Stable, controllable, and scalable manufacturing of B7-H3 UCAR-T, an allogeneic CAR-T product for advanced glioma, from healthy donors

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BACKGROUND

- CAR-T cell therapy has achieved great success in hematological malignancies and is gradually being used in solid tumors
- B7-H3 (CD276)-directed autologous CAR-T cell therapy has achieved some preliminary results. However, autologous products are expensive, time-consuming to manufacture, and significantly variable in T cells characteristics of patients
- We developed a B7-H3-directed allogeneic universal CAR-T cells (B7-H3 UCAR-T) for treatment of advanced glioma
- Our off-the-shelf product candidate manufactured with materials from healthy donors avoids many disadvantages of autologous CAR-T products

METHODS

- Our B7-H3 UCAR-T is produced using two key proprietary technologies: lentiviral expression system and gene editing system
- Modified B7-H3 CAR is transduced into T cells via lentivirus vectors
- Gene-encoded T cell receptor α chain (TRAC) and HLA-A molecules, which are highly associated with rejection reaction (other HLA-I molecules retained), are knocked out by CRISPR/Cas9 technology
- The B7-H3 UCAR-T not only eliminates GvHD and reduces HvGR but also has a longer persistence *in vivo*

RESULTS

Characteristics of B7-H3 UCAR-T

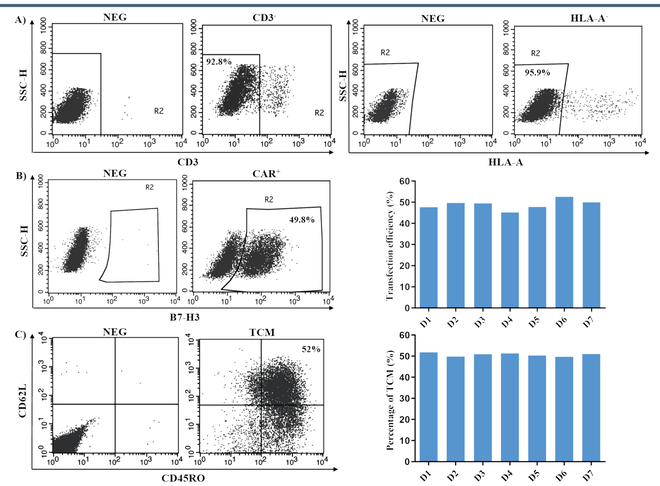


Figure 1. B7-H3 UCAR-T was manufactured by lentiviral transduction of the CAR transgene, followed by electroporation of TRAC⁻ and HLA-A⁻ targeting Cas9 RNP. A) TRAC and HLA-A knockout efficiency (>90%), B) CAR expression (>45%), C) TCM phenotype (approximately 50%)

Scalable Manufacturing Process of B7-H3 UCAR-T

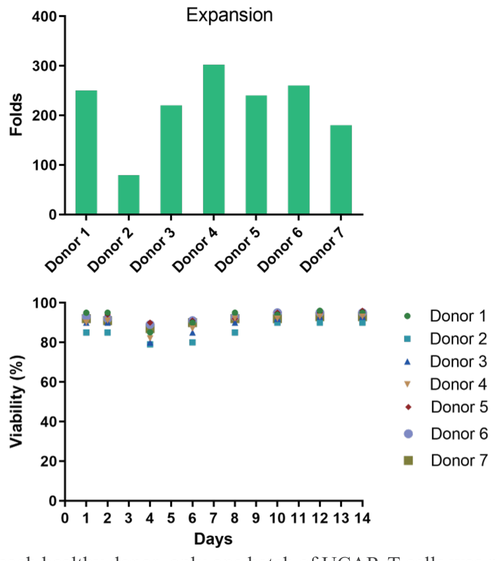


Figure 2. For each healthy donor, only one batch of UCAR-T cells was manufactured. Five of all the batches successfully expanded to >200-fold at harvest, and the viability of all the batches was above 90%

