expansion. We found that shortening ex vivo expansion of either TCR-specific murine Th17 cells or human CAR Th17 cells licenses the cell product to eradicate large tumors in low doses and generate long-lived memory against tumor.1 Therapeutic Th17 cells induce the systemic release of IL-6, IL-17, GM-CSF, and MCP-1 among other cytokines in tumor-bearing hosts, reminiscent of clinical cytokine release syndrome. As the toxicity of cytokine release is managed in patients through IL-6 blockade, we addressed the impact of IL-6 on efficacy and durability of Th17 cell therapy. We hypothesized that IL-6, induced by Th17 cells, was fueling the durable memory properties of this cell product.

Methods Th17 cells were expanded ex vivo using the TRP-1 transgenic mouse model in which CD4+ T cells express a TCR that recognizes tyrosinase-related protein 1 on melanoma. Naïve CD4+ T cells were polarized to the Th17 phenotype and infused into mice with B16F10 melanoma after a nonmyeloablative total body irradiation (5 Gy) preparative regimen.

Results IL-6 blockade, targeting either IL-6R or neutralization of the cytokine, did not significantly impact the primary immune response of adoptively transferred Th17 cells against tumor. However, administering IL-6 blockade acutely after Th17 transfer resulted in a higher incidence of tumor relapse upon secondary tumor challenge, thereby compromising long-lived antitumor immunity.1 Mounting a secondary response to tumor was dependent on CD4+ T cells, but not CD8+ T cells, persisting in the host. Mechanistically, IL-6 blockade reduced pSTAT3 and Bcl2 in transferred T cells but did not greatly impact the concentration of other systemic cytokines. As a small fraction of Tregs remain in the Th17 cell product ex vivo, we examined the engraftment of those Tregs after transfer. IL-6 was critical to suppress engraftment of FoxP3+ donor T cells from the CD4+ T cell product. Thus, IL-6 promoted robust tumor infiltration by donor effector over regulatory cells for early Th17 cells relative to cell products expanded longer durations ex vivo.1

Conclusions Overall, short-term expanded Th17 cells uniquely induced IL-6 unlike Th17 cells expanded longer ex vivo. IL-6 promoted Th17 survival, reduced engraftment of tumor-specific Tregs, and was critical to durable memory. This work may suggest that the universal strategy to inhibit IL-6 during cytokine release syndrome may come at the expense of long-term efficacy for specific cell therapy approaches.

REFERENCE
Abstracts

Ethics Approval: This study was approved by the Thomas Jefferson University Institutional Review Board (#14.0204) and the Institutional Animal Care and Use Committee (Protocol #01529).

REFERENCES


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NATURAL KILLER CELLS ENGINEERED WITH AN INDUCIBLE, RESPONSIVE GENETIC CONSTRUCT TARGETING TIGIT AND CD73 TO RELIEVE IMMUNOSUPPRESSION WITHIN THE GBM MICROENVIRONMENT

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Background: Solid tumors such as GBM are particularly difficult to treat, being largely resistant to traditional treatments, fueling interest in alternative treatment approaches, including cell-based immunotherapy. Natural killer (NK) cells have emerged as promising effectors to target GBM through genetic modifications and ex vivo manipulation. However, immunosuppressive conditions within the tumor microenvironment (TME) further complicate NK cell-based treatments. Specifically, within the TME tumor cells release of high levels of ATP extracellularly. While intracellular ATP is necessary for cell metabolism, extracellular ATP is converted into adenosine (ADO) by ectonucleotidases CD39 and CD73, both overexpressed on GBM. Extracellular ADO induces immunosuppressive suppression of NK cells through binding with A2A adenosine receptors (A2ARs) on NK cells, suppressing cytokine secretion, proliferation, and other functional activities. Adding to the suppression of NK cells is the interaction between CD155, expressed highly on GBM and other solid tumors, and T cell immunoreceptor with Ig and ITIM domains (TIGIT) expressed on NK cells. This interaction signals inhibition of NK cell cytolytic function, allowing for cancer cell immune-evasion.

Methods: To restore impaired NK cell anti-tumor activity, we have engineered NK cells to concomitantly target CD155 and CD73-induced immunosuppression on GBM using a tumor-responsive genetic construct. The construct is capable of blocking the immunosuppressive CD155/TIGIT interaction,