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DIPG-15. NOVEL CNS SENSING SYNNOTCH-CAR T CELLS FOR TARGETING DIFFUSE MIDLINE GLIOMA
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BACKGROUND: Diffuse midline glioma (DMG), including Diffuse intrinsic pontine glioma (DIPG), is an aggressive brain tumor in children with limited treatment options. Recent developments of phase I clinical trials have shown early promise for chimeric antigen receptor (CAR) T cells in patients with DMG/DIPG. However, several barriers such as the absence of tumor-specific antigens, restricted trafficking to the tumor site, and poor persistence hinder the full therapeutic potential of CAR T cell therapy in DMG/DIPG.

METHODS: To safely target the glioma-associated antigens (GAAs) without attacking normal tissues expressing the same antigens, we adopted a novel synthetic Notch (synNotch) receptor system and engineered T cell circuits employing a “prime-and-kill” strategy. In this system, a synNotch receptor recognizing the priming antigen, Brevican (BCAN), exclusively expressed on cells in the central nervous system (CNS) but not on non-CNS cells, locally induces the expression of a tandem CAR against GAAs, ephrin type A receptor (EphA2) and interleukin-13 receptor a2 (IL-13Ra2), there by homogenously eliminating DMG/DIPG cells. RESULTS: The α-BCAN synNotchβα-EphA2/IL-13Ra2 CAR (B-SYNC) T cells efficiently killed DMG/DIPG (BT-245, SF8628, SU-DIPGIII, and SU-DIPGIXVII) cells in vitro in the presence of priming cells (K562 cells expressing BCAN). Moreover, a single intravenous infusion of B-SYNC T cells significantly (P < 0.001) prolonged the survival of immunodeficient mice bearing aggressive, orthotopic SF8628 DIPG xenografts and completely eradicated the tumor in more than 50% (4/7) of mice. Strikingly, we observed excellent homing, priming, activation, and persistence of B-SYNC T cells in the brain stem of mice bearing SF8628 xenografts. In contrast, constitutively active α-EphA2/IL-13Ra2 CAR T cells or untransduced T cells demonstrated a failure to migrate to the brain stem and improve the survival of mice.

CONCLUSIONS: Collectively, our findings strongly support the development of clinical trials evaluating the efficacy of B-SYNC T cells in DMG/DIPG patients.