KDDF
Korea Drug Development Fund

Asset #26
NIH

Chimeric Adaptor Proteins (CAPs) Containing a Linker for Activation of T Cells (LAT) and a Kinase Domain for Use in T Cell-Based Immunotherapy

Therapeutic Area	Oncology	**Indications**	Hematological Malignancies and Solid Tumors
Modality	Protein	**Development Stage**	Pre-clinical

Overview

Background

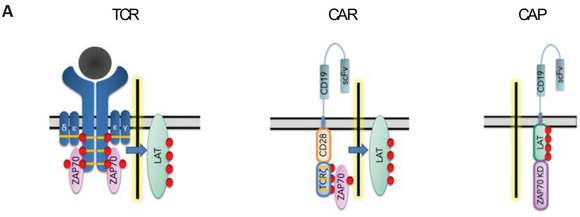
- T cell immunotherapy is used in the treatment of various pathologies – including cancers and infections. Current therapies employ chimeric antigen receptors (CARs) consisting of the intracellular fragment of CD3-zeta as the signaling domain with varied combinations of co-stimulatory, transmembrane, spacer/hinge, and extracellular targeting domains. While effective in treating hematological malignancies, CAR T cells need to be activated through T cell receptor (TCR) activation. Such activation is subject to various regulatory and inhibitory mechanisms that can limit their full therapeutic potential. Moreover, CAR T cells are less effective in the treatment of solid tumors due to exhaustion.

Technology Advantages

- Potential for demonstrable efficacy against solid cancers previously refractory to cellular immunotherapy via:
- Signaling through LAT allows circumvention of regulatory and inhibitory mechanisms involved in TCR activation
- Directly triggering the downstream signaling cascade could cause more potent activation of T cells
- LAT-based CAP-expressing T cells may be more resistant to PD-1-mediated T-cell exhaustion
- Signaling from CAPs consisting of LAT and ZAP70 kinase domain may be tunable

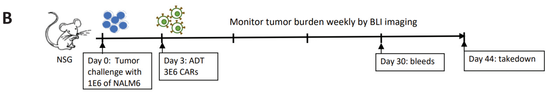
Key Data

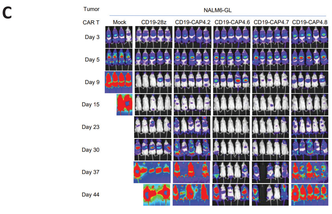
Schematic of TCR signaling, CAR signaling, and CAP signaling

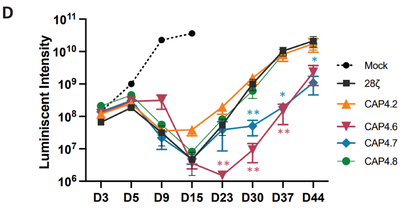


(A) While TCR and CAR must cross the signaling threshold (indicated as yellow highlighted bar) for productive T cell activation, CAP bypasses upstream steps.

CD19-CAP4 constructs show robust efficacy in an in vivo NSG leukemia







(B) In order to further differentiate CAP4 candidates, we evaluated their in vivo efficacy in an immunodeficient NOD/scid/gamma (NSG) mouse model (C and D) 28ζ -CAR-Ts and all tested CAP4-Ts exhibited early efficacy in reducing tumor burden as compared with mock-transduced T cells. By day 30, mice treated with 28ζ -CAR, CAP4.2, and CAP4.8 relapsed, while CAP4.6 and CAP4.7-treated mice achieved a more durable tumor regression.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2022-076358 (2022.09.13)

Patent Family
PCT, US, EP, CN

Publication(s)

- Balagopalan, L. et al. (2022). Generation of anti-tumor chimeric antigen receptors incorporating T cell signaling motifs. bioRxiv (Cold Spring Harbor Laboratory).
- Balagopalan, L. et al. (2018). Plasma membrane LAT activation precedes vesicular recruitment defining two phases of early T-cell activation. Nature Communications, 9(1).
- Yi, J. et al. (2019). TCR microclusters form spatially segregated domains and sequentially assemble in calcium-dependent kinetic steps. Nature Communications, 10(1).