OFF-THE-SHELF IPSC-DERIVED CAR-T CELLS TARGETING KLK2 DEMONSTRATE PROLONGED TUMOR CONTROL AND SURVIVAL IN XENOGRAFT MODELS OF PROSTATE CANCER

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Background Human kallikrein-related peptidase 2 (KLK2) is an antigen with prostate-restricted expression which is maintained during prostate cancer progression – making it an attractive therapeutic target for chimeric antigen receptor (CAR) T cells. While CAR-T cell therapies have shown remarkable success in hematologic malignancies, application to solid tumors has been broadly unsuccessful. Cost of treatment, manufacturing consistency, and scalability remain significant hurdles to broader patient access. To overcome these challenges, we are developing a KLK2 targeted off-the-shelf CAR-T cell product using our induced pluripotent stem cell (iPSC)-derived immunotherapy platform.

Methods A clonal master iPSC line was derived by knock-in of a CAR construct targeting KLK2 into the T-cell receptor alpha constant chain (TRAC) locus in a bi-allelic manner. Specificity of the engineering strategy and testing for random donor vector integration and transgene copy number were confirmed by PCR and DNA sequencing. A clonal master iPSC line containing the TRAC-edits was differentiated into T cells (CAR-KLK2 iT cells) and subsequently expanded using a stage-specific protocol.

Results iPSC-derived CAR-KLK2 iT cells expressed a cell-surface profile consistent with a pure population of T lymphocytes; no TCRαβ cell-surface expression was detected; cells showed homogenous expression of CD45/CD7 (>99%), and uniform CAR expression driven by TRAC (>99%). Notably, the complete loss of T-cell receptor expression by genetic knock-out eliminates the potential of graft-versus-host disease in an allogeneic setting. Preclinical in vitro analyses of these CAR-KLK2 iT cells demonstrated potent and specific cytotoxicity against multiple prostate cancer cell lines, including VCap cells which naturally express KLK2, PC3 cells engineered to express KLK2, and DU-145 cells engineered to express KLK2. In vivo, a multi-dose regimen of CAR-KLK2 iT cells controlled established (>100 mm3) VCap and PC3-KLK2 subcutaneous xenograft models with greater than 90% tumor growth inhibition and associated increased survival. Follow-up dose titration studies demonstrated that a single dose of CAR-KLK2 iT cells was sufficient to mediate approximately 70% tumor growth inhibition.

Conclusions These early preclinical in vitro and in vivo data suggest that CAR-KLK2 iT cells may have the potential to selectively eliminate prostate cancer cells. Since the behavior of engineered iT cells and additional edits in this novel platform are both currently not predictable, significant additional work is ongoing to generate an appropriate clinical candidate.