Sign in / Sign up
Access through your organization
Purchase PDF
Patient Access
Recommended articles
No articles found.

Advancing chimeric antigen receptor T-cell therapy frontiers in glioblastoma: Navigating the current landscape from clinical hurdles to breakthrough strategies

Raja Kumar Sarma[a], Archagesh Mallu[b], Rangaprasad Sharma[c], Deepak Gupta[d], Ajit Singh[e]

[a]Department of Pharmacology, NETAS Institute of Pharmaceutical Sciences, Nalgonda, Telangana, India, [b]Department of Pharmacology, Gandhi Medical College, Secunderabad, Telangana, India, [c]Department of Pharmacology and Drug Discovery Research Laboratory, Division of Cancer Research, Medanta-The Medicity, Gurugram, Haryana, India, [d]Medanta Institute of Education and Research, Gurugram, Haryana, India, [e]Medanta-The Medicity, Gurugram, Haryana, India

Received 22 June 2024, Revised 5 July 2024, Accepted 12 July 2024, Available online 24 July 2024, In press on-line 26 July 2024

Write an Chime demo record!

Editor: Marcella Bonsi

DOI: https://doi.org/10.1016/j.drudis.2024.103961

Cite this article as: Raja Kumar Sarma et al., Advancing chimeric antigen receptor T-cell therapy frontiers in glioblastoma: Navigating the current landscape from clinical hurdles to breakthrough strategies, Drug Discov Today (2024), https://doi.org/10.1016/j.drudis.2024.103961 ●

Open Rights and Content ●

Highlights

- Integrates recent advances in CAR T-cell therapy for glioblastoma, including clinical trials, pharmacokinetic considerations.
- Evaluates the clinical progress of antigenspecific and allogeneic CAR T platforms in recurrent and newly diagnosed glioblastoma.
- Explores tumor-specific antigens and Boolean-logic gated CAR strategies to enhance tumor antigen recognition and improve specificity.
- Explores strategies to enhance CAR T trafficking, persistence, and function in the glioblastoma microenvironment.
- Proposes a translational roadmap for next-generation CAR T therapies to achieve durable responses in glioblastoma.

Graphical abstract

Current challenges and emerging strategies to enhance CAR T-cell therapy for glioblastoma (GBM).

Introduction

Glioblastoma (GBM) is the most common and aggressive type of primary brain tumor, characterized by rapid growth and aggressively invasive cells [1] and current out-of-date 5-year survival rates of less than 5% despite current multimodal treatment strategies. The World Health Organization classifies GBM as a grade 4 tumor, with median survival rates ranging from 12 months and 2 years [2] and a lifetime cumulative risk of tumor is characterized by rapid cell proliferation, extensive infiltration into surrounding neural tissue, and widespread genetic and epigenetic [3,4] heterogeneity. The heterogeneity of GBM is the primary cause of treatment failure, with genetic and epigenetic alterations [5] contributing to tumor growth and resistance to standard therapies. The tumor microenvironment (TME) is a complex ecosystem that supports tumor growth, immune evasion, and therapeutic resistance. The TME includes immunosuppressive cells, such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which promote tumor progression and immunosuppression [6,7], and physical barriers, such as the blood–brain barrier (BBB) and dense extracellular matrix, which limit the delivery of therapeutic agents [8,9]. Immunosuppressive cytokines and chemokines further contribute to the immunosuppressive nature of the TME, creating a challenging environment for GBM treatment.

Chimeric immunotherapy, which includes T(h) T-lymphocytes, natural killer (NK) cells, monocytes/macrophages, and dendritic cells, has emerged as a promising approach for GBM treatment. Engineered immune cells, such as chimeric antigen receptor (CAR) T cells, have been modified to recognize specific tumor-associated antigens, which enhances their ability to target and eliminate tumor cells. However, the efficacy of these therapies is limited by the presence of glioma stem like cells, and significant intratumoral antigenic heterogeneity. The standard treatment approach involves surgical resection, followed by radiotherapy and chemotherapy with temozolomide (TMZ), which has led to only a few in vivo improvements in survival outcomes [10]. This highlights the inherent resistance to conventional therapies and the need for more effective treatments. Recent advances in CAR T-cell therapy for hematological malignancies have shown promising results, with high complete remission rates observed in some patients [11,12]. However, the application of this technology to solid tumors, such as GBM, presents unique challenges, including antigen heterogeneity, a profoundly immunosuppressive TME, and the presence of the blood–brain barrier (BBB), which limits the delivery of therapeutic agents. Further, we discuss advanced CAR engineering innovations such as dual-antigen targeting, Boolean-logic gated (BLG) CAR architectures, and next-generation allogeneic CAR platforms, including induced pluripotent stem cell (iPSC)-derived CAR T-cell technologies among emerging strategies to overcome these challenges. We also explore strategies to enhance CAR T-cell trafficking, persistence, and functionality in the glioblastoma microenvironment.

