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Enhancing T cell infiltration in glioblastoma: a review article on challenges and therapeutic strategies

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ABSTRACT

This review focuses on enhancing T-cell infiltration in glioblastoma (GBM) while overcoming its immunosuppressive tumor microenvironment (TME). Key strategies include targeting myeloid-derived suppressor cells (MDSCs) to reduce immunosuppression and repolarizing tumor-associated macrophages (TAMs) from an M2 (immunosuppressive) phenotype to an M1 (proinflammatory) phenotype to increase T-cell function. Administering chemokines can help attract more effector T cells to the tumor site. Combining immune checkpoint inhibitors (ICIs) with other treatments can further increase T cell activity. To make immunotherapy more effective in GBM, it is also essential to address the immunosuppressive signals in the TME, such as transforming growth factor beta (TGF-β) and interleukin-10 (IL-10).

Abbreviations

Ang-2	Angiopoietin-2
APCs	Antigenpresenting cells
BBB	Bloodbrain barrier
BTB	Bloodtumor barrier
CAR	Chimeric antigen receptor
CNS	Central nervous system
CSF	Colony-stimulating factor
CTLs	Cytotoxic T lymphocytes

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CXCR	C-X-C chemokine receptor
DC	Dendritic cell
ECM	Extracellular matrix
FUS	Focused ultrasound
GBM	Glioblastoma
HA	Hyaluronic acid
HCC	Hepatocellular carcinoma
HIFs	Hypoxia-inducible factors
ICAM-1	Intercellular adhesion molecule-1
ICIs	Immune checkpoint inhibitors
IDO	Indoleamine 2,3-dioxygenase
IL	Interleukin
RT	Radiotherapy
LNCs	Lipid nanocapsules
MDSCs	myeloid-derived suppressor cells
MPI	Magnetic particle imaging
NK	Natural killer
NPs	Inorganic nanoparticles
PFS	Progression-free survival
TAAs	Tumor-associated antigens
TAMCs	Tumor-associated myeloid cells
TAMs	Tumor-associated macrophages
TGF-ß	Transforming growth factor beta
TMB	Tumor mutational burden
TME	Tumor microenvironment
TMZ	Temozolomide
TNBC	Triple-negative breast cancer
Tregs	Regulatory T cells
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VSTs	Virus-specific T lymphocytes

1. Introduction

GBM is the most common primary malignant brain tumor in adults [1]. According to the 2021 World Health Organization classification, it is considered a grade 4 astrocytic glioma of the IDH-wild type [2,3]. Despite extensive research, survival rates for GBM remain poor, making it one of the most challenging cancers to treat [4]. Current treatment typically involves a multimodal approach that includes surgery, chemotherapy, radiation therapy, and immunotherapy. Cancer immunotherapy is a treatment methods that helps the immune system detect and destroy abnormal cells. ICIs, T-cell transfer therapy, monoclonal antibodies, treatment vaccines, and immune system modulators are the main types of immunotherapies. T-cell transfer refers to ways that increase the natural ability of host T cells to fight cancer [5]. T cells are essential in cancer immunotherapy because of their central role in antitumor immunity. T cells generally recognize tumor-specific antigens presented by APCs through the major histocompatibility complex (MHC). Two key types of T cells are involved in cancer immunity: CD8+ *T* cells, which directly kill tumor cells by releasing cytotoxic granules and inducing apoptosis, and CD4+ *T* cells, which support CD8+ *T*-cell activation and maturation while producing cytokines that activate other immune cells [6]. Tumors often escape the immune system by shaping a suppressive microenvironment [7].

Bas et al. [8] found that lower CXI levels were linked to shorter survival times both overall and in terms of progression-free survival (PFS) across various types of cancer. This suggests that CXI could be an important marker for identifying patients who are at higher risk and may need more focused treatment strategies. Sahin et al. [9] analyzed the Neutrophil-to-Eosinophil Ratio (NER) across several cancer types and found that higher NER levels were strongly linked to worse survival outcomes. Specifically, patients with elevated NER had a significantly higher risk of both death and disease progression. These findings suggest that NER could be an important and easy-to-measure biomarker to help physicians identify patients who are at higher risk and may need more treatment options. Vitale et al. [10] explored the connections between cancer risk, inflammation, and metabolic syndrome. They found that individuals with metabolic syndrome often experience low-grade, chronic inflammation, which can contribute to the development and progression of several types of cancer, including breast, colorectal, and liver cancer. These findings highlight the need to focus on managing metabolic syndrome and inflammation as part of cancer prevention strategies.

