MULTIPLE TARGETING OF SOLID TUMORS WITH iPSC-DERIVED GAMMA DELTA CAR T CELLS IN COMBINATION WITH THERAPEUTIC ANTIBODIES


Background CAR-T cell therapies have proven safe and efficacious for hematologic malignancies, but there remains a significant unmet need for effective cell therapy options for solid tumors. CAR-engineered induced pluripotent stem cell (iPSC)-derived effector cells allow for the treatment of cancer as an off-the-shelf allogeneic cell therapy. Gamma delta (\(\gamma\delta\)) T cells exhibit the cytolytic features of conventional alpha beta (\(\alpha\beta\)) CD8+ T cells with additional capabilities for innate recognition of tumors. For example, expression of CD16 on \(\gamma\delta\) T cells can mediate antibody-dependent cellular cytotoxicity (ADCC) against tumors. Here we describe development of an iPSC-derived \(\gamma\delta\) T cell platform which can target solid tumors through both CAR-mediated recognition and ADCC when combined with a therapeutic antibody.

Methods Primary \(\gamma\delta\) T cells were enriched and expanded in culture to enable reprogramming to iPSCs by delivery of pluripotency genes. These T cell derived iPSCs (TiPSCs) were used to produce \(\gamma\delta\) T cells using a proprietary differentiation process. The TiPSC line was engineered with a CAR targeting EGFR and a membrane bound form of IL-15 to enhance T cell persistence. Tumor spheroids were generated from EGFR+Her-2+ SKOV-3 ovarian tumor cells. Cytolysis of spheroids was evaluated using CAR-T cells alone or in combination with anti-HER2 antibody (trastuzumab).

Results Batches of CAR-T cells were generated using a proprietary differentiation process yielding >90% pure CAR-\(\gamma\delta\) T cells. The TiPSCs contained the rearranged \(\gamma\delta\) TCR gene and upon differentiation to T cells, uniformly expressed a \(V\gamma9V\delta2\) TCR and expressed high levels of CD16. CAR \(\gamma\delta\) T cells were effective in killing SKOV-3 spheroids. When cultured with SKOV-3 spheroids in an ADCC assay, CAR \(\gamma\delta\) T cells exhibited enhanced cytotoxicity in the presence of trastuzumab but not isotype control antibody. Activity of the \(\gamma\delta\) T cells was not reliant on additional exogenous cytokine due to the engineered form of membrane-associated IL-15.

Conclusions We have demonstrated that iPSC-derived \(\gamma\delta\) T cells mediate anti-tumor activity in human solid tumor models through multiple pathways. The combination of two modes of tumor recognition (CAR and CD16/antibody) enabled more potent killing of solid tumor spheroids. The ability to manufacture large batches of iPSC derived CAR \(\gamma\delta\) T cells will enable a true off-the-shelf allogenic cell therapy for solid tumors.