De novo-designed transmembrane domains tune chimeric antigen receptor function

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Using de novo designed single-pass α-helical transmembrane domains (TMDs) we have programmed specific oligomeric interactions in chimeric antigen receptors (CAR) [1]. The designed CARs self-assemble through computationally defined and crystallographically validated interfaces, enabling precise control of cellular receptor function (Figure 1). We demonstrate that the oligomeric state of the CAR transmembrane domain can be programmed using the designed TM domain, and this tunes the in vitro cytokine release and in vivo antitumor activity of mouse primary T cells, with higher order oligomers being more potent. We also show that the designed CARs stimulated lower T cell cytokine release compared to the commonly used CD28 TMD, which was found to elevate cytokine release through lateral recruitment of the endogenous T cell costimulatory receptor CD28. The use of orthogonal and modular TMDs in receptor design offers a promising new approach to precisely control receptor structure and activity for basic or applied synthetic biology.

Figure 1. Panel of de novo designed transmembrane domains spliced in a chimeric antigen receptor to control function.