Potent Anti-Tumor Activity of B7-H3 UCAR-T

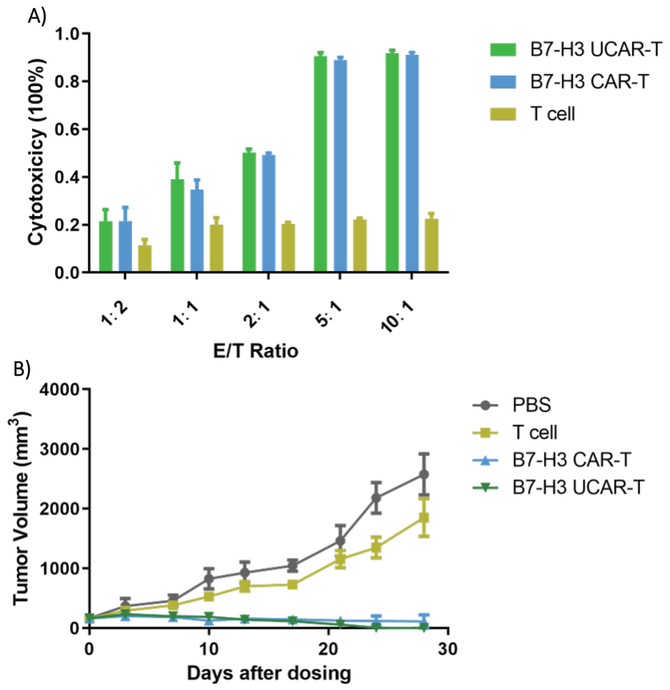


Figure 3. A) When co-cultured with U251 cells, B7-H3 UCAR-T exhibited >90% in vitro cytotoxicity at an effector-to-target ratio of 5:1, B) B7-H3 UCAR-T exhibited potent anti-tumor effect in the NSG mice model with U251 xenograft

Longer Half-Life of B7-H3 UCAR-T

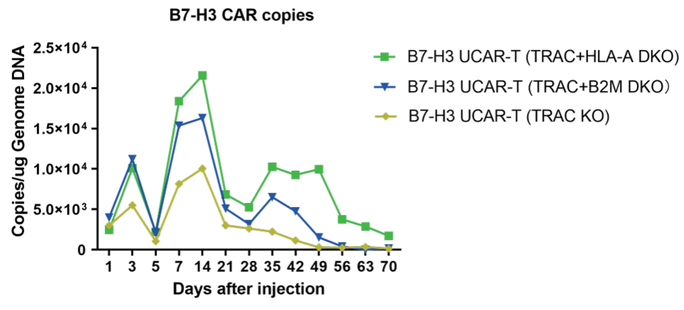
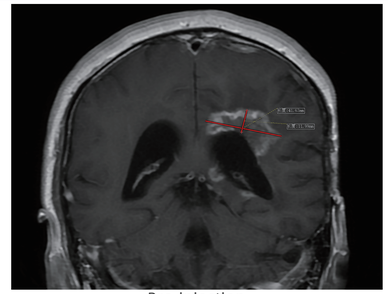
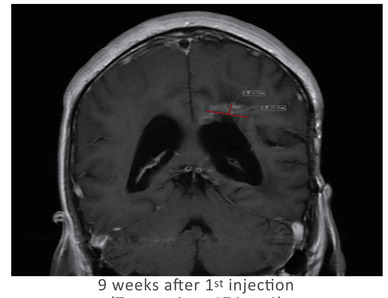


Figure 4. B7-H3 UCAR-T showed longer persistence (>70 days) and better expansion in hHSC-NCG mouse model compared with TRAC or TRAC/B2M knockout strategy

Patient MT027-005: a decrease of 65% in tumor size 9 weeks after the 1st injection



Pre-injection
(Tumor size: 499mm²)



9 weeks after 1st injection
(Tumor size: 174mm²)

Figure 5. This 55-years-old male patient was diagnosed with GBM (WHO IV) and received operation in 2019. His IHC test showed P53 (+++), ATRX (+++), ki-67 (20-50%), TERT (-), IDH1/2 (-), MGMT (+). He was treated with standard radiation therapy and TMZ chemotherapy after operation. Tumor recurrence was found in the re-examination in August 2020 and then treated with TMZ and bevacizumab but a new lesion developed. The patient was administered with MT027 for the first time in October 2021 and showed a decrease of 65% in tumor size 9 weeks after the 1st injection. He is still alive.

CONCLUSION

- These data demonstrate a stable, controllable, and scalable manufacturing process of MT027
- This UCART manufacturing process is also appliable for other targets of solid or hematological malignancies
- B7-H3 UCAR-T cells has potent antitumor activity for recurrent high-grade glioma

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