Combining a PRAME-specific TCR showing potent in vitro and in vivo anti-tumor reactivity and a favorable preclinical safety profile with a PD-1/41BB switch receptor results in highly efficient T cells

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Abstract

The development of effective adoptive T cell therapies to treat cancer patients has two main challenges. The first is identifying an antigen that is highly expressed in tumors with limited or no expression in normal tissues. The second is developing a receptor that specifically targets this antigen without causing toxicity to healthy cells. An additional challenge in the treatment of solid tumors is the need for tumor microenvironment (TME) including the T cell microenvironment (TDCM) that inhibits the T cell microenvironment (TDCM) that inhibits T cell proliferation and reduces the efficacy of T cell therapies. To overcome these challenges, we developed a new TCR specific for an HLA-A2-restricted PRAME-epitope with high natural anti-tumor reactivity and specificity. It's favorable preclinical profile qualifies the TCR for evaluation in clinical trials. In this study, we tested the efficacy of this TCR in human tumor xenograft models in vivo and in vitro.

PRAME as target antigen for adoptive T cell therapy and TCR isolation process

1. Isolation of patient T cells
2. Tumor regression
3. Expansion of modified T cells
4. Tumor regression

Selection of a PRAME-specific lead T cell candidate

PRAME-specific TCRs were recombined into tumor-specific effector (TCCR) without T cell receptor (TCR) expression in normal tissues. These TCRs were tested for their ability to induce T cell proliferation and cytotoxicity in response to PRAME-positive tumors.

TCR 4 shows in vitro and in vivo anti-tumor effects

TCR 4 shows a favorable in vitro safety profile.

Co-stimulation via PD-1/41BB chimeric switch receptor enhances function of PRAME-specific TCR-T cells

Summary

Medigene's well-established high-throughput TCR generation process enabled the identification of a lead candidate specific for an HLA-A2-restricted PRAME-epitope (TCR-4), demonstrating high natural affinity and potent preclinical in vitro and in vivo efficacy. Moreover, its favorable preclinical in vitro safety profile proves the value of this technology for developing TCRs with properties qualifying for clinical application.

Combining a PRAME-specific TCR with our PD-1/41BB switch receptor results in a very promising T cell product, especially for the treatment of solid tumors.