250 CHIMERIC ANTIGEN RECEPTORS CONTAINING CD30-DERIVED COSTIMULATORY DOMAIN ELICIT AUGMENTED T CELL EFFECTOR FUNCTIONS AND ANTI-TUMOR EFFICACY

Hyun-Il Cho, Chung-Hyo Kang*, Sang-Eun Lee, In-Sil Song, Jung-Min Ha, Hyun-Jung Sohn, Tai-Gyu Kim. *VGeCell Inc., Seoul, Republic of Korea*

Background Adoptive cell therapy utilizing chimeric antigen receptor (CAR)-engineered T cells has demonstrated a feasible, attractive "off-the-shelf" approach against numerous types of cancers. Successful tumor eradication depends primarily on providing optimized costimulatory signals capable of achieving robust CAR-T cell proliferation, persistence, and antitumor reactivity. Here, we assessed the capability of a novel CD30-derived costimulatory domain, a known TNFR superfamily member involved in anti-apoptosis as well as cell activation and proliferation, to generate effective CAR-T cells.

Methods We designed CD19-redirecting second-generation CARs incorporating the intracellular signaling domain of CD30 and evaluated the immune-phenotype, cytokine secretion, and real-time cytolytic activity of CAR-transduced T cells against CD19-expressing cells in comparison with other CARs containing CD28 or 4-1BB costimulatory domains. Subsequentially, their therapeutic efficacy was assessed with a pre-clinical Nalm-6-bearing xenogeneic model. We also engineered third-generation CARs combining CD30 and either CD28 or 4-1BB and conducted multiple repeat in vitro experiments evaluating their proliferation and cytolytic functionality against CD19-expressing tumors. Further, we tested the efficacy of third-generation CAR signaling after alteration with glypican-3 or mesothelin-targeting single chain fragment variable (scFv) domains.

Results T cells activated by a CD30-ζ signaling-CAR displayed enhanced effector functions with similar levels of proliferation, cytolytic efficacies, and cytokine secretion in vitro against CD19-expressing cancer cells as those of other CARs with CD28 or 4-1BB costimulatory domain, which are currently in clinical use. Administration of CD30-containing CAR-T cells into tumor-bearing mice resulted in improved human T cell persistence and tumor regression in a xenogeneic allograft model, which was similar to those achieved with CD28- or 4-1BB–signaling CAR-T cells. Furthermore, third-generation CARs including CD30 with either CD28 or 4-1BB costimulatory domain retained potent antitumor efficacies independent of their position. More significantly, CAR-T cells containing CD30-signaling revealed effective cytolytic activities against several solid cancer cell lines based on its scFv fragments.

Conclusions Our results demonstrate that the CD30-derived costimulatory domain could be an alternative for developing CAR-engineered therapeutics which may be applicable for various design of CAR constructs, with an emphasis on effectiveness against solid tumors.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0250