Immunotherapies, such as ICIs and adoptive T-cell therapies, are designed to restore or strengthen T-cell activity and improve the immune system's ability to fight cancer [11]. T-cell infiltration patterns in GBM clearly depend on the MGMT methylation status, which subsequently influences the therapeutic response to temozolomide (TMZ). Specifically, tumors with methylated MGMT, characterized by compromised DNA repair and heightened sensitivity to TMZ, show different patterns of lymphocyte infiltration compared to tumors with unmethylated MGMT. Immunotherapy has brought new hope for treating hepatocellular carcinoma (HCC), the most common type of liver cancer. ICIs, such as anti-PD-1 and anti-CTLA-4 therapies, have shown promising results in clinical trials, especially for advanced stages of HCC. However, many patients still experience limited or no response to these treatments. Factors like the liver's unique immune environment and the complexity of HCC itself contribute to this challenge. To overcome these barriers, researchers are testing combination treatments, such as pairing ICIs with targeted therapies, local treatments, or new agents like cancer vaccines. Personalized approaches and the identification of biomarkers to better predict who will respond to immunotherapy are also key areas of focus [12].

The link between MGMT methylation status and immune cell infiltration in GBM is still debated. Some studies report that unmethylated MGMT is associated with greater T cell infiltration, while others suggest that these tumors develop a more immunosuppressive microenvironment and respond less effectively to immunotherapy. These conflicting findings point to the complex interplay between MGMT status, DNA repair processes, and immune responses in GBM, underscoring the need for further research to better understand these relationships [13–18]. The heterogeneity of findings may present the multifaceted role of MGMT in tumor biology beyond its role in DNA repair, including potential effects on immunogenicity and the TME composition.

T-cell infiltration in central nervous system (CNS) cancers like GBM is particularly challenging because the CNS is an immune-privileged site. The blood–brain barrier (BBB) limits the entry of immune cells, making it difficult for T cells to penetrate and target brain tumors [19]. GBM exacerbates this effect by creating an immunosuppressive TME filled with regulatory T cells (Tregs), MDSCs, and immune checkpoint molecules such as PD-L1, which inhibit T-cell function. T cell exhaustion further weakens the body's immune response [20–22]. In the CNS, T cell activation is also hampered because antigen presentation is limited largely due to poor dendritic cell (DC) function and the absence of chemokine signals needed to attract T cells. Overcoming these barriers is critical for improving T cell based immunotherapies [22]. Promising strategies include targeting myeloid-derived suppressor cells (MDSCs) to reduce immunosuppression and reprogramming tumor-associated macrophages (TAMs) from an M2 (immunosuppressive) phenotype to an M1 (proinflammatory), thereby enhancing T cell function [23,24]. Additional approaches, such as administering chemokines to draw more effector T cells into the tumor and combining ICIs with other therapies, can further increase anti-tumor T cell activity [25,26]. Addressing the immunosuppressive factors in the TME, such as TGF-β and IL-10, is crucial for improving the effectiveness of immunotherapies in GBM [26,27]. Recent clinical trials, including KEYNOTE-522, IMpassion031, and GeparNUEVO, have changed the way we approach early-stage triple--negative breast cancer (TNBC) [28]. These trials explored combining ICIs with chemotherapy to improve treatment outcomes. In KEYNOTE-522, adding pembrolizumab to chemotherapy not only increased the rate of complete tumor response but also improved

survival, leading to its approval for use in high-risk early TNBC. Similarly, IMpassion031 showed that atezolizumab increased the tumor response when used with chemotherapy, although the long-term survival benefits are still being studied. The GeparNUEVO trial, while showing a small improvement in tumor response, demonstrated better long-term outcomes when adding durvalumab to chemotherapy. These trials highlight the growing role of ICIs in treating early TNBC, though further research is needed to refine how to choose the best treatments for different patients. This review focuses on enhancing T cell infiltration in GBM while overcoming its immunosuppressive TME.

2. BBB and GBM

2.1. Structure and function of the BBB

The BBB is a selective structure within the neurovascular unit that controls the movement of molecules between the bloodstream and the brain, helping maintain CNS homeostasis [29]. Made up of endothelial cells, astrocytes, and pericytes, the BBB protects the brain by blocking harmful substances and pathogens while still allowing the passage of essential nutrients [30,31]. Although this barrier is critical for normal CNS function, its altered permeability in GBM complicates drug delivery and limits T cell infiltration, posing a major challenge for effective treatment [29].

2.2. Alterations in the BBB in GBM

GBM profoundly disrupts the blood–brain barrier (BBB), causing it to become more permeable and less selective, especially in tumor-dense regions where vasogenic edema develops [32,33]. Tumor cells release factors such as vascular endothelial growth factor (VEGF), which drive angiogenesis and weaken the tight junctions between endothelial cells, leading to the formation of a leaky blood–tumor barrier (BTB) [34]. Dysfunction in pericytes and astrocytes further increases vascular permeability, enabling the influx of nutrients and growth factors that fuel tumor progression [29]. This remodeling is illustrated in Fig. 1.

While BBB disruption can enhance the delivery of some chemotherapeutics, the heterogeneous nature of the BTB and increased interstitial pressure limit drug penetration, especially for larger molecules such as antibodies [33]. Importantly, this disrupted environment limits effective T cell infiltration. While TAMs and microglia are present in large numbers, they often adopt a protumor phenotype that suppresses antitumor immune activity [35]. These obstacles to immune cell entry, combined with the tumor's ability to evade detection, underscore the need for strategies that enhance T cell access and function within the GBM microenvironment [5,32,35–37]. Table 1 provides an overview of the BBB alterations caused by GBM.

