Using a PSMA-Specific Low-Molecular-Weight Compound for Prostate Cancer Treatment with Rapidly Switchable Universal CAR-T: Overcoming the Challenges of Cellular Immunotherapies in Solid Tumors

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Introduction

The Prostate Specific Membrane Antigen (PSMA) is a suitable target for treatment of advanced and metastatic prostate cancer (PCa), but also broadly expressed on tumor non-vasculature beyond PCa. PSMA is also known to be expressed on a number of normal tissues, albeit to a much lower extent, which necessitates additional safety mechanisms for CAR-T therapy. We explored the possibility to use a clinically-characterized radiolabeled peptide motif binding to the aromatic groove of PSMA to a small-sized TM (TMpPSMA, MW 2.3 kDa) rapidly switch on and off UniCAR-T. The TM showed very good binding affinity to its target (Fig. 2) and favorable pharmacokinetic properties (Fig. 3 A, B). As shown previously, PSMA-targeting peptide TM demonstrated a very fast accumulation and good penetration of tumor lesions as shown in mouse models and humans5.

Dose-dependent Anti-Tumor Response of TmpPSMA Redirected UniCAR-T

An important safety aspect of the UniCAR platform is that CAR-engineered T cells can be rapidly switched on and off allowing driving T cell responses dependent on the properties of the corresponding TM. In in vitro experiments it was confirmed that after withdrawal of TmpPSMA cytotoxic reactivity of UniCAR-T7 against target cells is immediately abrogated (Fig. 6).

References

4. Amch et al., A therapeutic PSMA ligand for PET imaging and restaging of T cells expressing the universal chimeric antigen receptor (CAR) in Oncology & Immunology 6, 134-136 (2015).

Conclusion

The re-direction of universal CAR-T (UniCAR-T) against less differentially expressed solid tumor antigen PSMA is feasible and effective

- The utilization of a small-synthesized peptide with favorable PK properties (short half-life in PB and rapid internalization on target cells) allows rapid switch on/off of UniCAR-T
- The incorporation of CO3X, signaling domain overcomes immunosuppression in a Pca model

IND was submitted for a phase I study, expected to start in second half of the year

References

4. Amch et al., A therapeutic PSMA ligand for PET imaging and restaging of T cells expressing the universal chimeric antigen receptor (CAR) in Oncology & Immunology 6, 134-136 (2015).