124 FUNCTIONALIZING CAR T CELLS FOR SELECTIVE PROLIFERATION AND DUAL-TARGETING USING THE MEDITOPE TECHNOLOGY

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Background Meditope is a small cyclic peptide that was identified to bind to cetuximab within the Fab region. The meditope binding site can be grafted onto any Fab framework, creating a platform to uniquely and specifically target monoclonal antibodies. Here we demonstrate that the meditope binding site can be grafted onto chimeric antigen receptors (CARs) and utilized to regulate and extend CAR T cell function. We demonstrate that the platform can be used to overcome key barriers to CAR T cell therapy, including T cell exhaustion and antigen escape.

Methods Meditope-enabled CARs (meCARs) were generated by amino acid substitutions to create binding sites for meditope peptide (meP) within the Fab tumor targeting domain of the CAR. meCAR expression was validated by anti-Fc FITC or meP-Alexa 647 probes. In vitro and in vivo assays were performed and compared to standard scFv CAR T cells. For meCAR T cell proliferation and dual-targeting assays, the meditope peptide (meP) was conjugated to recombinant human IL15 fused to the CD215 sushi domain (meP-IL15:sushi) and anti-CD20 monoclonal antibody rituximab (meP-rituximab).

Results We generated meCAR T cells targeting HER2, CD19 and HER1/3 and demonstrate the selective specific binding of the meditope peptide along with potent meCAR T cell effector function. We next demonstrated the utility of a meP-IL15:sushi for enhancing meCAR T cell proliferation in vitro and in vivo. Proliferation and persistence of meCAR T cells was dose dependent, establishing the ability to regulate CAR T cell expansion using the meditope platform. We also demonstrate the ability to redirect meCAR T cells tumor killing using meP-antibody adaptors. As proof-of-concept, meHER2-CAR T cells were redirected to target CD20+ Raji tumors, establishing the potential of the meditope platform to alter the CAR specificity and overcome tumor heterogeneity.

Conclusions Our studies show the utility of the meCAR platform for overcoming key challenges for CAR T cell therapy by specifically regulating CAR T cell functionality. Specifically, the meP-IL15:sushi enhanced meCAR T cell persistence and proliferation following adoptive transfer in vivo and protects against T cell exhaustion. Further, meP-ritiuximab can redirect meCAR T cells to target CD20-tumors, showing the versatility of this platform to address the tumor antigen escape variants. Future studies are focused on conferring additional 'add-on' functionalities to meCAR T cells to potentiate the therapeutic effectiveness of CAR T cell therapy.

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