2.3. Impact of the BBB on T cell infiltration

Although the BBB is partially disrupted in GBM, the tumors still use multiple strategies to limit T cell infiltration [37]. They secrete immunosuppressive cytokines such as TGF-β and IL-10 and reduce the expression of endothelial adhesion molecules like ICAM-1 and VCAM-1, which are critical for T cell migration [5,37]. As a result, many circulating T cells are unable to cross into the tumor because of this altered endothelial environment. The GBM TME, a dynamic mix of cells and factors, is a critical therapeutic target, though its heterogeneity presents challenges. Notably, GBM TME lacks fibroblasts, unlike other tumors. Understanding each patient's unique TME is crucial for effective targeting, as its immune components contribute to tumor progression [38,39]. Targeting chemokines, which influence tumor angiogenesis, stemness, proliferation, and survival, offers a promising approach to enhance antitumor immunity, particularly given the overexpression of chemokine receptors like C-X-C chemokine receptor (CXCR)1, CXCR2, CXCR4, and CCR5 in GBM, melanoma, and breast tumor growth and metastasis

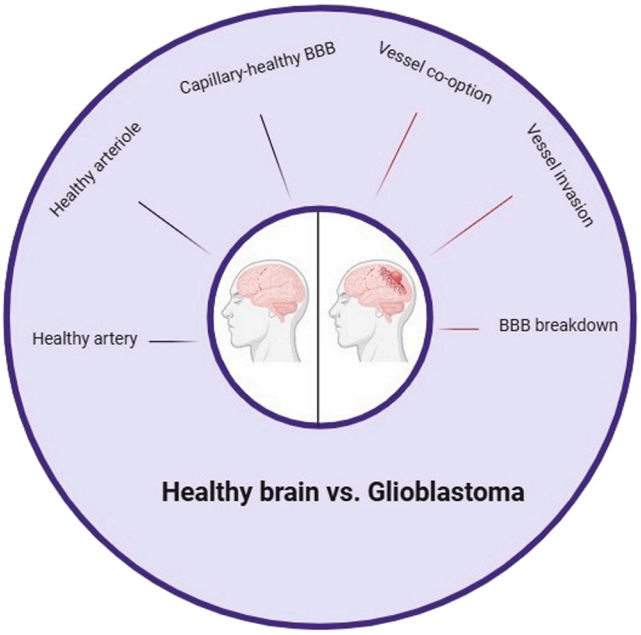


Fig. 1. Vascular and cellular changes in a healthy brain versus a GBM-affected brain.
The schematic compares a healthy brain with a brain affected by GBM, emphasizing vascular and cellular alterations. The healthy brain illustrates intact vascular structures: a healthy artery, arteriole, and capillary with a functional BBB. The GBM-affected brain depicts a tumor mass and progressive vascular changes [1]: vessel co-option, with cancer cells clustering around existing vessels [2]; vessel invasion, where cancer cells penetrate the vessel wall; and [3] BBB breakdown, showing a disrupted endothelial layer and tumor cell infiltration into surrounding tissue.

Table 1
Key mechanisms of BBB alterations in glioblastoma.

Mechanism	Alteration	Impact on drug delivery	Impact on immune cell infiltration
VEGF secretion	Disruption of endothelial tight junctions	Increases drug delivery to tumor regions with permeability	Allows limited immune cell entry but mostly supports immunosuppressive cells
Loss of pericytes	Weakens blood vessel stability	Results in heterogeneous permeability, with some areas poorly accessible	Limits effective T cell trafficking and adhesion
Decreased ICAM-1/VCAM-1 expression	Reduced T cell adhesion to endothelial cells	Limited penetration of immune checkpoint inhibitors and large molecules	Prevents T cells from transmigrating across the BBB
Immunosuppressive cytokine secretion	Secretion of TGF-β and IL-10	Minimal effect on drug delivery	Suppresses effector T cell migration into the tumor environment
Angiogenesis and abnormal vasculature	Formation of leaky and abnormal blood vessels (BTB)	Allows delivery of certain small molecule drugs, but regions are heterogeneous	Supports entry of TAMs and Tregs, with reduced infiltration of effector T cells

[40].