Antigens and CAR T-cell therapy: the established foundation

CAR T-cell therapy: principles and evolution

Chimeric antigen receptors (CARs) are engineered, modular receptors that enable immune T cells with the ability to recognize and eliminate tumor cells via an antigen-specific manner [13]. As shown in Figure 1, the structure of CARs typically consists of an extracellular binding single-chain variable fragment (scFv) domain, a transmembrane domain, and intracellular signaling modules that activate T cell functions upon antigen recognition, including proliferation, cytokine production, and cytotoxicity. Reference.

Autologous CAR T-cell therapy: the established platform

Autologous CAR T-cell therapy is a novel approach to treat GBM, an aggressive glioma that has shown such a poor prognosis. Most patients survive only about 12 to 15 months, even with standard treatment combinations. The current standard of care for GBM includes surgical resection, followed by radiotherapy and chemotherapy with temozolomide (TMZ). This approach also addresses key challenges of heterogeneity and the presence of glioma stem like cells, which contribute to tumor recurrence. CAR T-cell therapy offers a promising alternative, with the potential to overcome these limitations and improve patient outcomes.

Allogeneic CAR T-cell therapy: toward off-the-shelf solutions

Allogeneic CAR T-cell therapy is an revolutionary leap in cancer immunotherapy that progresses from patient-specific autologous approaches to off-the-shelf solutions. This approach addresses key limitations of autologous CAR T-cell therapy, such as manufacturing challenges, delays in treatment initiation, and variability in patient response. The use of healthy donor cells in allogeneic CAR T-cell therapy offers several advantages, including the potential for more consistent and rapid manufacturing, enhanced quality control, and the ability to treat patients with urgent needs. However, this approach also introduces new challenges, such as the risk of graft-versus-host disease (GVHD) and the rapid clearance of allogeneic CAR T cells by host immune cells, which can limit their persistence and efficacy. To overcome these challenges, researchers are exploring various strategies, including gene editing to enhance the persistence and function of allogeneic CAR T cells, the use of immunosuppressive agents to prevent GVHD, and the development of novel delivery systems to improve the targeting and distribution of allogeneic CAR T cells to the tumor microenvironment. The ongoing research and development in this field aim to address these challenges and pave the way for more effective and accessible CAR T-cell therapies for patients with various cancers, including those with solid tumors like glioblastoma.

Antigens CAR T-cell therapy: the established foundation

Antigens for overcoming tumor challenges

Resistance pentosical research projects and clinical trials have concentrated on customized CAR constructs to enhance CAR T-cell tumor production, persistence, and combination treatments, including chemotherapy and immunotherapy. The ongoing research and development in this field aim to address these challenges, with the ultimate goal of developing more effective and accessible CAR T-cell therapies for patients with various cancers, including those with solid tumors like glioblastoma.

Future perspectives

Future CAR T-modalities for glioblastoma must overcome intrinsic immunosuppressive barriers, enhance tumor infiltration, and ensure durable responses. Promising approaches include dual-antigen targeting, armored CARs, and combinatorial strategies with chemotherapy, radiotherapy, and immunotherapy. Advances in manufacturing, standardization, and clinical applicability (iPSC, [111]), is likely to accelerate the translation of these therapies. Ongoing research and clinical trials will refine these strategies, as single-antigen targeting has shown promising results in preclinical studies.

Conclusions

Chimeric antigen receptor (CAR) T-cell therapy has shown promising results in preclinical studies, indicating their adaptive cellular immunotherapies can be administered to the central nervous system and induce immune responses. The results have shown promising results in preclinical studies, with the potential to overcome the immunosuppressive TME, restore immune function, and target tumor-specific and tumor-associated antigens.

CRediT authorship statement

Raja Kumar Sarma: Writing – original draft, Conceptualization. **Archagesh Mallu:** Visualization, Supervision, Conceptualization. **Rangaprasad Sharma:** Writing – review & editing, Validation. **Ajit Singh:** Writing – review & editing, Validation.

Clinical trial number

Not applicable.

Ethics approval

The article did not involve any human or animal subjects.

Funding

No funding was received to assist with the preparation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to acknowledge Administration and management of NETAS Group of Institutions for their moral support.

References [SU]

1. et al.
Glioblastoma CD70+ cells define a SOX2- cancer stem cell-independent tumorigenic hierarchy
Nature Neuroscience (2024)

2. et al.
From concept to cure: the evolution of CAR T-cell therapy
Mol Ther (2022)

3. et al.
Design of dimerbased chimeric antigen receptors through genomic screens identifies potent CAR T cell signaling
Nature Biotechnology (2024)

4. et al.
Design and engineering of logic gravity receptors: gates based on the activity of the human CPEB3 ribozyme in mammalian cells
Nature Biotechnology (2024)

5. et al.
CAR T-cell therapy for glioblastoma: a review of the first decade of clinical trials
Neuro Oncol (2024)

6. et al.
CAR T-cell therapies are coming after glioblastoma: an overview of ongoing phase clinical trials and future perspectives
Cancers (2024)

7. et al.
Glioblastoma: pathogenesis and immunotherapy
Mol Ther Oncol (2024)

