#2062: Efficacy of Function-enhanced, Re-activatable, Dual-specific CAR T cells Pre-loaded with Oncolytic Virus for Immunotherapy of High-Grade Glioma

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ABSTRACT

- High-grade gliomas (HGG) include the most common and aggressive brain tumors in adults and have a dismal prognosis.
- Chimeric antigen receptor (CAR) T cells have emerged as a promising therapeutic in hematologic cancers but have limited benefit in solid tumors including HGG.
- This is thought to be in part because HGG tumors have an immune-suppressive tumor microenvironment (TME).
- Oncolytic viruses (OVs) have a strong activating, anti-suppressive immune effects.
- CAR T cells loaded with OV, when given to animal models, create a novel population of anti-tumor antigen and anti-viral antigen dual specific (DS) CAR T cells.
- There is an optimal amount of virus loading required for effect and avoidance of innate/adaptive immune response.
- These DS CAR T cells are more effective, persistent, and responsive to re-stimulation.
- In HGG animal models treated with anti-tumor antigen CAR T cells loaded with OVs, we can reactivate these CAR T cells by adjuvant systemic OV administration and generate long-term cures.
- We hope to utilize this novel technique to develop a clinical trial.

METHODS

- OVs including reovirus and vesicular stomatitis virus (VSV) were utilized.
- Female C57BL/6 ages 4-8 weeks were obtained from Jackson Laboratories.
- An EGFRvIII third-generation MSGV1 retroviral CAR construct was used, containing the CD28, 4-1BB, and CD3z moieties, in tandem with the scFv derived from the human monoclonal antibody 139 and the marker Thy1.1.
- Tumors were given subcutaneously or within the brainstem using B16EGFRvIII or CT2AEGFRvIII murine cell lines.

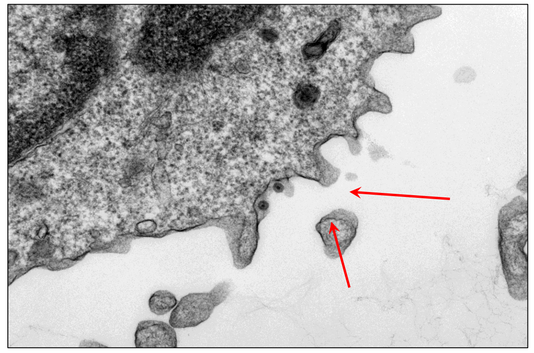
MAIN TAKEAWAY

- Loading CAR T cells with an oncolytic virus creates dual specific CAR T cells that are more effective, persistent, and responsive to re-stimulation and can generate long-term cures in mouse models of high-grade glioma.

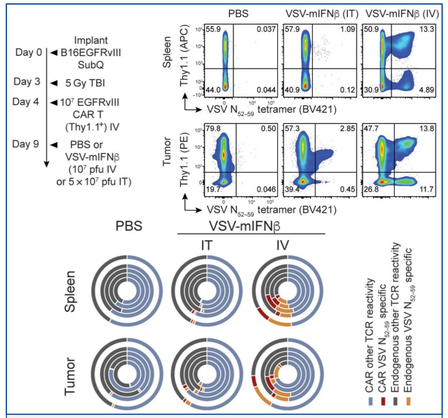
Electron microscopy, MOI 1.0

Reovirus

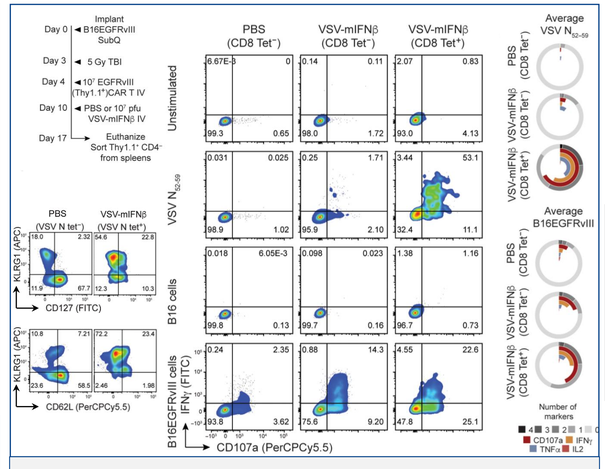
1000 nm



RESULTS

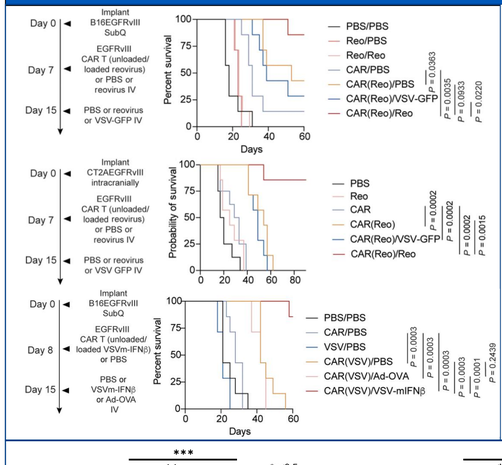


CAR T cells with TCR reactivity to a VSV immunodominant epitope expand following infection with VSV

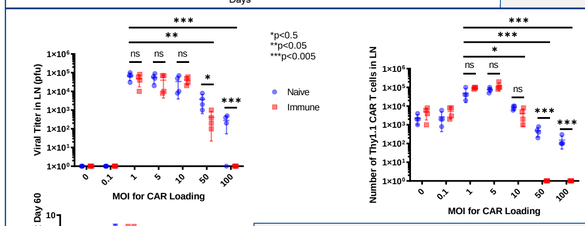


DS CAR T cells have improved function against target cells and acquire a distinct memory phenotype.

RESULTS (CONT.)



Loaded CAR T + adjuvant OV causes cures regardless of tumor or loaded CAR T/adjuvant virus pair.



Optimal CAR T loading (reovirus) prevents immune clearance and retains efficacy.

CONTACT INFORMATION

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Laura Evgin et al., Oncolytic virus–mediated expansion of dual-specific CAR T cells improves efficacy against solid tumors in mice. Sci. Transl. Med.14, eabn2231(2022).DOI:10.1126/scitranslmed.abn2231