2.4. Pathologic mechanisms of the effects of the GBM on BBB permeability

GBM actively alters the BBB to create a supportive microenvironment and avoid immune detection. By upregulating VEGF, it disrupts endothelial tight junctions, leading to a leaky BTB that delivers nutrients and growth factors to fuel tumor growth [37,41]. Additionally, a variety of studies have demonstrated that the GBM can modulate the expression of chemokines and their receptors to influence the recruitment of specific immune cells [42–45]. While this may allow some immune cells, such as TAMs and Tregs, to infiltrate the tumor, these cells are often skewed toward an immunosuppressive phenotype. GBM-derived factors, including prostaglandin E2 and indoleamine 2,3-dioxygenase (IDO), further suppress effector T cell function and promote an immune-tolerant environment [42–46]. This creates a paradoxical environment, that is permissive to protumor immune cells but resistant to antitumor T cells. Overcoming these barriers is crucial for enhancing T cell infiltration [36]. Invasive and noninvasive therapeutic approaches are continuously being developed to improve drug delivery systems [36, 37].

Nanotherapies and nonionizing energies in GBM therapy are among the latest advancements to overcome the BBB. Numerous studies have discovered various nanostructures, including carbon dots, inorganic nanoparticles (NPs), polymeric NPs, nanogels, etc., containing active anti-GBM agents such as immune cells, antiangiogenic drugs, and chemosensitizers to facilitate opening of the BBB [47–51]. Deng K et al. designed paclitaxel-derived carbon dots that effectively penetrate the BBB and induce ferroptosis in GBM cells [52]. Zhang et al. created biomimetic nanogels that, upon near-infrared irradiation, disintegrated to release temozolomide and indocyanine green, enabling controlled BBB permeation and deep tumor drug penetration; this approach significantly suppressed orthotopic GBM growth and extended survival in mice [53]. Kuang et al. employed monocyte-hitchhiking liposomal nanoparticles combined with low-dose radiation to improve drug delivery to GBM: the nanoparticles “hitchhike” circulating monocytes recruited by radiation, then release doxorubicin within the tumor, triggering immunogenic cell death. This approach reprogrammed the tumor microenvironment by polarizing TAMs to the M1 phenotype, enhancing dendritic cell maturation and T cell activation [54]. Enhancing BBB permeability in a controlled manner, while simultaneously promoting T cell entry and function, is critical for improving outcomes in GBM immunotherapy.

3. T cell trafficking to the CNS

3.1. Adhesion molecules and chemokines involved

T cell entry into the CNS parenchyma involves two steps: transmigration across the BBB into the perivascular space, and passage through the glia limitans into the parenchyma [55]. BBB endothelial cell activation leads to increased expression of adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and selectins (E- and P-selectin), facilitating initial T cell attachment and rolling [56].

Circulating T cells express integrins (LFA-1, VLA-4) that mediate strong adhesion and arrest on the endothelium. Chemokines (CCL19, CCL21, CXCL12) guide T cell movement through chemotactic signaling, enhancing integrin activation and diapedesis [57]. After T cells crosse the BBB and entere the perivascular region, they use matrix metalloproteinases to disrupt the glia limitans and enter brain tissue [58].

3.2. Differences in T cell trafficking in GBM

Tregs are found within the GBM parenchyma, where they exert immunosuppressive effects and are thought to suppress protective antitumor immune responses in various solid cancers [59,60]. In GBM, tumor cells release lipid factors such as CCL22, which help recruit and retain Tregs within the TME [61,62]. These cells create an immunosuppressive microenvironment that actively excludes cytotoxic T cells [62].

Endothelial cells in the GBM BBB exhibit reduced expression of adhesion molecules (ICAM-1, and VCAM-1), hindering T cell adhesion and migration [63,64]. These changes decrease T cell entry into the tumor, contributing to immune evasion by the cancer.

Upregulation of immune checkpoint molecules such as PD-L1 on tumor and stromal cells further inhibits T cell migration and function. T cell activation is suppressed by these checkpoint interactions, which reduce T cell trafficking to the tumor location [65,66].

GBMs overexpress extracellular matrix (ECM) components, such as collagen and hyaluronic acid (HA), form physical barriers, entrap immune cells, and impair immune surveillance [67]. Reduced T cell infiltration was observed in tumor regions of human and mouse GBMs with high levels of HA, compared with tumor regions with low levels of HA [68]. On the other hand, high concentrations of ECM components might reduce tumor access to nutrients and oxygen, resulting in hypoxia and metabolic stress in the tumor and further inhibition of T cell migration [69,70].

The vascular structure of glioma is noticeably abnormal due to angiogenesis, which results in a defective vasculature that is leaky, irregular, and poorly perfused [71,72]. Its aberrant vasculature prevents T cells from efficiently entering the tumor [73,74]. Moreover, it causes an increase in tumor hypoxia and a decrease in the effectiveness of chemotherapy [74].

