

Abstract title: "AFFINITY-TUNED" HER2-SPECIFIC CAR T-CELLS SHOW GRADATED INTERFERON RESPONSE BUT EARLY SATURATING ANTITUMOR EFFECT IN VITRO

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Abstract text:

On-target/off-tumor toxicity is a major limitation of applying CAR T cells in solid tumors, leading to adverse effects on normal tissues thus impeding treatment efficacy. We hypothesized that it is possible to generate effectors by 'affinity tuning' of CARs that still recognize the tumor but are no longer activated at the low TAA densities characteristic of normal cells.

As a first step, five different HER2-specific CD28-costimulated CARs with gradually increasing affinities were virally transduced into peripheral T lymphocytes. The constructs were expressed at similar levels (~60%). We then investigated the activation and antitumor functions of these CAR T products upon targeting immobilized HER2 as well as HER2 positive MDA-HER2 and JIMT-1 tumor cell lines. The HER2-negative MDA cell line and unmodified T cells served as negative controls.

In the presence of both immobilized and cell-membrane-bound HER2, the amount of secreted IFN γ increased proportionally with the affinity of the constructs. In contrast, IL-2 secretion was saturated throughout the affinity range. Also, all, except the lowest affinity product, successfully eliminated the HER2-positive target cells with no significant difference between the killing efficiencies. Confirming specificity, there was no target recognition and tumor lysis in co-cultures with HER2-negative target cells and with non-transduced T cells.

Based on these results, we will next investigate the activation pattern of various affinity HER2-specific CAR T cells against normal tissue cells expressing low levels of HER2 and validate our results in an animal model.