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.
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 microenvironment (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:**


*Co-senior authorship
†Co-first authorship