In addition, aberrant blood vessels in gliomas form a vascular niche home to cells known as glioma stem cells, which constitute a tiny portion of the tumor but are thought to be a source of treatment resistance [75]. Moreover, GBM cells may secrete chemokines that preferentially attract immunosuppressive cells (e.g., CCL2 and CXCL8 recruiting myeloid cells) rather than effector T cells. This mismatch of chemokine signals contributes to poor T cell trafficking into tumors [76]. Targeting these pathways is a promising strategy, for example, enhancing T cell–endothelium adhesion or providing missing chemokine gradients can improve T cell homing to the GBM. Preclinical studies have shown that overexpressing the appropriate chemokine receptors on T cells significantly increases their tumor entry. CAR-T cells engineered to express CCR2 (a receptor for CCL2, a chemokine that GBM often produces) displayed enhanced accumulation and antitumor efficacy in GBM models with high CCL2 levels [77]. In some studies of malignant pleural mesothelioma and lung carcinoma (which also express CCL2), CCR2-transduced CAR-T cells infiltrated tumors more efficiently and even completely eradicated established lesions, whereas CCR2-negative T cells did not [78,79]. Similarly, arming T cells with receptors for CXCL8 (IL-8), namely CXCR1 or CXCR2 can improve their trafficking into solid tumors. CXCR1/2-engineered T cells were shown to penetrate tumors more deeply, an effect that was further amplified when local radiation was applied to induce IL-8 release from tumor cells [77]. These findings highlight the need to align T cell chemokine responsiveness with the tumor’s chemokine profile in order to overcome barriers to their migration.

4. GBM microenvironment and T cell exclusion

4.1. Immunosuppressive factors in GBM

A major challenge in GBM treatment is the ability of tumors to evade the immune system, particularly by excluding T cells from the TME. The GBM microenvironment is a highly complex and dynamic system made up of diverse cells, soluble factors, physical barriers, and metabolic conditions that work together to suppress immune activity, ultimately supporting tumor growth and survival [7,80,81]. It is particularly

enriched with immunosuppressive cells and molecules that inhibit cytotoxic T lymphocytes (CTLs), which play a central role in eliminating tumors [82,83]. Among these, TAMs, mainly of the M2 phenotype in GBM, are major contributors to this immunosuppressive state. These cells secrete anti-inflammatory cytokines such as IL-10 and TGF-β, impairing CTL and natural killer (NK) cell functions. Additionally, TAMs express PD-L1, which engages PD-1 on T cells, leading to T cell exhaustion and reduced antitumor activity [84].

MDSCs significantly contribute to the immunosuppressive GBM microenvironment [67]. These immature myeloid cells, which accumulate in response to tumor signals, inhibit T cell activation and expansion by releasing immunosuppressive cytokines (IL-10), reactive oxygen species, and nitric oxide. MDSCs also promote Treg proliferation and increase the production of immunosuppressive molecules, further dampening the antitumor immune response [85].

Tregs, a subset of CD4+ *T* cells, maintain immune tolerance and prevent autoimmunity. In the GBM microenvironment, Tregs are activated and expanded, exerting potent immunosuppressive effects [78]. They suppress effector T cell function through IL-10 and TGF-β release, and CTLA-4 expression. Increased Tregs in the GBM microenvironment are associated with poorer prognosis, as they impair antitumor immunity and promote tumor growth [86].

The microenvironment of GBM contains an increased number of immunosuppressive cytokines, notably TGF-β and IL-10. TGF-β is a potent cytokine that plays an essential role in promoting the formation of tumors and evading the immune system. Within GBM, TGF-β inhibits the proliferation and destructive capabilities of T and NK cells, induces the proliferation of Tregs, and promotes M2 TAMs. IL-10, a highly effective cytokine that suppresses the immune system, is produced mainly by TAMs and Tregs in the microenvironment of GBM. IL-10 inhibits the production of proinflammatory cytokines by effector T cells and DCs, leading to impaired antigen presentation and restricted T cell activation. Increased levels of TGF-β and IL-10 in GBM are essential in suppressing the immune response towards tumors and eradicating T cells from the tumor site [87,88].

Immune checkpoint molecules, such as PD-L1, are also exploited by GBM to evade immune detection. PD-L1, which is present on tumor cells and immune cells such as TAMs and MDSCs, interacts with the PD-1 receptor on T cells, suppressing T cell proliferation, cytokine generation, and cytotoxicity. This contact effectively inhibits the T cells, preventing them from initiating an attack on the tumor. Upregulation of PD-L1 in GBM contributes to an immunosuppressive environment. In addition to these soluble factors, physical barriers within the GBM microenvironment hinder T cell access to the tumor, limiting the effectiveness of immunotherapies [89,90]. Addressing these factors is key to improving immunotherapy. For example, Ravi et al. reported that a subset of GBM-infiltrating myeloid cells that release IL-10 can drive profound T cell dysfunction; blocking the IL-10/JAK-STAT pathway helped restore T cell activity in a preclinical model [91]. Similarly, TGF-β in the GBM milieu is known to inhibit T cell proliferation and effector functions, and strategies to neutralize TGF-β or its signaling can reinvigorate T cell responses [92].

4.2. Physical barriers

The GBM tumor vasculature is highly abnormal, and characterized by inconsistent structure and leakiness, leading to irregular blood flow and tumor hypoxia. This not only promotes the growth of the tumor, but also inhibits the access of immune cells and therapeutic agents to the central region of the tumor. Endothelial cells covering these blood arteries typically exhibit elevated immune molecules, including PD-L1 and FasL. These molecules can trigger apoptosis in T cells that infiltrate the tumor, consequently contributing to their elimination from the TME [93].

