

## MCC-Rady Padres Pedal the Cause Spring 2021

Tissue-resident memory cells in pediatric high-grade gliomas



Anusha Preethi Ganesan, PhD (Rady Children's)  
P. Vijayanand, PhD (MCC, LJI)

### Scientific Abstract:

High-grade gliomas are the most common malignant brain tumors in children. Despite advances in treatment, the majority of pediatric high-grade gliomas (pHGG) remain incurable and newer treatments are urgently needed. Numerous lines of evidence support an important role for T cell-mediated immunosurveillance of the CNS in protecting against cancer. Immunotherapies that boost the anti-tumor responses of T cells have been successful in adult cancers, however translation of their success to pediatric tumors is hindered by a lack of understanding of the immune microenvironment within these tumors. We found significant infiltration of pHGG with CD8<sup>+</sup> tissue-resident memory (T<sub>RM</sub>) cells which has been shown to be critical players in anti-tumor immunity in non-CNS tumors. The goal of this project is to define the functional role of CD8<sup>+</sup> T<sub>RM</sub> responses in pHGG and investigate the molecular mechanisms involved in CD8<sup>+</sup> T<sub>RM</sub> cell generation and function within pHGG in the brain. We will perform *in vivo* mechanistic studies in murine glioma models and patient-derived xenograft models using T<sub>RM</sub> cell genetic deletion or adoptive transfer studies. We will undertake an unbiased and comprehensive approach to define transcriptomic and epigenomic profile of purified CD8<sup>+</sup> T<sub>RM</sub> cells at a single-cell level in a well-characterized cohort of patients with pHGG. Utilizing state-of-the-art genomic tools such as single-cell RNA-seq, ATAC-seq and TCR-seq, we will evaluate CD8<sup>+</sup> T<sub>RM</sub> functional phenotype, TCR/BCR sequence and clonality in pHGG. Integrated bioinformatics analyses of these datasets will reveal novel immune pathways that may be targeted to bolster CD8<sup>+</sup> T<sub>RM</sub> responses for treatment of pHGG.

### Lay Abstract:

High-grade gliomas (pHGG) are the most common brain tumors in children and carry poor prognosis, hence there is significant unmet need for improved treatment. Immunotherapy is rapidly emerging as a promising new treatment modality for cancer with durable remission and lesser toxicity than those associated with conventional therapies. Our prior research in pediatric brain tumors has revealed that pHGG are specifically infiltrated by a distinct subset of CD8<sup>+</sup> T cells called tissue-resident memory (T<sub>RM</sub>) cells, contrary to the general view that the brain is immunologically silent. T<sub>RM</sub> cells are critical players in anti-tumor immunity and hence understanding how these cells function and how they are generated within pHGG is of great importance. The primary aims of this project are: 1) To elucidate the functional significance of CD8<sup>+</sup> tissue-resident memory cells in anti-tumor immune responses in pHGG; and 2) To identify molecular mechanisms driving differentiation and function of HGG-infiltrating CD8<sup>+</sup> T<sub>RM</sub> cells. We will perform *in vivo* studies in preclinical glioma models by deleting or transferring T<sub>RM</sub> cells and evaluate the resulting impact on glioma growth. We will utilize cutting-edge molecular tools to assess the factors that promote the generation and function of T<sub>RM</sub> cells within pHGG. The results from this study will reveal novel molecular pathways to bolster CD8<sup>+</sup> T<sub>RM</sub> cells to promote anti-tumor immunity in pHGG, which will pave the way for clinical translation in children with pHGG, for whom there are otherwise limited therapeutic options.