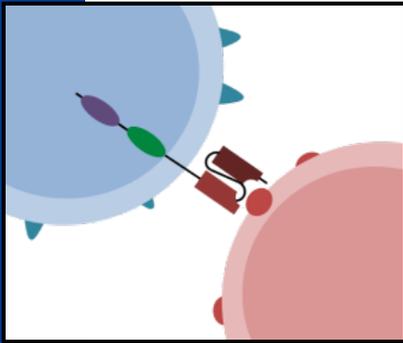


# Glioma Stem Cell Targeting CAR-T Cell Constructs with Phage Display Derived Peptide Oligomers



*A chimeric antigen receptor-expressing T cell that targets and kills glioma stem cells. The CAR construct works by using novel phage display-derived peptide oligomers as a substitute for the scFv region to enable T cell targeting of glioma stem cells and T-cell activation by incorporating co-stimulator and intracellular signaling regions. The oligomers were generated through in vitro and in vivo selection methods using cell lines and xenograft mice. The specific binding to glioma stem cells has been confirmed through flow cell sorting techniques. In xenograft mice, fluorescently labeled peptides preferentially bound to glioblastoma tissue. CAR-T constructs have been shown to recognize patient-derived glioma stem cells in vitro.*

## COMMERCIAL OPPORTUNITY

- Gliomas include all tumors arising from the supportive tissue of the brain, and Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor. GBM remains an incurable condition, typically associated with high mortality and morbidity. There are about 17,000 new GBM cases per year, and virtually all GBMs recur following first line therapy.
- Current standard of care consists of maximal surgical resection, concurrent chemotherapy and radiation therapy, followed by maintenance chemotherapy. However, tumor recurrence is inevitable with a median PFS of 7-10 months, and median survival of 15-16 months. Glioblastoma stem cells are a subpopulation of tumor cells that possess the ability of self-renewal and tumor recapitulation. Developing effective strategies to specifically target GSCs may improve control of GBM.
- The marketplace is attractive for CAR-T development, as Novartis received approval in August 2017 for Kymriah, its anti-CD19 CAR-T therapy for pediatric B-cell ALL. The trial had an overall response rate of 82.5% (52/63). Although the list price for Kymriah is \$475,000 for a one-time treatment, Novartis has said only those patients who respond by the end of the first month will need to pay. In October 2017, Gilead's Yescarta, an anti-CD19 CAR-T, was approved for large B-cell lymphoma and is listed at \$375,000. In 2017, Gilead acquired Kite Pharma for \$11.7B, and in 2018, Celgene acquired Juno Therapeutics for \$9B. Juno is also developing a CD-19 CAR-T therapy.

## TECHNOLOGY

Two strategies were used for phage display screening to isolate lung cancer derived metastatic brain tumors binding peptides. In the in vitro screening method, negative selection was used with extracellular matrix and non-stem glioma cells followed by positive selection with glioma stem cells. In the in vivo strategy, positive selection of phage occurred with mice with intracranial xenografts, followed by phage tail injections, and harvesting the tumor for dissociation and phage isolation. A series of chimeric antigen receptors (CARs) were designed that display phage peptide sequences, arranged in tandem, at the N-terminus of the CAR molecule. CAR cDNA was cloned into a retroviral expression vector used for clinical CAR-T cell manufacture, and the resulting constructs were used to transduce human primary T cells. Six of the seven CAR designs were expressed in transduced cells. One of them reacted specifically to GSC by secreting interferon- $\gamma$ , following an overnight co-culture assay.

## PUBLICATION/PATENT

- Provisional patent application was filed on October 1, 2018 for Drs. Liu and Abate-Daga.

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### LICENSING OPPORTUNITY



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