GBM tumors exhibit increased interstitial pressure and a dense ECM, both of which serve as physical barriers to the infiltration of immune cells. Rapid tumor growth and the formation of leaky arteries result in increased interstitial pressure, inducing fluid accumulation in the tumor tissue. A high pressure level compresses the blood arteries, limiting the movement of immune cells within the tumor tissue. Furthermore, the ECM in GBM comprises significant amounts of proteins, including collagen and fibronectin, resulting in the formation of a tight and inflexible microenvironment. The dense ECM functions as a physical challenge, obstructing the infiltration of T cells and other immune cells into the central region of the tumor. The concurrent elevation of interstitial pressure and the presence of a dense ECM play key roles in facilitating immune evasion in GBM [94,95].

4.3. Metabolic barriers

The metabolic microenvironment of GBM also has a significant effect on the initiation of the immune response and the eradication of T cells. The TME exhibits substantial metabolic alterations that facilitate tumor expansion and viability, while generating adverse conditions for immune cells [96].

Hypoxia, which is generally related to a lack of oxygen, is a distinctive characteristic of the GBM microenvironment resulting from the presence of aberrant tumor blood vessels and the rapid growth of the tumor. Hypoxia significantly impacts both tumor cells and immune cells. Tumor cells respond to low-oxygen conditions by increasing the expression of hypoxia-inducible factors (HIFs) that stimulate the growth of new blood vessels, alter metabolic processes, and evade the immune system [97]. In addition, hypoxia enhances the expression of PD-L1 on both tumor cells and immunological cells, thereby contributing to the exhaustion of T lymphocytes. Recent studies have indicated that hypoxia significantly contributes to T cell exhaustion and is a main challenge in the immunotherapy of solid tumors. T cell exhaustion and loss of mitochondrial mass have been reported in nasopharyngeal carcinoma [98,99]. Liu et al. [100], reported a high abundance of exhausted T cells and B cells in both GBM and lower-grade glioma in a high-HIF1A expressing group. Xun et al. [101] reported the role of hypoxia in immunotherapy resistance through $ALCAM^{high}$ macrophage-exhausted T cells. Furthermore, hypoxia inhibits the activity of cytotoxic T cells and enhances their attraction and stimulation of immunosuppressive cells such as TAMs, MDSCs, and Tregs. The presence of low levels of oxygen in the GBM microenvironment disrupts metabolic processes and interferes with the body's immune reaction to the tumor, allowing it to escape the immune system [102]. Targeting metabolic barriers such as low glucose levels, a low pH, hypoxia, and the generation of suppressive metabolites has been introduced as a promising therapeutic strategy for different types of cancer. It has been reported that targeting metabolic barriers of immune responses in the TME in combination with other therapeutic strategies could increase response rates. Various studies support that reversing hypoxia-induced resistance can increase the efficacy of immunotherapy in curing cancer [103–105].

GBM cells undergo metabolic reprogramming to facilitate their rapid proliferation and survival, frequently to the disadvantage of surrounding immune cells. The "Warburg effect" where GBM cells rely on glycolysis even under aerobic conditions, leads to increased glucose consumption and nutrient scarcity in T cells. Glycolysis also results in the production of lactate, acidifying the TME and impairing T cell function while promoting immunosuppressive cell activity [106]. Furthermore, GBM cells release enzymes such as IDO, which deplete tryptophan, an essential amino acid for T cell function. Nutrient competition and metabolic alterations create a hostile environment for T cells, contributing to their exclusion and immune suppression [107].

The complex immunosuppressive GBM microenvironment, which involves cellular, soluble, physical, and metabolic factors, hinders antitumor immune responses. Understanding these processes is crucial for developing effective immunotherapies to overcome GBM immune evasion and improve patient outcomes. Immunosuppressive therapies are essential in this area of research.

5. Strategies to enhance T cell infiltration in GBM

5.1. Modifying the BBB

Focused ultrasound (FUS) is a promising noninvasive therapeutic approach that uses focused, high-energy ultrasound beams in a selected region. The application of FUS for antitumor purposes is based on the thermal ablation of targeted lesions to induce an immune response by producing mild heat in the lesions [108,109]. Another mechanism, called acoustic cavitation, disrupts the BBB through mechanical lysis of the tissue by applying acoustic pressure, causing microbubbles to expand and contract rapidly. This generates permeable spaces in the BBB through the collapse of the cellular structure, leading to BBB disruption [110]. By activating inflammatory pathways, FUS upregulates adhesion molecules such as P-selectin and ICAM-1, effectively promoting immune cell extravasation into the TME [111]. Furthermore, FUS-mediated transient BBB opening enhances the delivery of critical ICIs, such as PD-1, increasing drug concentrations at the tumor site [112]. This opening also facilitates the migration and infiltration of immune cells, notably CD8+ *T* cells, leading to improved antitumor responses. Additionally, FUS modulates the secretion of chemokines such as CXCL10 and cytokines such as IL-2, recruiting and activating immune cells within the TME [113]. Finally, FUS plays a role in shifting TAMs from an immunosuppressive state to a proinflammatory state, further enhancing the antitumor immune response [114]. FUS brain tumor immunotherapy is limited by the need for precise ultrasound control to avoid off-target effects, variability in BBB opening, and the lack of long-term safety data. The risks of tissue damage and edema require careful monitoring [115].

