DEVELOPMENT OF OPTIMIZED CAR T CELLS FOR THERAPY OF Glioblastoma

Jonathan Khan*, 1 Winson Cai, 1 Yanhong Yang, 1 Lauren Dong, 1 Kelsey Hopland, 1 Kenny Kwik-Hai Yu, 1 Ruby Freeman, 1 Terence Purdon, 1 Viviane Tabar, 1 Taha Merghoub, 1 Jedd Wolchok, 2 Renier Brentjens, 1 Memorial Sloan Kettering Cancer Center, Floral Park, NY, USA; 2 Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Background Glioblastoma (GBM) is the most lethal form of primary brain tumor in adults, with a 95% five-year mortality rate. Current therapy consists of surgical resection, chemotherapy, and radiotherapy. However, there remains an urgent need for novel therapies as recent trials have failed to improve overall survival. 1 A new approach to target GBM is the administration of Chimeric Antigen Receptor (CAR) T cells to treat relapsed/refractory disease. 2 To date, multiple clinical trials employing CAR T cells targeting disparate antigens in the context of GBM have been completed; and analysis of data accrued from these trials identified antigen loss and the upregulation of T cell inhibitory pathways to be major limitations of CAR T cell antitumor efficacy. 3, 4 Accordingly, we have identified B7-H3 as a potential target antigen for CAR T cell therapy of GBM, and the Programmed Death-1/Programmed Death Ligand-1 (PD-1/PD-L1) axis as an inhibitory pathway suitable for combinatorial immunotherapy with CAR T cell therapy of GBM.

Methods B7-H3 expression on U251, U87, and 4 primary GBM cell lines was evaluated by flow cytometry, while patient tumor samples were analyzed by immunofluorescence. B7-H3 targeting CAR T cells were engineered by transducing primary human T cells with a retroviral vector encoding either a CD28-based CAR, or a CD28-based CAR containing a PD-1 blocking scFv. In vitro luciferase-based killing assays, and Luminex-based quantification of cytokine release were used to characterize CAR function. NSG mice were engrafted with U251 GBM cell line and treated with a single peripheral infusion of CAR T cells. Tumors were harvested at various time points following CAR T cell treatment and characterized for T cell infiltrate, T cell phenotype, and expression of checkpoint pathways.

Results We demonstrate that B7-H3 is a suitable antigen for CAR T cell therapy of GBM, and that B7-H3-targeting CAR T cells are able to safely, and efficiently control disease progression in a disease-relevant xenograft model. We also show that GBM tumor cells upregulate PD-L1 in direct response to CAR T cell activity, and that CAR T cells upregulate PD-1 following activation through the CAR. We subsequently demonstrate that concomitant PD-1 blockade augments the antitumor capabilities of B7-H3-targeting CAR T cells through increased T cell engraftment and improved effector function to confer durable, long-term remissions in a disease-relevant preclinical model.

Conclusions These data demonstrate the concomitant PD-1 blockade is safe and efficient method for improving the anti-tumor capabilities of B7-H3 targeting CAR T cells in the context of GBM.

REFERENCES


Ethics Approval The human biospecimen analyses were approved by Memorial Sloan Kettering Cancer Center IRB #09-156.