8. et al.
Advances in CAR T cell therapy for recurrent glioblastoma: current clinical experience demonstrating feasibility and safety
J Neurosurg Pediatr (2024)

9. et al.
Immune cell therapy: advances in digestive system malignant tumors
Mol Ther (2024)

10. et al.
Overcoming immunosuppressive barriers and resistance to CAR T therapy in glioblastoma
Nat Commun (2024)

11. et al.
Dual-antigen-targeted extracellular vesicles CD133 / EGFRvIII-loaded CAR T cells for enhanced antigen recognition and tumor clearance
Mol Ther (2024)

12. et al.
Multivalent and bioorthogonally S-1,3-Glucan and EphA2 for enhanced glioblastoma CAR therapy
Adv Mater (2024)

13. et al.
Chimeric antigen receptor T cell therapy for recurrent glioblastoma: current status and future directions
Cancers (2024)

14. et al.
Chimeric antigen receptor T-cell therapy in solid tumors: challenges and clinical applications
Front Immunol (2023)

15. et al.
Allogeneic CAR T therapy technologies: but the promise remains
Cell Stem Cell (2024)

16. et al.
Recent updates on allogeneic CAR T cells in hematopoietic malignancies
Front Immunol (2024)

17. et al.
Reverse advances in autologous chimeric antigen receptor T cell therapy
Cancer Biol Med (2024)

18. Sarki D, Mustafa A, Ka-Lorenzo C, Ismail A, Ahmed N, Ahmed A, Ahmed N, Gottschalk S.
Co-targeting but all important: how the folate, hexose, and mannose receptors contribute to the CAR fitness of glioblastoma

Sarki D, Mustafa A, Ka-Lorenzo C, Ismail A, Ahmed N, Ahmed A, Ahmed N, Gottschalk S.

Front. Immunol. (2025)

S. Majumdar *et al.*
The impact of CD3ζ ITAM multiplicity and sequence on CAR T-cell survival and function
Front. Immunol. (2024)

P. Gonzalez-Garcia *et al.*
Discordant CAR-T cell signaling: implications of divergence from physiological T cell activation
J. Transl. Med. (2025)

H. Kang *et al.*
Logical regulation of endogenous gene expression using programmable, multi-input processing CRISPR guide RNAs
Nucleic Acids Res. (2024)

M. Zhao *et al.*
Construction of multilayered gene circuits using de-novo-designed synthetic transcriptional regulators in cell-free systems
J. Biol. Eng. (2024)

S. Sundar
CAR T-cell therapies: a comparison of strategies for glioblastoma multiforme treatment
J. High Sch. Sci. (2025)

D. Zhou *et al.*
Advances in CAR-T therapy for central nervous system tumors
Biomark. Res. (2024)

M. Hamieh *et al.*
Programming CAR T cell tumor recognition: tuned antigen sensing and logic gating
Cancer Discov. (2023)

A. Majumder
Evolving CAR-T-cell therapy for cancer treatment: from scientific discovery to cures
Cancers (Basel) (2023)

S.V. Belokon *et al.*
A critical review of CAR-T therapies for glioblastoma: what's wrong with the current attempts?
Hematol. Oncol. Stem Cell Ther. (2025)

G. Dagar *et al.*
Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments
J. Transl. Med. (2023)

S.J. Bagley *et al.*
Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results
Nat. Med. (2024)

C.E. Brown *et al.*
Bioactivity and safety of IL13Rα2-redirected chimeric antigen receptor CD8+ T cells in patients with recurrent glioblastoma
(2016)

D.M.O. Rourke *et al.*
A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma
(2017)

K. Qian *et al.*
CAR-T cell products in solid tumors: progress, challenges, and strategies
(2024)

S.L. Goff *et al.*
Pilot trial of adoptive transfer of chimeric antigen receptor transduced T cells targeting EGFRvIII in patients with glioblastoma
(2020)

C.E. Brown *et al.*
Off-the-shelf, steroid-resistant, IL13Rα2-specific CAR T cells for treatment of glioblastoma
Neuro-Oncology (2022)

H. Miao *et al.*
EGFRvIII-specific chimeric antigen receptor T cells migrate to and kill tumor deposits infiltrating the brain parenchyma in an invasive xenograft model of glioblastoma
(2014)

C.E. Brown *et al.*
Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial
Nat. Med. (2024)

There are more references available in the full text version of this article.

Cited by (0)

View full text

© 2026 Elsevier B.V. All rights are reserved, including those for text and data mining, AI
© 2026 Elsevier B.V. All rights are reserved, including those for text and data mining, AI
training, and similar technologies.

ELSEVIER

About ScienceDirect ↗ Remote access Contact and support ↗
Terms and conditions ↗ Privacy policy ↗ Cookie settings

RELX™

All content on this site: Copyright © 2026 Elsevier B.V., its licensors, and contributors. All rights are reserved, including those for text and data mining, AI training, and similar technologies. For all open access content, the relevant licensing terms apply.

FEEDBACK