DEVELOPMENT OF A MOLECULAR TARGETED CYTOKINE THAT SPECIFICALLY EXPANDS VGAMMA9VDELTA2 T CELLS AND POTENTIATES ANTI-TUMOR ACTIVITY

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Background Vgamma9Vdelta2 (Vg9Vd2) T cells are an ideal target for cancer immunotherapy due to their ability to recognize stress-related ligands from transformed cells and eliminate them with broad, potent cytotoxicity. One limitation restraining the ability of Vg9Vd2 T cells from eliminating tumors is that they are a rare population in peripheral blood. Efforts to expand Vg9Vd2 T cells in vivo have typically relied on treatment with bisphosphonates and low-dose interleukin-2 (IL-2). This combination is limited by rapid clearance of the molecules, competition for IL-2 and dose-limiting toxicities. Using our molecular targeted cytokine (MTC) platform, we developed an alternative strategy to specifically expand Vg9Vd2 T cells utilizing a detuned IL-2 variant targeted to the Vg9Vd2 T cell receptor.

Methods Human IL-2 was engineered to eliminate CD25 binding and have reduced affinity for CD122. A high-affinity single-domain antibody specific to the Vg9-subunit of the Vg9Vd2 T cell receptor targets this cytokine to cells expressing the target antigen and thereby restricts IL-2 activity to Vg9Vd2 T cells. The ability of this Vg9Vd2-targeted MTC (anti-Vg9xIL2-X) to selectively bind and activate Vg9Vd2 T cells was assessed in vitro utilizing human PBMCs from healthy donors and dissociated tumor cells (DTCs) from various indications. IL-2 signaling and cell proliferation were analyzed by flow cytometry. Cancer-specific target cell killing was determined by coculturing Vg9Vd2 T cells with labeled tumor cells or healthy B cells. Expansion of Vg9Vd2 T cells in vivo was analyzed in NSG-B2M KO mice engrafted with human PMBCs.

Results Anti-Vg9xIL2-X bound Vg9Vd2 T cells and activated STAT3 signaling in a target-dependent manner. Treatment with anti-Vg9xIL2-X led to a dramatic increase in proliferation and accumulation of Vg9Vd2 T cells in healthy human PBMCs and DTCs. Anti-Vg9xIL2-X-driven expansion of Vg9Vd2 T cells increased expression of cytotoxic effector molecules, including IFNg and granzyme-B, leading to potent in vitro anti-tumor activity across numerous cancer cell types. The killing activity was selective for transformed cells as healthy cells were largely spared. Treatment with anti-Vg9xIL2-X also improved antibody dependent target cell killing by Vg9Vd2 T cells. Finally, dosing of human PBMC-engrafted mice with anti-Vg9xIL2-X was well-tolerated and resulted in an increased prevalence and specific expansion of Vg9Vd2 T cells.

Conclusions Using our MTC platform, we have developed a targeted cytokine that specifically activates and expands Vg9Vd2 T cells. By restraining IL-2 activity to this subset, we hope to limit IL-2-mediated toxicity and enhance Vg9Vd2 T cell anti-tumor activity across numerous cancer types.

REFERENCES

Ethics Approval All animal studies were conducted in accordance with AAALAC regulations and were approved by the IACUC for Explora BioLabs (#SP17-010-013).