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

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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-CD3z-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.

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