## 375 IN VIVO GENERATION OF UNIVERSAL CAR T CELLS THAT MEDIATE DURABLE ANTI-TUMOR IMMUNITY THROUGH COMBINATORIAL TARGETING WITH BISPECIFIC SMALL MOLECULE ADAPTERS

Kristen Mittelsteadt*, Isabel Leung, Kelsey Lynch, Haiyan Chu, Chang-Chih Wu, Seungjin Shin, Ryan Larson, Andrew Scharenberg, Byoung Ryu, Laurie Beitz. *Umoja Biopharma, Seattle, WA, USA*

**Background** Chimeric antigen receptor (CAR) T cell therapies have demonstrated limited efficacy against solid tumors, in part due to challenges overcoming solid tumor heterogeneity and CAR T cell exhaustion associated with the immunosuppressive tumor microenvironment (TME). Our integrated platform aims to overcome these roadblocks by engineering T cells in vivo to express a universal TagCAR which binds to a common tag on bispecific adaptor TumorTags, bridging TagCAR T cells to TumorTag-bound tumor- and TME-associated antigens, including folate receptor (FR) which is upregulated on many tumor types as well as immunosuppressive tumor-associated macrophages. Additionally, our TagCAR T cells are engineered to express a rapamycin-activated cytokine receptor (RACR) which selectively provides survival signals to TagCAR T cells in the presence of rapamycin. Here, we identify a universal TagCAR that demonstrates potent in vitro and in vivo anti-tumor polyfunctionality against $FR^+$ target cells with a folate receptor-targeting TumorTag (UB-TT170).

**Methods** PBMCs from healthy donors were transduced in vitro with surface-engineered lentiviral vectors with TagCAR/RACR payloads. Resultant TagCAR T cell anti-tumor activity and persistence was assessed using a co-culture approach with FR-expressing tumor cells and titrated doses of UB-TT170. To assess in vivo anti-tumor activity, lentiviral particles containing TagCAR/RACR payloads were administered to PBMC-humanized NSG mice with established $FR^+$ xenograft solid tumors to generate TagCAR T cells in vivo. Mice were treated with UB-TT170 and efficacy was determined by assessing tumor regression and UB-TT170-mediated TagCAR T cell expansion.

**Results** TagCAR T cells containing a CD8α hinge/transmembrane domain and 41bbζ endodomain were superior to other construct candidates in eliminating $FR^+$ target cells in the presence of UB-TT170 in vitro. These TagCAR T cells demonstrated UB-TT170-mediated expansion and proinflammatory cytokine production in the presence of $FR^+$ target cells, and repeated elimination of target cells and enhanced persistence properties with serial antigen-exposure. Cells transduced with this vector exhibited RACR-mediated expansion and improved function in the presence of rapamycin. Administration of TagCAR/RACR payload-containing lentiviral particles to PBMC-humanized NSG mice resulted in generation of TagCAR T cells in vivo, which expanded and mediated clearance of $FR^+$ solid tumors with UB-TT170

**Conclusions** We have identified a universal TagCAR that displays robust anti-tumor activity and persistence qualities against $FR^+$ target cells in vitro and in vivo with UB-TT170. These data support development of this platform as a new cellular therapy approach against solid tumors, using combinatorial targeting of tumor- and TME-associated antigens with an in vivo-generated universal TagCAR and multiple TumorTags.

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