TARGETING COLD TUMORS USING IPSC-DERIVED CAR T CELLS DIRECTED TO THE IMMUNE CHECKPOINT MOLECULE AND TUMOR-ASSOCIATED ANTIGEN B7-H3

1Jon Tuncel*, 1Bahram Valamehr, 1Xu Yuan, 1Francisco Martinez, 1Nicholas Brookhouse, 1Philip Chu, 1Duygu Ozmadenci, 2Zachary Davis, 1Robert Blum, 1Bryan Hancock, 1Bjørn Gaertner, 1Nicholas Zorko, 1Shohreh Sikaroudi, 1Miguel Meza, 1Thomas Dailey, 2Martin Felices, 1Frank Cichocki, 1Lauren Fong, 1Tom Lee, 1Raedun Clarke, 1John Goulding, 1Ryan Bjordahl, 1Jeffrey Miller. 1Fate Therapeutics, Inc. (FHQ1), San Diego, CA, USA; 2University of Minnesota, Minneapolis, USA; 1Fate Therapeutics, Inc. (FTP1), San Diego, CA, USA

Background B7 homolog 3 protein (B7-H3) is a cell-surface protein that is broadly expressed on tumors as well as tumor-associated stromal cells, where it provides inhibitory signals to T and NK cells. Inhibition of B7-H3 using antibody-based modalities has shown promising, albeit incomplete, suppression of tumor progression in clinical studies. Induced pluripotent stem cell (iPSC)-derived chimeric antigen receptor T (CAR-T) cells targeting B7-H3 antigen may offer a unique approach for the treatment of immunologically cold tumors, as treatment may provide an influx of CAR-T cells to tumors that are largely devoid of endogenous infiltrating lymphocytes.

Methods Here we used a unique iPSC engineering strategy to deliver a single tricistronic expression cassette encoding a highly tuned CAR construct consisting of a single-domain camelid antibody against B7-H3 fused to a (CD28-CD3ζ-1XX) signaling domain, an interleukin (IL)-7 receptor fusion protein, and a high affinity non-cleavable version of the CD16 Fc receptor (hnCD16) into the T-cell receptor α constant (TRAC) locus. These engineered iPSC-derived CAR-T cells demonstrate high potency and fitness and can, unlike naturally occurring T cells, mediate antibody-dependent cell-mediated cytotoxicity (ADCC) to enable combination with monoclonal antibody therapy for treatment of heterogenous tumors.

Results In preclinical studies, these multi-functional B7-H3 single-domain/1XX iPSC-derived CAR-T cells demonstrated improved tumor control compared to MGA271-scFv/1XX CAR-T cells. Additional preclinical studies confirmed antigen specificity and broad application in targeting various tumor lines. Furthermore, coactivation of hnCD16 markedly improved cytotoxicity against a variety of target cells both in vitro and in vivo, illustrating the potency of coordinated expression of these two pathways in CAR-T cells. Further preclinical studies are ongoing and will be discussed.

Conclusions Taken together, these results provide a tantalizing outlook for the effectiveness of multiplexed-engineered, iPSC-derived CAR-T cells targeting B7-H3, including in combination with therapeutic antibodies, for off-the-shelf treatment of solid tumors.

Ethics Approval All animal experiments were reviewed and approved by Fate Therapeutics Animal Care Committee (IACUC) under the protocol 2019-11-01 O’Rouke.