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POSTER ABSTRACTS

703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Antagonizing Vasoactive Intestinal Peptide (VIP) Receptors on CAR T Cells Improves Efficacy and Persistence

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Vasoactive intestinal peptide (VIP) is an emerging checkpoint pathway for T cell function [1]. VIP is expressed by both T cells [2,3] and tumor cells [1] and is upregulated during TCR activation [1,4,5]. Augmentation of the VIP/VIPR axis during expansion of primary human T cells enhances less differentiated T cell phenotypes, anti-tumor cytotoxicity, and in vivo persistence [6]. In this work, we elucidate the mechanisms by which the VIP/VIPR axis is a critical and targetable immune checkpoint pathway for chimeric antigen receptor (CAR) T cell therapy. By engineering CAR T cells to secrete novel and potent VIPR antagonistic peptides, these cells can overcome the immunosuppression of VIP-rich tumor microenvironments.

First, we demonstrated that VIP suppresses CAR T cell function as evident by reduced expansion with exogenous VIP supplementation, which can be rescued by the addition of VIPRa peptides. The VIP/VIPR axis is relevant to CAR T cell signaling as these cells produce VIP after antigen stimulation and upregulate VIPR expression. In fact, polyfunctionality and cytotoxic killing is enhanced by VIPR knockout of CAR T cells. Together, these results demonstrate the critical role of the VIP/VIPR axis in CAR T cell function. To harness this axis, CAR T cells were engineered to secrete VIPRa peptides (VIPRa CAR T) to provide continuous and localized delivery of VIPRa peptides.

Continuously delivered VIPR antagonism increases the viability and proportions of less-differentiated and less-exhaustive phenotypes of CAR T cells at baseline. Functionally, VIPRa CAR T cells have a proliferative advantage and enhanced activation compared to parental CAR T cells. RNA sequencing was performed on VIPRa CAR T cells before and after antigen-stimulation to illuminate in-depth phenotypic and functional differences compared parental CAR T cells. Finally, these novel CAR T cells were tested in xenograft and syngeneic mouse models. VIPRa CAR T cells show improved tumor control and persistence as evidence long-lived circulating cells in the peripheral blood. To validate the clinical relevance of this target for CAR T therapy, patient-derived xenograft (PDX) pancreatic tumors were assayed to show robust expression of VIP. VIPRa CAR T cells significantly reduced tumor burden and improved survival in PDX tumor-bearing mice.

Collectively, this data demonstrates that targeting VIP is a novel and successful approach to improving CAR T cell anti-tumor efficacy. VIPR antagonism enhances initial CAR T cell phenotypes and function, which has the potential to improve CAR T cell therapy for a variety of tumor types. The mechanisms by which CAR T cell-mediated delivery of VIPRa peptides can modulate tumor microenvironments in a syngeneic model are currently being evaluated. VIPRa CAR T cells are a uniquely improved cellular therapy capable of enhanced anti-tumor function against clinically relevant tumors.

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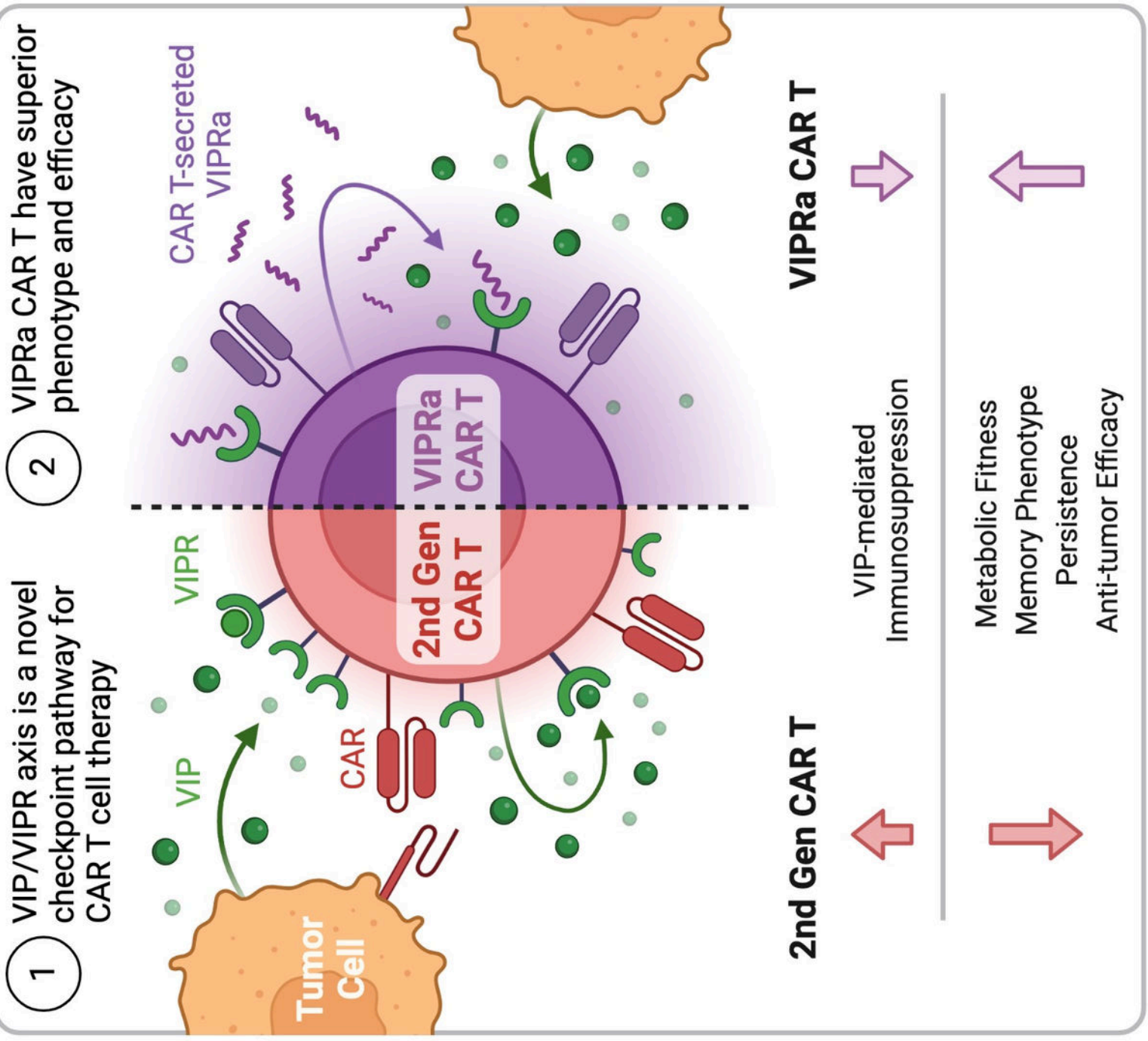

Figure 1