PRIMING OF SYNNOTCH CAR T CELLS VIA CNS-SPECIFIC ANTIGEN ALLOWS SPATIAL AND TEMPORAL REGULATION OF CAR EXPRESSION, EFFECTIVE HOMING AND PERSISTENCE OF T CELLS IN THE CNS, RESULTING IN THE COMPLETE ERADICATION OF AGGRESSIVE GLOBLASTOMA

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Background: The CAR T cell therapies have failed to produce long-term remission in glioma patients. One of the key challenges in the development of an effective CAR-T therapy is the absence of target antigens that are tumor-specific and have homogenous expression. To safely target glioblastoma-associated antigens (GAAs) in the tumor without attacking normal tissue expressing the same GAAs outside of the brain, we adopted a novel synthetic Notch (synNotch) receptor system and established a “prime and kill” sequential two-receptor CAR circuit. We used glioblastoma- (GBM) specific neoantigen EGFRvIII as a priming signal for synNotch receptor and have reported robust antitumor response in the mice bearing intracerebral PDX tumor with heterogenous EGFRvIII expression. However, less than 20% of adult GBM cases express EGFRvIII. Furthermore, EGFRvIII expression can diminish over time even after its detection in the primary GBM, and the EGFRvIII-synNotch primed CAR T cells may deplete EGFRvIII-expressing GBM cells via their cytotoxic effects, thereby losing the priming signal. To overcome these inherent challenges of the EGFRvIII-priming strategy, we used CNS (Central Nervous System) tissue-specific antigens as the priming signal to drive localized expression of the CAR against EphA2 and IL-13Rα2 and bypassed the need for tumor-specific antigen.

Methods: We have found BCAN (also known as Brevican) as the most promising priming antigen based on the specific and robust priming among several CNS-specific cell surface proteins that we evaluated. We created a synNotch-CAR circuit in which BCAN primes the T cells to induce expression of a CAR that recognizes IL-13Rα2 and EphA2.

Results: When mice bearing intracerebral GBM6 PDX received a single intravenous (IV) infusion of T cells engineered with the α-BCAN synNotch α-EphA2/IL-13Rα2 CAR (B-SYNC) circuit, all mice (10/10) demonstrated complete regression of the tumor. Furthermore, these B-SYNC T cells were significantly more efficacious than constitutively expressed EphA2/IL-13Rα2 CAR T cells. The enhanced in vivo efficacy and superior persistence of B-SYNC T cells were associated with its tissue-resident and memory stem-cell-like phenotype.

Conclusions: Taken together, the B-SYNC approach represents a robustly efficacious and conceptually novel T cell therapy with the CNS tissue-specific CAR activation. This also enhances the translational significance of synNotch-CAR T cells by widely extending the eligibility to EGFRvIII-negative glioma patients. We are currently developing a phase I study to evaluate the safety as well as the homing and priming status (i.e. expression of CAR) of the IV-infused B-SYNC T cells in patients with GBM.