CAR T CELL PRODUCTION EXPANDS ENDOGENOUS T CELL REPERTOIRE RECOGNIZING ADDITIONAL TUMOR ANTIGEN(S)

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Background Glioblastoma (GBM) is an aggressive and heterogeneous brain tumor that currently has no curative treatment. Our group identified CD70, which is overexpressed by low-/high-grade gliomas and associated with poor patient survival. We established a CAR-T cell therapy platform targeting CD70-expressing gliomas, which showed efficient antitumor activity preclinically. Modification of CD70CAR to express IL-8 receptors (8R-70CAR) enhanced tumor trafficking and persistence, resulting in improved antitumor efficacy and long-lasting immunity to tumor rechallenge. These findings culminated in a phase-I trial of 8R-70CAR T cells (NCT05353530) for patients with newly diagnosed GBM that will begin at UF soon. However, CAR T cell therapy currently faces obstacles such as single antigen targeting in heterogeneous tumors and maintenance of activation of CAR T cells. Cytomegalovirus pp65 protein is a tumor-specific target in GBM. A combinatorial approach against CD70 and pp65 may result in enhanced effect against heterogeneous GBM.

Methods Healthy donor peripheral blood mononuclear cells were stimulated with anti-CD3/CD28 Dynabeads and retrovirally transduced with 8R-70CAR. Frequencies of 8R-70CAR- and pp65-specific T cells were evaluated by flow cytometry.

Results The pp65-specific CD8+ T cell population was expanded post DynaBeads activation to a frequency tenfold over baseline (figure 1). Single-specific (CD70 CAR+ only and pp65-specific only) and double-specific (CD70 CAR+ and pp65-specific) T cells were successfully generated. Importantly, these cells secreted greater IFN-g when tumor cells expressed both targets (figure 2).

Conclusions The CAR T cell production process significantly expands pp65-specific T cells, resulting in enhanced antitumor efficacy through recognition of both tumor targets. Our CAR T cell product may contain T cell repertoires that effectively target multiple tumor antigens.

REFERENCES