ENHANCERS OF INNATE AND ADAPTIVE IMMUNITY COMBINE WITH MEMBRANE BOUND IL15 TO INCREASE THE EFFICACY OF TUMOR INFILTRATING LYMPHOCYTE (TIL) THERAPY FOR TUMORS WITH IMMUNOSUPPRESSIVE MICROENVIRONMENTS

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Background The clinical impact of tumor infiltrating lymphocytes (TIL) cell products is currently limited by suboptimal persistence and potency, as well as the need for high-dose adjuvant IL-2 treatment, which is associated with severe toxicities. Thus, we engineered an IL-2-independent TIL product, based on regulated expression of interleukin 15 (cytoTIL15 cells), which has shown anti-tumor efficacy and persistence in human melanoma PDX models. Since the immuno-suppressive tumor microenvironment (TME) hinders cell therapies, we hypothesized that combining pleotropic cytokines of the interferon (IFN), IL-1, or TNF families with IL-15 would further enhance antitumor activity and that our cytoDRiVE® platform would allow pharmacologic control of these potent immune mediators. We tested constitutive and regulated combinations of a representative member of these cytokines with IL-15 in human TIL for in vitro polyfunctionality and in vivo antigen-independent persistence. We also engineered mouse pmel-TCR cells with cytokine combinations for evaluation in the syngeneic B16 melanoma model.

Methods Human TIL were expanded and engineered with lentiviral vectors to express IL-15 with IFN-alpha, IL-18 (IL-1 family member) or undisclosed TNFSF-X (TNF superfamily member). Expanded TIL were immunophenotyped and assessed for polyfunctionality by flow cytometry after CD3/CD28 stimulation. Engineered TIL were transferred into NSG mice to assess antigen-independent TIL persistence in the absence of exogenous IL-2. Cytokines modified with our carbonic anhydrase 2 (CA2)-based cytoDRiVE® drug responsive domain (DRD) were evaluated for control of protein levels with the CA2 ligand, acetazolamide (ACZ). Cytokine expression was evaluated in flow cytometry and Meso Scale Discovery assays. To assess anti-tumor and TME remodeling capabilities, we used a syngeneic model with transduced pmel-TCR cells adoptively transferred into mice bearing B16 melanomas.

Results Engineered TIL expressing both IL-15 and either IFN-alpha, IL-18 or TNFSF-X showed similar fold expansion, immunophenotype and polyfunctionality in vitro as TIL expressing only IL-15. Combination cytokine-expressing TIL showed similar in vivo antigen-independent persistence in the absence of IL-2 as TIL engineered with only IL-15. As compared to control pmel cells, sub-optimal cell doses of pmel T cells expressing both IL-15 and either IFN-alpha or, IL-18, showed improved efficacy and TME remodeling, while combining IL-15 with TNFSF-X resulted in significant tumor growth arrest of B16 melanoma tumors without escape.

Conclusions While IL-15 drives expansion and persistence of cytoTIL15 cells without IL-2, adding pleotropic and highly immune-stimulatory members of the IFN, IL-1 or TNF families may provide enhanced efficacy for patients with solid tumors marked by an immunosuppressive TME.

Ethics Approval All animal studies were IACUC approved.