442-F OPTIMIZATION OF A HUMAN SCFV-BASED PSMA-CAR T CELL THERAPY FOR THE TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

[1]Lupita S Lopez*, [2]Jason Yang, [3]Ziyou Cui, [2]Wen-Chung Chang, [3]Vivien Chan, [2]Saul Priceman. *[1]City of Hope Irell and Manella Graduate School, Duarte, CA, USA; [2]City of Hope, Duarte, CA, USA; [3]Eureka Therapeutics, Emeryville, CA, USA*

Background Metastatic castration resistant prostate cancer (mCRPC) is an incurable disease with poor overall survival rates. Recently, immunotherapeutic approaches used to treat mCRPC have focused on targeting prostate-specific membrane antigen (PSMA), a validated tumor associated antigen using a humanized murine monoclonal antibody specific to PSMA, clone J591. When used as the antigen-binding domain in chimeric antigen receptor (CAR) T cell therapy, the single chain variable fragment (scFv) derived from clone J591 has shown anti-tumor activity but has been associated with macrophage activation syndrome and in extreme cases resulted in fatalities. In addition, the murine origins of the scFv can lead to immunogenicity and the generation of human anti-mouse idiotype antibodies. This creates a need to develop a fully human scFv that is safe and efficacious in treating mCRPC.

Methods First, we interrogated the impact of a fully human scFv heavy and light chain orientation on CAR T cell functionality. We then tested different linker and transmembrane domain combinations on the stability and functionality of a highly optimized human PSMA-CAR (hPSMA-CAR). The scFv underwent affinity maturation to improve binding kinetics to PSMA. To increase the polyfunctionality (activation, expansion, cytokine secretion) of the hPSMA-CAR, we introduced a novel membrane bound IL-12 (mbIL12) molecule.

Results At each stage of development, a lead candidate was chosen and used for the following optimization step. Our hPSMA CAR had improved stability and activity with a CD28tm domain and dCH2 spacer but polyfunctionality was suboptimal to J591 CAR. Affinity maturation incurred differential stability and activity in primary T cells, with one clone performing comparably to the parental scFv but not substantially improving the polyfunctionality. Addition of mbIL12 to the hPSMA-CAR increased their expansion, cytokine secretion and anti-tumor cell activity in recursive tumor cell challenge assays compared to the single CAR controls and the J591 CAR. Current in vivo work using PSMA expressing cell lines will elucidate which hPSMA-CAR is safe and efficacious.

Conclusions Here, we describe the optimization and characterization of a fully human scFv-based PSMA-CAR. Importantly, although we have increased the activity of the hPSMA CARs we have retained its specificity PSMA, highlighting its promise for future clinical development.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0442-F