246 ALLOGENEIC "OFF-THE-SHELF" γδ T CELLS MODIFIED WITH CD27-CONTAINING CAR FOR TARGETING CD70$^+$ CANCERS

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Background CD70, a member of the TNF receptor ligand family, represents a compelling target for the development of CAR T cell therapies due to its high expression in multiple solid and hematologic malignancies. Although CAR T cells have shown remarkable clinical benefit in hematologic malignancies, efficacy in solid tumors has highlighted key challenges. Among the emerging strategies to improve clinical responses is the use of alternative cytotoxic effector cells with multifunctional tumoricidal activity. γδ T cells combine innate and adaptive immunity to recognize and kill malignant cells. In addition, the infiltration of γδ T cells into various cancer types, including those expressing CD70, significantly correlates with survival. Strategies for targeting CD70 have explored scFvs or engineering its natural receptor (CD27) as the antigen-recognition moiety of a CAR. Recent studies demonstrate improved preclinical antitumor activity using the CD27 ligand compared to scFv-based CAR, suggesting functional advantages associated with a CD27-based CAR approach.[1] Here we report on the functional characterization and manufacturability of γδ T cells expressing CD27-based CAR for targeting a set of CD70$^+$ cancers.

Methods Healthy donor PBMCs were used to activate, expand, and engineer cytotoxic Vδ1 T cells to express CD27-containing CAR. In vitro phenotype and antitumor functionality of Vδ1 CAR T cells were determined using flow cytometry and cell-based cytotoxicity assays against a panel of cell lines having a broad range of CD70 expression. Human tumor xenograft models in immunodeficient mice were used to evaluate in vivo efficacy after a single dose of CD27-containing CAR Vδ1 T cells.

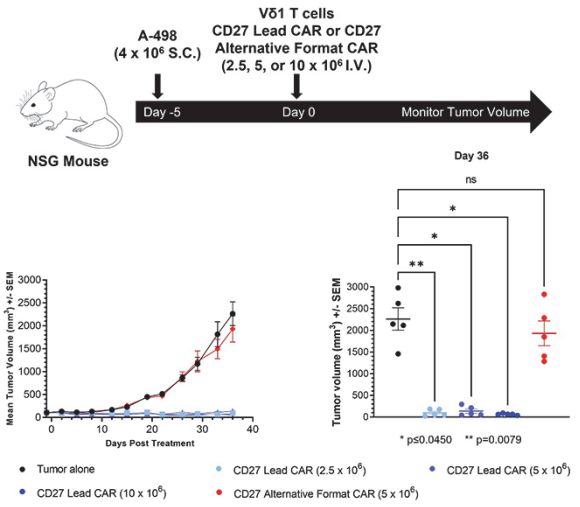
Results Vδ1 T cells modified to express CD27-containing CAR were successfully generated and expanded, indicating product expansion was not hindered by putative risks for CD70-mediated fratricide. The resulting Vδ1 CAR T cells expressed a predominant naïve-like memory phenotype and were associated with potent in vitro cytotoxicity, production of proinflammatory cytokines, and proliferation against CD70+ tumor cell lines. To assess the potential impacts of soluble CD27 (sCD27) on cytotoxicity, exogenously added sCD27 resulted in no change in anti-tumor activity. Lastly, highly potent tumor growth inhibition was observed against tumor xenografts in immunodeficient mice (figure 1).

Conclusions In summary, these preclinical data support further development and clinical evaluation of an allogeneic γδ CAR T cell therapy utilizing the CD27 natural receptor CAR format for targeting CD70+ cancers.

REFERENCE

1. Sauer T, Parikh K, Sharma S, Omer B, Sedloev D, Chen Q, Angenendt L, Schliemann C, Schmitt M, Müller-Tidow C, Gottschalk S, Rooney CM. CD70-specific CAR T cells have potent activity against acute myeloid leukemia without HSC toxicity. *Blood*. 2021; Jul 29;**138**(4):318-330.

Ethics Approval All mouse experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals and followed all institutional and national guidelines with appropriate protocol review and approval.



Abstract 246 Figure 1 Efficacy of CD27-containing CAR Vδ1 T cells in an RCC Model
The top panel illustrates the study design, and the bottom panels report the average tumor volumes for the duration of the study (left) and statistical comparison between treatment groups and the tumor alone control group at the end of the study (right).

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