Osmotic disruption of the BBB involves the infusion of hyperosmolar agents (e.g., mannitol) into cerebral vessels to cause reversible dehydration of endothelial cells, subsequently leading to disruption of the integrity of the tight junctions between them [116]. Osmotic disruption has shown promising results in increasing the concentration of chemotherapeutic agents used to treat CNS lymphoma [117], GBM [118], metastatic and primary brain tumors, and oligodendrogliomas [119].

Various transport mechanisms are designed to transport therapeutics such as drugs or cells across the BBB. Liposomes, solid lipid nanoparticles, albumin nanoparticles, and polymeric nanoparticles are the most common nanocarriers developed for this purpose. In particular, liposomal nanoparticles enhance immunogenic cell death, T-cell activation, the M1-type response, and DC maturation [54,120–122]. Conjugated chimeric antigen receptor (CAR) T cells and pexidartinib-containing liposomes have been linked to enhanced T cell migration through the BBB and intensified antitumor function in mouse models of GBM [54,119–123]. Furthermore, the administration of angiopep-2 and IP10-EGFRvIII scFv fusion protein-modified nanoparticles, cationic lipid nanoparticles, and phosphorus dendrimer nanocomplexes resulted in increased infiltration of endogenous T cells in the GBM [54,121–127].

5.2. Enhancing T cell trafficking

To address the challenges depicted in Fig. 2, another approach for enhancing the migration of CAR-T cells across the BBB involves engineering CAR-T cells that express specific molecules. Activated leukocyte cell adhesion molecule (ALCAM/CD166) is a member of the immunoglobulin superfamily, that mediates cell-cell interactions. Higher expression of ALCAM in HTLV-1 infected T cells facilitates T cell homing to the CNS, and ALCAM blockade significantly reduces the migration of T cells through the BBB [128]. The upregulation of ALCAM could be a promising therapeutic approach to assist the diapedesis of lymphocytes across the BBB [129,130]. Engineered CAR-T cells expressing CXCR3 and CXCR4, which bind to several chemokine ligands, could effectively enhance T-cell migration [131]. Fig. 3 illustrates the generational advancements in CAR-T cell designs. Targeting the IL-13 receptor alpha 2 receptor, which is overexpressed by GBM cells, has been shown to be effective in increasing T-cell homing in GBM patients in a phase I clinical trial accompanied by promising efficacy results [132]. Furthermore, GBM cells overexpress mutant epidermal growth factor receptor variant III (EGFRvIII). Engineered CAR-T cells targeting EGFRvIII are potential therapeutic options that are under evaluation in several clinical trials (e.g., NCT03283631, NCT02664363, NCT02209376, and NCT03726515) [133]. The development and validation of these CAR-T cells involve a multistep process, as illustrated in Fig. 4.

Inflammatory cytokines increase the expression of adhesion molecules that facilitate the migration of T cells. Increased colony-stimulating factor (CSF) levels of chemokines under inflammatory conditions increase T cell trafficking through the choroid plexus. Abluminal inflammatory chemokines, including those in the CCL2-CCR4/CCR and CCL5-CCR5 axes, stimulate the diapedesis of T cells through tricellular junctions and play essential role in the recruitment of T cells in GBM [134–136]. The T cell migration peak occurs at 100 ng/ml CCL5 and CCL2 [134]. Upregulation of CCL20 in the choroidal epithelium is associated with increased CCR6-dependent migration of Th17 cells [137]. A high concentration of IL-1β is related to impaired integrity of tight junctions and increased T cell migration through the endothelium [134]. CCL4 has been shown to induce the migration of cytolytic T cells into GBM [138]. Furthermore, gradients of other inflammatory chemokines, including CXCL10, CXCL9, and CXCL11, which bind to CXCR3, have been shown to intensify T-cell infiltration [139]. The CXCL12-CXCR4/CXCR7 axis also plays a vital role in increasing T cell migration [140]. In addition, astrocytes regulate T cell entry by releasing tumor necrosis factor-α, IL-12, TGFβ, and IL-6 [141].

5.3. Altering the GBM microenvironment

One treatment method for GBM involves targeting immunosuppressive cells and factors. This can be achieved by modulating ICIs, such as anti-PD-1/PD-L1 or anti-CTLA-4 agents, and focusing on immunosuppressive cells such as Tregs, MDSCs, and TAMs.

