Background While CAR-T have demonstrated potent activity against hematologic tumors, less success has been seen with solid tumors. Here we report generation of TSCM-enriched allogeneic MUC1-C-specific CAR T cells, P-MUC1C-ALLO1, with potential for a broad range of solid tumors. The proliferative capacity and metabolic profile of TSCM CAR-T are well-suited to activity in the solid tumor setting. MUC1 is comprised of an N-terminal subunit (MUC1-N) tethered to a C-terminal subunit (MUC1-C), forming a stable complex on the cell surface. During tumorigenesis, MUC1 becomes both overexpressed and hypo-glycosylated on many carcinomas. Furthermore, MUC1 undergoes proteolytic cleavage in the tumor microenvironment, leaving behind a proteolytic ‘stump’ of MUC1-C that is over-represented in cancer, making it an attractive therapeutic target.

Methods P-MUC1C-ALLO1 is manufactured using the piggy-Bac® DNA Delivery System for CAR insertion and the Cas-CLOVER™ Gene Editing System to knockout both the TCR and MHC class I proteins. The addition of a selectable marker within the transposon allows for selection of a fully CAR-positive population while any residual TCR-positive cells are removed at the end of production to prevent TCR-mediated GvHD. Lastly, inclusion of a proprietary ‘booster molecule’ in our allogeneic process further improves cell expansion, along with phenotype and function, and enables the production of up to hundreds of patient doses from a single manufacturing run.

Results Significant doses of P-MUC1C-ALLO1 products made from multiple healthy donors were achieved and comprised of an exceptionally high-percentage of desirable TSCM cells. Preclinical evaluation of these products showed potent tumor killing and cytokine secretion against MUC1-C-positive breast and ovarian tumor cell lines. P-MUC1C-ALLO1 demonstrates potent cytotoxicity against tumor cells, and minimal killing of normal MUC1-C-positive human primary cells. In a triple negative breast cancer xenograft model, MUC1C CAR-T eliminated established MDA-MB-468 tumor cells, mounted robust T cell expansion in peripheral blood and maintained a favorable TSCM percentage over time. Likewise, in an orthotopic ovarian cancer xenograft model, intraperitoneally administered MUC1C CAR-T eliminated established OVCAR3 cells to levels below the limit of detection. All together, these data demonstrated the efficacy of the MUC1C CAR-T cells and the robustness of the allogeneic platform.

Conclusions P-MUC1C-ALLO1 is an allogeneic TSCM CAR-T therapy that has a potential to treat multiple MUC1-expressing indications. P-MUC1C-ALLO1 displayed specificity for tumor vs. normal cells as well as in vivo efficacy against xenograft models of breast and ovarian cancer. This allogeneic cell therapy is advancing rapidly towards the clinic.

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