IM-05. MULTISPECIFIC CAR T CELLS FOR THE TREATMENT OF HIGH GRADE GLIOMA
Kevin Bielamowicz, Kristen Fousek, Tiara Byrd, Kevin Chow, Zhongzhen Yi, Simone Krebs, Gianpietro Dotti, Stephen Gottschalk, Meena Hegde, and Nabil Ahmed; Baylor College of Medicine, Houston, TX, USA

BACKGROUND: High grade gliomas (HGG) carry a dismal prognosis. Our group has shown that patients’ HER2-specific chimeric antigen receptor (CAR) T-cells kill autologous HGG, yet 40% of tumors recur in experimental animals. Recurrences are composed of HER2 negative escape variant cells that maintain positivity for two other glioma antigens, IL13Rα2 and EphA2. We hypothesized that co-targeting of these escape variants will enhance the anti-glioma activity of CAR T cells.

OBJECTIVES: Objectives: The intent of this project is to develop a multi-specific T-cell product for the adoptive immunotherapy of HGG. DESIGN/METHOD: We generated and tested the effector functions of patients’ T-cells co-expressing CARs for HER2, IL13Rα2 and EphA2 against autologous HGG cells derived from surgical excision samples. RESULTS: Primary patient HGG samples exhibited varied expression of the three target antigens, HER2, IL13Rα2 and EphA2. In order to render single patients’ T cells tri-specific, we designed a transgene incorporating 3 encoding regions for HER2, IL13Rα2 and EphA2 CARs separated by 2A sequences in a single cassette driven by a CMV promotor. We used a retroviral system to stably integrate this transgene into the primary T cell genome. CAR-specific flow cytometry indicated proportionate stable expression of individual CAR molecules on the T cell surface. These T cells show distinct specificity for each of the three glioma antigens evidenced by activation, proliferation, and cytolytic function in immunoassays. Further, preliminary in vitro testing in glioma cell lines shows the ability to target populations of tumor cells that are not eliminated by unspecific products. CONCLUSION: The heterogeneity of antigenic expression in HGG and antigen escape justify targeting multiple glioma antigens simultaneously. We have successfully generated and tested a multi-specific T cell product for adoptive transfer that could offset antigen escape and exhibit an enhanced anti-glioma efficacy.