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Armoring CAR-T Cells Against Exhaustion: Engineering Strategies for Glioblastoma

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Journal of Immunotherapy Publish Ahead of Print, August 27, 2026. | DOI: 10.1097/CJI.0000000000000617

PAP INFOGRAPHIC

[Abstract](#) In Brief

Glioblastoma (GBM) is the most lethal primary brain tumor, with a median survival of 15 months despite intensive treatment. Chimeric antigen receptor (CAR) T-cell therapy, while transformative in hematological malignancies, consistently fails in GBM because the immunosuppressive tumor microenvironment (TME) drives T-cell exhaustion. We examined transcriptional programs, microenvironmental factors, and metabolic competition that collectively drive exhaustion in this context. Then we reviewed 5 convergent engineering strategies: localized cytokine delivery to bypass autocrine deficits; adjunctive antibody therapies to remodel the TME; oncolytic viruses armed with chemoattractants or cytokines as immunomodulators; coexpression of cytokine or chemokine receptors to provide survival signals; and multiplexed CRISPR-Cas9 editing to disrupt exhaustion checkpoints and enable site-specific CAR integration. Locoregional delivery consistently outperforms systemic administration, demonstrating that physical barriers are as critical as cellular engineering. Despite this progress, antigen heterogeneity, metabolic limitations, and the need for combinatorial targeting remain the principal unresolved challenges. An overview of the key concepts discussed in this review is presented in the graphical abstract.

