Preclinical Development of LYL119, a ROR1-Targeted CAR T-Cell Product Candidate Incorporating Four Novel T-Cell Reprogramming Technologies to Overcome Barriers to Effective Cell Therapy for Solid Tumors


Methods

These four T-cell reprogramming technologies are combined to create LYL119, an investigational Nature. 2020;370:1328–1334.

Results

Increased expression of NR4A3

Conclusions

Background

Figure 1: LYL119 process.

Abbreviations

(A,B) stained with isotype control IgG1. Cytokine secretion post stimulation

References

Figure 5: Following serial antigen stimulation, ROR1 CAR T cells generated with Stim-R technology showed enhanced antitumor activity and increased retention of memory T cells following serial stimulation (Figure 2). (A) LYL119 CAR T cells showed a trend of higher IFNγ and IL-2 production after repeated

Figure 6: LYL119 CAR T cells showed superior target clearance compared to controls. (Figure 2) LYL119 CAR T cells demonstrated improved survival of tumor-bearing mice compared to controls (Figure 2). (C) Composite tumor growth curves from A and B. (D) ROR1 CAR T cells have reduced expression of TIGIT and increased CD127 expression after four stimulations. Shapes correspond to CAR T cells derived from each donor. Asterisks indicate significant differences compared to KO and control-

Figure 3: Transcriptional analysis revealed that NR4A3 KO reduces terminal exhaustion and enhances memory-naive cell proportions following serial reprogramming with antigen.

Figure 2: A B C C6

Figure 4: NR4A3 KO + c-Jun ROR1 CAR T cells demonstrate potent antitumor activity in vivo

Figure 7: LYL119 demonstrates prolonged cytokinesis and enhanced cytokine production in vitro compared to control cells (Figure 2). (B) LYL119 CAR T cells incorporating NR4A3 KO + c-Jun + Epi-R + Stim-R technologies showed improved target clearance and cytokine activity.

Figure 8: ROR1 CAR T cells manufactured with Stim-R technology exhibited higher peak CAR T-cell numbers in the blood, prolonged persistence, and improved antitumor activity in vivo

Figure 9: Serial stimulation Day 10 (Stim 3), CD8+ T-cell single-cell RNA-seq

LYL119 CAR T cells incorporating NR4A3 KO + c-Jun + Epi-R + Stim-R technologies demonstrated superior in vivo and in vitro activity.

Serial stimulation Day 1

Serial stimulation days 3-7

Serial stimulation Day 10 (Stim 3)