COSTIMULATORY ANTIGEN RECEPTOR (COSTAR): A NOVEL PLATFORM THAT ENHANCES THE ACTIVITY OF TUMOR INFILTRATING LYMPHOCYTES (TILS)

Sujita Sukumaran*, Milena Kalaitidou, Michelle Mojadidi, Clare Yarka, Yong (Stella) Ouyang, Eric Gschweng, Gray Kueberuwa, John Bridgeman, Bob Hawkins, Rubén Alvarez-Rodríguez. *Instil Bio, Inc., Dallas, TX, USA*

Background Major limiting factors for cell therapy in solid tumors include clonal heterogeneity and the related lack of universally expressed tumor-specific antigens. As the only truly polyclonal cell product in advanced development, tumor infiltrating lymphocytes (TILs) offer the broadest diversity of tumor reactivity but can be limited by suboptimal effector function in situ. Here we present a novel platform designed to leverage the diverse TCR repertoire of TILs while amplifying their anti-tumor activity via a synthetic costimulatory antigen receptor (CoStAR).

Methods A CoStAR molecule encoding an extracellular folate receptor alpha (FOLR1)-targeting single-chain fragment variable (scFv) and intracellular CD28 and CD40 signaling sequences was transduced into peripherally harvested T cells (healthy donor) and primary ovarian cancer TILs. Coculture experiments were performed with engineered cell lines and autologous tumor digests expressing varying levels TCR-stimulus and/or FOLR1. Cytolytic activity, activation markers, proliferation and cytokine secretion were measured.

Results Anti-FOLR1 CoStAR T cells activated with TCR stimulation and FOLR1 displayed increased activation markers (eg, CD137, > 50% increase), improved cytolytic activity, cytokine production (eg, IL-2, >15-fold) and ~7-fold increased proliferation when compared to either unmodified cells or when stimulated via TCR alone. Importantly, no T cell effector function, as measured by cytolytic activity, cytokine secretion, upregulation of activation markers or proliferation, was observed when CoStAR T cells were cocultured with targets expressing only FOLR1, underscoring the costimulation-only mechanism of action and reliance on native TCR repertoire for tumor recognition. Furthermore, increased activity was also observed when primary ovarian cancer anti-FOLR1 CoStAR TILs were cocultured with autologous tumor.

Conclusions CoStAR is a novel platform that leverages synthetic biology and T-cell-intrinsic circuits to create a product with markedly increased functional activity including cytotoxicity, proliferation, and cytokine expression while retaining broad, patient-specific neoantigen recognition to limit both antigen escape and off-tumor toxicity. Instil plans to initiate its first-in-human clinical trial with ITIL-306, an investigational anti-FOLR1 CoStAR TIL product in 1H 2022. Additional scFv targets are being evaluated for clinical application across a broad range of solid tumor histologies.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.198>