Overview

Background: Tumor Infiltrating Lymphocyte (TIL) therapies have shown significant solid tumor activity in patients, but many current TIL regimens require lymphodepletion and high-dose IL-2 after cell infusion. Removing these requirements that cause systemic toxicity while maintaining TIL product functionality by ex vivo engineering of the TIL product with transient expression of machinery could dramatically improve the patient experience, expand the eligible patient population, and allow repeat dosing.

Methods: mRNAs encoding for membrane-bound (mb) IL-2 or IL-12 were delivered directly to the cytolytic cells of TILs expanded from either melanoma, lung, or ovarian solid tumors using the microfluidic Cell Squeeze® technology.

mbl-2 binds IL-2R and drives STAT5 phosphorylation and proliferation without rhl-2

Figure 2: Coexpression post-SQZ® TILs from melanoma and ovarian tumors were thawed and cultured for 6 days in IL-2 and cultured for 6 days in IL-2 and stimulated with mbIL-2 (green), mbIL-7 (red), and mbIL-2/12 (yellow) and quantified for mbIL-2 (A) and mbIL-7 (B) expression (C). Percent expression of mbIL-2 for (N=5; median+IQR) and mbIL-7 (N=5; median+IQR) at 6 hours post-stimulus at a single time point (D) and a representative dot plot of single donor data from (E) the first independent experiment for mbIL-2 expression. (F) Percent expression at a representative donor from (G) the second independent experiment for mbIL-7 expression (N=5; median+IQR).

mbl-12 TILs upregulate CD62L and CD127, markers of central memory T cells

Figure 3: Conceptual kinetics of mbl-12 vs Systemic IL-2 TILs showing the upregulation of CD62L and CD127, markers of central memory T cells following donor-specific sqz® stimulation.

Future Targtes: Pre-conditioning cytokine IL-7 and pro-survival protein Bcl-2

Engineered mbl-2/12 Tumor Infiltrating Lymphocytes: Summary

- Through microfluidic Cell Squeeze® delivery of mRNAs, we engineered primary human TILs with transient expression of membrane-bound cytokines IL-2 and IL-12
- mbl-2 signals through endogenous IL-2R to phosphorylate STAT5 and drive survival and proliferation in the absence of exogenous IL-2 support
- mbl-12 induces upregulation of CD62L, a marker of central memory T cells which are T cell subtype known to confer superior antitumor immunity
- mbl-12/12 TILs release more IFN-γ than Control TILs + mbl-2 (positive control; current clinical standard) when cultured with patient-matched tumor cells

Overall, enhanced SQZ® TILs can potentially alleviate current requirements for toxic high-dose IL-2 support and lymphodepleting preconditioning regimens.