Preclinical Characterization of Allogeneic CAR γδ T Cell Therapy for Prostate Cancer Targeting a Novel Dimeric Epitope on PSMA


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INTRODUCTION

PSMA is a transmembrane glycosylated heterodimer overexpressed in 94% of prostate cancers and demonstrates increased expression in advanced stages of the disease. Originally, antibody and PSMA-CAR T cells have shown signs of activity but have limited therapeutic index. We are developing an allogeneic CAR γδ T-cell platform with evaluation induced antibody profiles that may increase CAR α-PSMA expression and immunomodulatory treatments that enhance target recognition, antigen presentation, and adoptive targeting and inhibit innate pro-tumor-associated tissues. Here, we characterized γδ T-cell responses and CAR activity developed from a set of naïve α-PSMA and characterized lead candidates with unique epitopes targeting homodimeric PSMA. Formation of homodimers is necessary to elicit maximum binding of the homodimeric epitope and to ensure potential recognition of other epitopes from linear epitopes and potentially reduce off-targeting of PSMA-α CAR T cells.

METHODS

Phage display was used to identify anti-PSMA scFv sequences, which were reformatted into IgGs and expanded into mAbs using ELISA. Range of EC50 values are shown for all mAbs tested. Lead 1 mAb was selected for further characterization using ELISA and flow cytometry. Lead 2 mAb was identified with dnTGF-βRII and characterized for robust CAR expression and expansion. Lead 1 and Lead 2 mAbs were screened for their ability to induce CAR expression and CAR T-cell expansion in vitro and in vivo. Lead 1 CAR T cells were cultured with PC3-PSMA and analyzed by flow cytometry, whereas Lead 2 CAR T cells were expanded in 3 donors compared to the benchmark J591 and compared to Lead 1 CAR T cells. Graphs detail tumor volumes determined for the entire study duration.

Anti-PSMA antibodies obtained from phage display bind specifically to PSMA with varying affinities

Lead anti-PSMA antibodies bind to membrane-distal, conformational epitopes distinct from that of J591, a well-known benchmark

Anti-PSMA CAR Vδ1 T cells expand robustly in multiple donors and are efficacious against PCA cell line in vitro

Anti-PSMA CAR Vδ1 T cells armored with dnTGFβRII show enhanced tumor control in the presence of TGFβ1

SUMMARY & CONCLUSIONS

Vδ1 T cells remain a promising frontier for immunotherapy of solid tumors. Novel licensed lead PSMA CARs target conformational, membrane-distal epitopes that are distinct from the previously linear epitope for PSMA, a well-known clinical benchmark. Binding to unique, conformational epitopes may reduce off-targeting of PSMA-α CARs. Potential tumor growth inhibition by lead PSMA CAR Vδ1 T cells, in addition to CAR targeting, was observed in an in vitro target re-challenge assay to assess cytotoxic ability of armored anti-PSMA CAR T cells. A functional advantage with armoring on anti-PSMA-CAR Vδ1 T cells was demonstrated for the anti-PSMA-CAR Vδ1 T cells in vivo. In summary, these preclinical data further development of an allogeneic γδ CAR T-cell therapy for prostate cancer.

REFERENCES

6. Demetrio Cardenas, Yvan Chanthery, Shon Green, Marissa Herrman, Kevin P. Nishimoto, Blake T. Aftab, Arun Bhat

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