DEVELOPMENT OF CLAUDIN 18.2 TAC T CELLS FOR THE TREATMENT OF GASTRIC CANCER

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Background The T cell antigen coupler (TAC) is a novel, proprietary chimeric receptor that facilitates the re-direction of T cells to tumor cells and activates T cells by co-opting the endogenous T cell receptor complex with the goal to elicit a safe and durable anti-tumor response. In preclinical models of cancer, TAC-engineered T cells effectively eradicate tumor cells in vitro and in vivo without TAC-related toxicities. TAC01-HER2, a first-in-class TAC T product targeting HER2 (ERBB2), has recently entered a phase I/II clinical trial in patients with HER2-positive solid tumors. Here, we present the development of a new TAC T product targeting Claudin 18.2 (CLDN18.2) to treat gastric cancer. CLDN18.2 belongs to a family of Claudin tight junction proteins whose expression is naturally exclusive to normal stomach. In gastric cancer cells, however, cell polarity is perturbed, leading to tumor-selective surface expression of CLDN18.2. Thus, CLDN18.2 is a preferred antigen for the specific targeting of tumor cells via TAC T cells.

Methods The functionality of the CLDN18.2-TAC receptor was characterized using a variety of in vitro and in vivo assays. In vitro assays were based on flow cytometric analysis of TAC surface staining and cytokine release. Cytotoxicity was assessed via luminescence-based co-culture assays and real-time microscopy. In vivo studies examined the anti-tumor effect of TAC-engineered T-cells against established CLDN18.2 expressing tumor xenografts.

Results T cells virally transduced with the CLDN18.2-TAC transgene demonstrated satisfactory surface expression of the TAC receptor and showed increased cytokine production when activated by CLDN18.2 expressing target cells in vitro. Secretion of IL2, IFN γ and TNF α were comparable with cytokine levels produced by activated HER2-TAC T cells used as a positive control. In vitro cytotoxicity assays demonstrated a strong anti-CLDN18.2 response and killing of CLDN18.2 expressing target cell lines. No increases in cytokine levels and no cytotoxicity were observed in non-transduced T cells and CLDN18.2-TAC T cells co-cultured with CLDN18.2-negative target cells, indicating that the T cell response is specific to the CLDN18.2 antigen. Intravenous administration of CLDN18.2-TAC T cells in mice carrying CLDN18.2-positive tumor xenografts led to a sustained anti-tumor response.

Conclusions The in vitro and in vivo data confirm strong and specific activity of CLDN18.2-targeted TAC T cells against CLDN18.2-expressing cancer cells and highlight the versatility of the TAC platform for therapeutic applications in solid tumors.

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