T cells transgenic for a highly potent PRAME-specific TCR and a chimeric PD1-41BB co-stimulatory receptor represent a promising approach for the treatment of solid tumors

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Abstract
T cell receptor (TCR)-based immunotherapies have great potential for the safe and efficacious treatment of patients with cancer, but current clinical trials using adoptive T cell therapy have met with limited success due to the lack of a suitable TCR, which would elicit the desired immune response as well as to the tolerance-inducing microenvironment of tumors. We report the generation of a murine TCR, which is highly expressed in various solid tumor types including lung, breast, bone metastases, melanoma, and gastrointestinal malignancies. The TCR was designed to mimic a human anti-PRAME TCR to which a co-stimulatory transmembrane domain from 4-1BB (PD1-41BB) was added to create a novel receptor that is superior to the TCR/4-1BB fusion receptor. The receptor was characterized using ELISpot readout of primary patient T cells and naive T cells transduced with TCR-41BB as well as by in vitro cellular experiments. The results show that the TCR/4-1BB fusion receptor shows a superior functional response compared to the wild-type TCR in vitro and in vivo. This receptor is highly active in most murine cancer cell lines and human cancer cell lines in ex vivo assays and is not only able to activate naive T cells but also to prime T cells from healthy donors. Furthermore, the co-stimulatory TCR/4-1BB fusion receptor exhibits an improved functionality in comparison to the TCR in vivo. This observation was confirmed by in vivo experiments in which tumor volumes were measured at various time points. The results indicate that the TCR/4-1BB fusion receptor is highly active in vivo and is capable of eradicating tumor cells. Therefore, we conclude that the TCR/4-1BB fusion receptor is a promising candidate for the treatment of solid tumors.

Co-stimulation via PD1-41BB enhances function of PRAME-TCR-T cells

Adoptive T cell therapy and TCR isotype process

Selection of a PRAME-specific lead T cell receptor

Expression of PD1-41BB leads to a higher percentage of poly-functional T cells and to a superior poly-cytokine signature

Expression of PD1-41BB leads to tumor rejection in vivo

Summary
Medigene’s well-established high-throughput TCR generation process enabled the identification of a TCR lead candidate (TCR-41BB) that is superior to a HLA-A2-restricted PRAME-epitope, demonstrating high natural affinity and potent anti-tumor efficacy.

Disclosures
All authors are or were employees of Medigene Immunotherapies GmbH or Medigene AG.