REGIONAL ADMINISTRATION OF IL-12 ENDOWED CAR T CELLS EFFECTIVELY TARGETS SYSTEMIC DISEASE

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Background While chimeric antigen receptor (CAR) T cell therapy has shown impressive clinical efficacy for hematological malignancies,¹ efficacy remains limited for solid tumors due in large part to the immunosuppressive tumor microenvironment.² Tumor-associated glycoprotein 72 (TAG72) is an aberrantly glycosylated protein overexpressed on ovarian cancer³ and is an exciting target for CAR T cell immunotherapy. Our lab previously developed a second-generation TAG72 CAR T cell product and showed its potency against TAG72-expressing ovarian tumor cells both in vitro and in preclinical mouse models.⁴ We report here further modification of our TAG72 CAR T cells, with incorporation of interleukin-12 (IL-12) and interleukin-15 (IL-15), and evaluate the therapeutic benefits in peritoneal ovarian tumor models.

Methods In this preclinical study, we build upon our earlier work with in vitro and in vivo evaluation of 9 different second-generation TAG72 CAR constructs varying in single-chain variable fragment, extracellular spacer, transmembrane, and intracellular co-stimulatory domains. We then engineer CAR T cells with two types of cytokines – IL-12 and IL-15 – and put these engineered cells against challenging in vivo tumor models.

Results Through in vitro and in vivo studies, we identify the most optimal construct with which we aim to evaluate in a phase 1 clinical trial targeting TAG72-positive ovarian cancer in 2021. Despite thorough optimizations to the CAR backbone, CAR T cells can be additionally engineered for improved anti-tumor response. Therefore, we further engineered CAR T cells with IL-12 or IL-15 production that greatly improves the effectiveness of TAG72-CAR T cells in difficult-to-treat in vivo tumor models. We observed that modification of CAR T cells with IL-15 displayed toxicity when regionally delivered in vivo, yet introduction of IL-12 not only demonstrated safe and superior therapeutic responses, but also allowed the regional administration of CAR T cells to address systemic disease. We are now expanding these findings by evaluating these therapies using syngeneic immunocompetent mouse tumor models.

Conclusions The tumor microenvironment (TME) harbors various factors that thwart the killing of tumor cells by CAR T cells. Thus, CAR T cells will likely require further engineering to overcome this barrier. We show that amplifying cytokine pathways is one way to overcome the TME and improve the efficacy of CAR T cell therapy for solid tumors.

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