

**MULTIPLEXED TCR-T CELL THERAPY TARGETING MAGEA1 AND PRAME ENHANCES THE ACTIVITY OF ADOPTIVE T CELL THERAPY IN PRE-CLINICAL MODELS**

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**Background** Adoptive cell transfer with genetically engineered T cells holds great promise for treating solid tumors. To date, clinical investigations of TCR-engineered T cell therapies (TCR-T) have targeted one antigen at a time and have produced response rates ranging from 30-50%. Unfortunately, complete responses have been rare, and responses are often short-lived. One possible reason why patients rapidly relapse is that their tumors exhibit substantial heterogeneity of antigen expression: not every cancer cell within a tumor expresses the target of a mono TCR therapy and, even when they do, the target is expressed at variable levels among the individual tumor cells. This suggests that TCR-T targeting one antigen could allow the cells lacking the treated antigen to escape and drive relapse.

**Methods** To address antigen heterogeneity, we are developing multiplexed TCR-T cell therapy in which a patient is treated with multiple TCR-T cell products, chosen from a collection of pre-vetted TCRs matched to the patient's tumor antigens and HLA type. As proof-of-concept, we selected two different cancer/testis antigens targeted by two different TCRs. One of these antigens, MAGEA1, was identified as the target of expanded tumor infiltrating T-cells from a head & neck cancer patient using TScan's screening technology.<sup>1</sup> The other one, PRAME, is highly expressed in a variety of cancers. Using our ReceptorScan platform, we developed two high affinity TCRs that recognize HLA-A\*02:01-restricted epitopes from MAGEA1 and PRAME, and assessed the benefits of combining these two TCR-T cell products using a variety of pre-clinical models.

**Results** Individually, both TCRs show strong cytotoxic activity *in vitro* when co-cultured with HLA-matched cancer cell lines expressing endogenous MAGEA1 and PRAME. Additionally, in xenograft mouse models, each TCR was able to control the growth of tumors expressing their cognate antigens. To test whether the two TCRs exhibit additive or synergistic activity, we developed two different tumor models. In one model, we used a cancer cell line that expresses both MAGEA1 and PRAME. In the other model, a mixture of two different cell lines expressing either MAGEA1 or PRAME were grown as xenograft tumors in mice. Notably, when treated with multiplexed MAGEA1/PRAME TCR-T, the mice achieved longer lasting tumor control compared to TCR-T targeting a single antigen.

**Conclusions** These findings support the hypothesis that multiplexed TCR-T mimics the natural oligoclonal T-cell response to cancer and has the potential to overcome antigen heterogeneity, which may contribute to the observed lack of durability in monotherapy TCR-T clinical trials.

**REFERENCE**

1. Luoma AM, Suo S, Wang Y, Gunasti L, Porter CBM, Nabils N, Tadros J, Ferretti AP, Liao S, Gurer C, Chen YH, Criscitiello S, Ricker CA, Dionne D, Rozenblatt-Rosen O, Uppaluri R, Haddad RI, Ashenberg O, Regev A, Van Allen EM, MacBeath G, Schoenfeld JD, Wucherpennig KW. Tissue-resident memory and circulating T cells are early responders to pre-surgical cancer immunotherapy. *Cell*. 2022;**185**:2918-2935.

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