

POSTER PRESENTATION

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Enhancing T cell persistence of CAR-redirectioned T cells in solid tumors

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T cell persistence is likely to promote long-term anti-tumor effects after adoptive T cell transfer. We have recently shown that incorporation of the ICOS intracellular domain into chimeric antigen receptors (CARs) significantly increased Th17 cell persistence *in vivo*, compared to CARs with CD28 or 4-1BB intracellular domains [1]. Here, we hypothesized that CD4⁺ and CD8⁺ T cells require distinct cytokine and costimulation signals for optimal persistence. To test this hypothesis, we compared the *in vivo* antitumor effects and persistence of combined CD4⁺ T cells (bulk or Th17-polarized) and CD8⁺ T cells redirected with CARs containing CD28, 4-1BB or ICOS-based costimulatory domains. Using multiple mouse tumor models, we demonstrate that the ICOS intracellular domain significantly enhanced the *in vivo* persistence of CAR-expressing CD4⁺ T cells, and that both persistence and tumor infiltration were further enhanced by culturing these cells under Th17-polarizing conditions. Importantly, Th17-polarized CD4⁺ T cells expressing an ICOS-based CAR significantly increased the circulatory persistence of bulk CD8⁺ T cells expressing either CD28- or 4-1BB-based CARs. We further demonstrate that the antitumor effect of CAR-expressing CD8⁺ T cells was enhanced when co-injected with ICOS-redirectioned Th17 cells. Collectively, our data suggest that combining Th17 CD4⁺ T cells redirectioned with an ICOS-based CAR with CD8⁺ CAR-T cells will enhance their persistence and antitumor efficacy.

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