
Masashi Nomura, MD, PhD
Liz Perez*
Dana Silverbush, PhD
Mario Suvà, MD, PhD
Hannah Weisman, BS
Yixin Zhang, BS

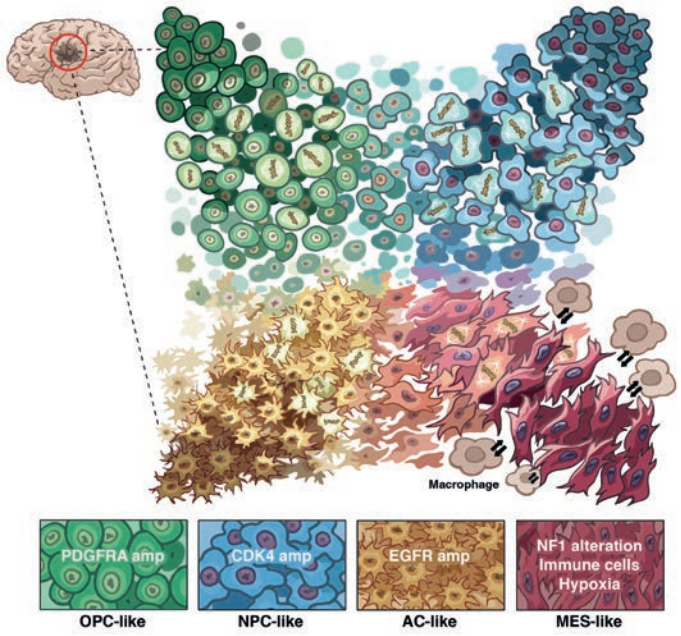
*Graduate student

The Suvà laboratory is primarily focused on developing and applying single-cell genomic technologies to dissect the biology of brain tumors, in particular adult and pediatric high-grade gliomas and medulloblastoma. We study patient samples at single-cell resolution and establish genetically and epigenetically relevant cellular models directly from clinical 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. We seek to redefine tumor cell lineages and stem cell programs across all types of gliomas, and to leverage the information for renewed therapeutic attempts targeting cellular states. The laboratory is also invested in single-cell genomics efforts to dissect the immune system of gliomas, and in charting the cellular programs in sarcomas.

Gliomas are heterogeneous disease in which intra-tumoral heterogeneity contributes to disease progression and therapeutic failure. Glioma cells vary in stemness, proliferation, invasion, chemoresistance, apoptosis, and metabolism. Various factors contribute to this heterogeneity, on the one hand, branched genetic evolution of cancer cells generates distinct tumor sub-clones; on the other hand, it is also becoming increasingly clear that gliomas cells display functional properties related to developmental pathways and transcriptional programs, such as those associated with the self-renewal of tissue stem cells and their differentiation into specialized cell types. In order to dissect those influences and obtain a comprehensive view of gliomas biology, my laboratory is leveraging single-cell expression profiling across the spectrum of human gliomas, directly in patient samples. Analysis of transcriptomes of individual cells from human malignancies offers a compelling approach to dissect the cellular state and infer partial genetic information from cancer cells in an unbiased way. We seek to discover novel therapies for gliomas.

Assessing Malignant Cells Heterogeneity at the Single-Cell Level in Gliomas

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 intra-tumoral heterogeneity is increasingly appreciated as a determinant of treatment failure and disease recurrence. The Suvà Lab is performing large-scale single-cell RNA-seq analyses in IDH-mutant gliomas, histone H3-mutant midline gliomas, IDH-wildtype glioblastoma, and medulloblastoma to assess tumor cell lineages, stem cell programs and genetic heterogeneity at an unprecedented scale and depth. Our work in IDH-mutant gliomas highlighted a rare subpopulation of actively dividing stem/progenitor cells, solely responsible for fueling tumor growth in patients. Single cell profiling of H3K27-mutant pediatric gliomas highlighted specific vulnerabilities and revealed a differentiation block, maybe explaining the more aggressive



Model for the cellular states of glioblastoma and their genetic and micro-environmental determinants. Mitotic spindles indicate cycling cells. Lighter/darker tones indicate strength of each program. Intermediate states are shown in between the four states and indicate transitions.

nature of this cancer type. More recently, we provided a comprehensive model of glioblastoma biology that integrates single-cell expression programs, genetic composition and tumor subtypes (see figure). Our study of medulloblastoma single-cell programs provided clarifications on tumor histogenesis and classification. Overall, our goal is to identify both lineage-defined and somatically-altered therapeutic targets in brain cancer in both children and adults.

