IN VIVO-GENERATED TAGCAR T CELLS INHIBIT SOLID TUMOR GROWTH FOLLOWING TREATMENT WITH BISPECIFIC SMALL MOLECULE TUMORTAGS

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Background Chimeric antigen receptor (CAR) T cells are potent cancer-killing drugs that have revolutionized the treatment of hematologic malignancies, with potential application as a pan-cancer therapy. To realize this potential, Umoja’s platform is designed to address several challenges facing autologous CAR T cell therapies.

Methods VivoVec products will be off-the-shelf lentiviral vectors that engineer T cells in vivo, forgoing costly cell therapy manufacturing and toxic lymphodepletion associated with ex vivo approaches. The resulting in vivo engineered T cells will express an anti-fluorescein CAR (TagCAR) that facilitates tumor targeting using fluorescein-conjugated small molecule ligands (TumorTags). This approach enables us to target multiple tumor and stromal antigens with our single TagCAR, potentially allowing us to overcome tumor heterogeneity, immunosuppressive tumor microenvironments, and antigen loss that undermine traditional fixed-specificity CAR therapies.

Results UB-VV200 is a VivoVec drug product candidate that generates TagCAR T cells in vivo. UB-VV200 particles are surface-engineered to express anti-CD3 single chain variable fragment and T cell costimulatory ligands in a multidomain fusion protein format. UB-VV200 particles displayed dose-dependent and selective binding, transduction, and activation of T cells following culture with PBMCs.

To direct TagCAR T cells to their tumor targets, we developed TumorTags, which are tumor antigen ligands conjugated to fluorescein. Folate receptors alpha (FRa) and beta (FRb) and prostate-specific membrane antigen (PSMA) are well-established tumor-specific targets. UB-TT440 binds PSMA, which is expressed on prostate tumors, as well as most tumor-driven neovascularature. UB-TT170 targets tumors and their microenvironment by binding to FRa and FRb, which are expressed on tumor cells and associated macrophages, respectively. To characterize the bispecific nature of our TumorTags, we determined their on-cell binding affinity to TagCAR T cells and antigen-expressing tumor cells. Both TumorTags displayed dose-dependent and antigen-dependent binding, with Kd values in the picomolar to nanomolar range. Importantly, TagCAR T cells mediated antigen-specific and dose-dependent cytolytic activity, cytokine release, and proliferation in response to TumorTag treated tumor cells in vitro.

Finally, Umoja’s integrated platform was efficacious against solid tumors in vivo. UB-VV200 particles generated TagCAR T cells in non-activated PBMC-humanized NSG MHC-I/II double knockout mice bearing PSMA+ FRa+ MDA-MB-231 tumors without any evidence of acute toxicities. In response to either PSMA (UB-TT440) or FRa (UB-TT170) targeting TumorTags, TagCAR T cells proliferated and inhibited tumor growth.

Conclusions These data demonstrate that, in comparison to autologous CAR T cells, UB-VV200 together with TumorTags have the potential to be a more accessible and more affordable off-the-shelf pan-cancer therapy.

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