HHS Public Access

Author manuscript

Nat Rev Cancer. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

Nat Rev Cancer. 2022 April ; 22(4): 194. doi:10.1038/s41568-022-00451-8.

BIDIRECTIONAL CART.BITE CELLS BRING NEW HOPE

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The approval of the first chimeric antigen receptor (CAR) T cell therapy targeting CD19 for certain patients with a form of B cell malignancy by the US food and drug administration (FDA) in 2017 was a landmark moment for cancer immunotherapy and has since revolutionized the treatment of haematological cancers. Yet, several major hurdles must be addressed before this live cell therapy is applicable in solid cancers, including heterogeneous target antigen expression and outgrowth of tumours lacking the antigen targeted by CAR T cells, which may lead to treatment resistance and tumour recurrence.

In a study published in 2019, Choi et al. navigated antigen specificity and heterogeneity — obstacles for the development of CAR T therapy for glioblastoma (GBM) — by a CAR T therapy based multi-antigen targeting strategy in mice. GBM harbors oncogenic alterations in epidermal growth factor receptor (*EGFR*), leading to amplification and/or overexpression. The EGFR mutant EGFRvIII is a tumour-specific surface marker in GBM. Of all GBMs, 60–90% possess overexpress EGFR, and ~30% express EGFRvIII. Previous research using CAR T cells targeting EGFRvIII in patients with GBM reported the outgrowth of EGFRvIII-negative, wild-type EGFR-positive GBM cells, despite an effective elimination of EGFRvIII-positive GBM cells. Thus there is a need to overcome target antigen heterogeneity to achieve more thorough killing of GBM cells. Choi et al. set out to target both EGFR and EGFRvIII. They integrated a CAR targeting EGFRvIII along with a bispecific T cell engager (BiTE) targeting wild-type EGFR to obtain a single construct of CART. BiTE. T cells transduced with CART.BiTE express CARs targeting EGFRvIII-positive cells, and secrete BiTEs to enable attacking of EGFRvIII-negative, EGFR-positive GBM cells that otherwise could escape the killing. The two arms of BiTE are designed to bind CD3 on T cells and EGFR on GBM cells, leading to T cell activation and subsequent tumour cell lysis. Indeed, when CART.BiTE cells were intracranially delivered into GBM-bearing mice, the secreted BiTEs redirected CAR T cells to EGFR-positive GBM cells and recruited and activated un-transduced bystander T cells against EGFR-positive GBM cells for enhanced efficacy. Finally, CART. BiTE cells did not cause detectable toxicity in mice. However, although GBM metastases outside the central nervous system (CNS) are rare, intracranial delivery strategy warrants caution when extra-CNS metastasis is present.

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Competing interests

The authors declare no competing interests.

Oncogenic *EGFR* alterations are found in diverse tumour types, such as head and neck, lung, colon and breast cancers. Two main classes of inhibitors targeting EGFR, monoclonal antibodies (for example, cetuximab) and tyrosine kinase inhibitors (for example, gefitinib), have been among the earliest targeted therapies that block growth signals. Over the years, both have manifested various therapy resistance mechanisms in different solid tumours, primary and/or acquired ones, dampening their efficacy, which was quite disappointing. We previously generated a bispecific recombinant immunotoxin targeting overexpressed EGFR and EGFRvIII and showed its antitumour efficacy in GBM as well as head and neck cancer. Hopefully, these multi-antigen targeting strategies will eventually improve the outcomes of patients with relevant cancer types.

References

Choi et al. CAR- T cells secreting BiTEs circumvent antigen escape without detectable toxicity. Nat. Biotech 37, 1049–1058 (2019)