FUNCTIONAL CHARACTERIZATION OF GUCY2C-TAC T CELLS FOR THE TREATMENT OF COLORECTAL CANCER USING PRECLINICAL MODELS

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Background The T cell antigen coupler (TAC) is a novel chimeric receptor that facilitates the redirection of T cells to tumor cells and activates T cells by co-opting the endogenous T cell receptor complex with the goal to elicit safe and durable anti-tumor responses. TAC01-HER2, a first-in-class TAC T product targeting HER2 (ERBB2), has entered a phase I/II clinical trial in patients with HER2-positive solid tumors. Here, we present preclinical results from TAC T cells targeting guanylyl cyclase 2C (GUCY2C). GUCY2C belongs to a family of membrane-bound mucosal guanylate cyclase receptors normally expressed on the apical brush border of intestinal epithelia, a site inaccessible to T cells. In cancer, however, GUCY2C expression is frequently elevated in primary and metastatic colorectal carcinomas and is no longer confined locally, which allows for the specific targeting of tumor cells.

Methods GUCY2C-TAC receptors were humanized using rational mutational changes to the nanobody framework amino acids. The resulting constructs were functionally characterized using in vitro and in vivo models. In vitro assays included T cell proliferation, repeat killing assay, and cytotoxicity via real-time microscopy co-culture assays. In vivo studies examined the anti-tumor effects in liquid and solid tumor models.

Results In vitro, T cells engineered with the humanized GUCY2C-TAC receptors showed strong and antigen-specific activation when co-cultured with a variety of cancer cells ectopically and naturally expressing GUCY2C. Activation was followed by T cell proliferation and strong GUCY2C-specific anti-tumor cytotoxicity. GUCY2C-TAC T cells showed activity in a serial cytotoxicity assay, designed to test T cell fitness through chronic antigen stimulation. This assay was accompanied by complex phenotype analysis testing for T cell exhaustion, memory and activation markers. In vivo, intravenous administration of GUCY2C-TAC T cells in mice carrying GUCY2C-positive tumor xenografts led to effective tumor rejection in both liquid and solid tumor models.

Conclusions In vitro and in vivo data confirm strong and specific activity of T cells engineered with humanized GUCY2C-TAC receptors. Taken together, these data support further development of GUCY2C-TAC T cells for therapeutic applications in colorectal cancer.

Ethics Approval Animal studies performed for the work presented in this abstract were conducted under the Animal Utilization Protocol (AUP) # 20-10-37 and approved by the Animal Research Ethics Committee at McMaster University (Hamilton, ON, Canada).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0347