Dissecting the Ecosystem of Gliomas

The composition of the tumor micro-environment (TME) has an important impact on tumorigenesis and modulation of treatment responses. For example, gliomas contain substantial populations of microglia and macrophages, with putative immunosuppressive functions but whose precise programs remains uncharted at single-cell resolution. In addition, very little is known about the functional state of T cells in human gliomas. As is the case in diverse other conditions, the CNS may create a unique microenvironment that impacts T cell function by distinct mechanisms.

The laboratory leverages single-cell analyses in clinical samples to dissect the functional programs of immune cells in gliomas that can be used to elucidate mechanisms relevant to immuno-oncology. We profile both dysfunctional T cells that express multiple inhibitory receptors and T cells that are functional based on expression of multiple genes required for T cell cytotoxicity. We find these modules to be distinct from observations in other types of tumors (such as melanoma), underscoring the necessity to perform these analyses directly in gliomas. By analyzing modules of co-expressed genes in subsets of T cells in patients with glioma we seek to shed light on mechanism of activation and exhaustion in patient tumors and to highlight candidate novel regulatory programs that can be exploited for therapeutics.

Selected Publications:

Neftel C†, Laffy J†, Filbin MG†, Hara T†, Shore ME, Rahme GJ, Richman AR, Silverbush D, Shaw ML, Hebert CM, Dewitt J, Gritsch S, Perez L, Gonzalez Castro LN, ..., Louis DN, Regev A, Bernstein BE, Tirosh I*, **Suvà ML***. An integrative model of cellular states, plasticity and genetics for glioblastoma. *Cell*. 2019 Aug 8;178(4).

Hovestadt V†, Smith KS†, Bihannic L†, Filbin MG†, Shaw ML, Baumgartner A, DeWitt JC, Groves A, Mayr L, Richman AR, Shore M, ..., Regev A, Gajjar A, Orr BA, Slavc I, Robinson GW, Bernstein BE*, **Suvà ML***, Northcott PA*. Resolving the cellular architecture of medulloblastoma by single-cell genomics. *Nature*. 2019 Aug;572 (7767).

Filbin MG†, Tirosh I†, Hovestadt V†, Shaw ML, Escalante LE, ..., Getz G, Rozenblatt-Rosen O, Wucherpfennig KW, Louis DN, Monje M, Slavc I, Ligon KL, Golub TR, Regev A*, Bernstein BE*, **Suvà ML*** Developmental and oncogenic programs in H3K27M gliomas dissected by single-cell RNA-seq. *Science*, 2018 Apr 20;360(6386).

Venteicher AS†, Tirosh I†, Hebert C, Yizhak K, Neftel C, Filbin MG, Hovestadt V, ..., Cahill DP, Rozenblatt- Rosen O, Louis DN, Bernstein BE, Regev A*, **Suvà ML***. Decoupling genetics, lineages and micro-environment in IDH-mutant gliomas by single-cell RNA-seq. *Science*. 2017 Mar 31; 55(6332).

Tirosh I†, Venteicher AS†, Hebert C, Escalante LE, Patel AP, Yizhak K, Fisher JM, ..., Rivera MN, Getz G, Rozenblatt-Rosen O, Cahill DP, Monje M, Bernstein BE, Louis DN, Regev A*, **Suvà ML***. Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. *Nature*. 2016 Nov 10;539(7628).

*Co-senior authorship
†Co-first authorship