165 GENERATING ENHANCED TUMOR INFILTRATING LYMPHOCYTES THROUGH MICROFLUIDIC CELL SQUEEZING

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Background Tumor Infiltrating Lymphocyte (TIL) therapies have shown significant solid tumor activity in patients, but current TIL compositions require patient lymphodepletion and high dose IL-2 after cell infusion to support clinical activity. Removing this requirement through ex vivo engineering of the TIL product with mRNA could enhance potency, expand the potential patient population, and potentially allow for repeat dosing and concomitant treatment with checkpoint therapies.

Methods To transiently overexpress both membrane-bound cytokines and costimulatory molecules, we used microfluidic cell squeezing (Cell Squeeze®) to deliver mRNA directly to the cytosol of expanded tumor reactive CD8 human TILs (AGX-148). After mRNA delivery, the TILs were cultured in media with varying levels of exogenous IL-2 and characterized by flow cytometry.

Results We demonstrated that multiple mRNA constructs delivered simultaneously by microfluidic cell squeezing to human TILs are highly expressed (>80% of cells) for multiple days while maintaining high viability (>80%) in vitro. Membrane bound cytokines are able to support cell expansion in the absence of exogenous IL-2 at rates comparable to control cells incubated with a high concentration of IL-2 for up to 3 days. Furthermore, we have identified a membrane-bound cytokine that alters the TIL phenotype as quantified by multiple markers, including increased L-selectin (CD62L), which is an indicator of central memory T cells.

Conclusions Through microfluidic cell squeeze delivery of mRNAs, we have created enhanced TILs with high levels of membrane-bound cytokines and/or costimulatory molecules in vitro. These cells are able to proliferate without exogenous IL-2 and have an improved phenotype.

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