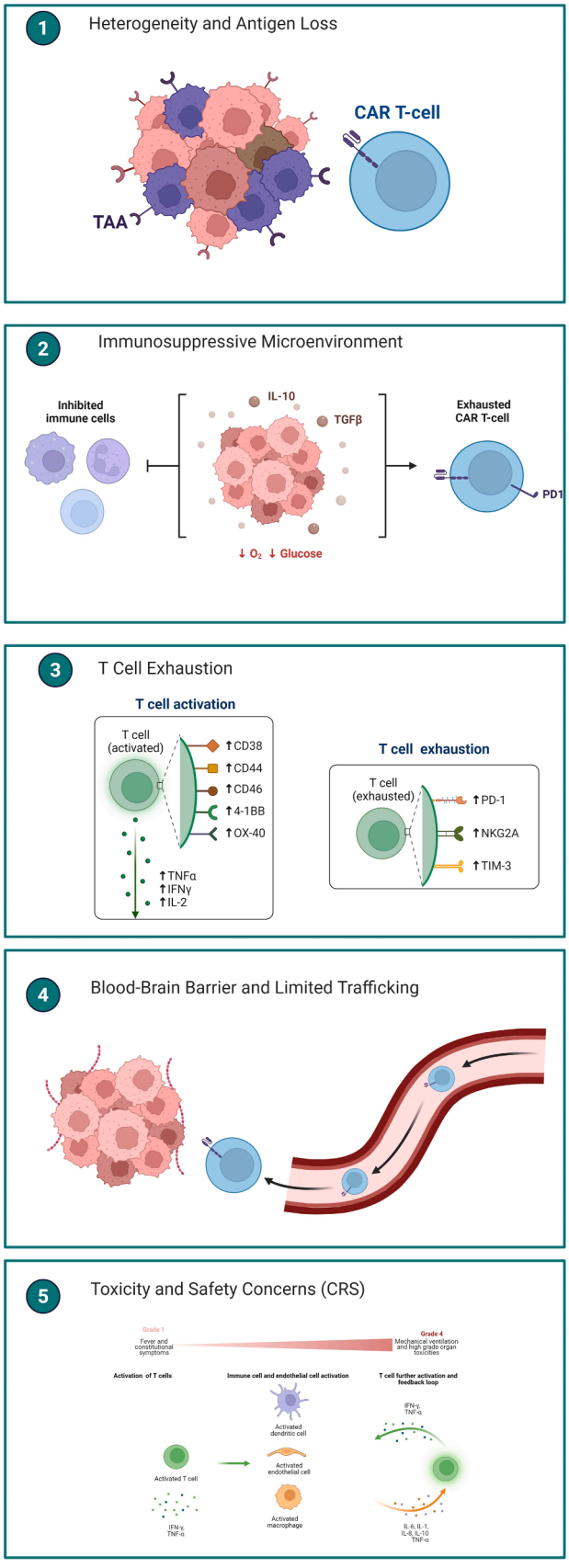
Anti-PD-1/PD-L1 antibodies block the interaction between PD-1 on T cells and PD-L1 on tumor cells, reinvigorating exhausted T cells and promoting their activity, while CTLA-4 blockade enhances T-cell activation by preventing CTLA-4 from binding to CD80/86 on APCs and depleting Tregs. Monoclonal antibodies targeting PD-1 or PD-L1 have been approved for treating cancers such as melanomas [142–146]. The PD-1/PD-L1 inhibitors used in glioma trials include pembrolizumab and nivolumab [147,148].

However, anti-PD-1/PD-L1 monotherapy has shown limited success in GBM, with minimal improvements in patient survival, possibly due to the highly immunosuppressive TME [148–153]. Despite these challenges, specific combination therapies may still offer potential benefits [154].

Similarly, CTLA-4 blockade has shown promising results in animal models; but has not been as effective in human GBM trials [155–157]. A lack of immune cell recruitment, an immunosuppressive TME, and the molecular heterogeneity of GBM are likely contributing factors that limit success [158,159].

Tregs contribute to GBM resistance to treatment by suppressing antitumor immune responses. The overexpression of TGF-β in GBM plays a significant role in Tregs activity [160,161]. TGF-β inhibitors have been tested but have shown limited success as monotherapies [162–165]. Similarly, while targeting TGF-β expression in vitro has produced promising results, these results have not been replicated in clinical trials [166–168].

MDSCs and TAMs also suppress antitumor immune responses, reducing the effectiveness of T cells [169,170]. Consequently, the selective inhibition of myeloid cells represents a promising therapeutic approach for patients [171]. One strategy involves targeting the CSF-1/CSF-1R pathway, which is critical for macrophage survival and proliferation. CSF-1R inhibitors have been shown to decrease tumor



(caption on next column)

Fig. 2. Main primary barriers to effective CAR T cell therapy in solid tumors. Panel 1–5 depicts tumor heterogeneity and antigen escape, with tumor cells (pink and purple) expressing variable TAAs (TAAs, Y-shaped structures). A CAR T cell (blue) targets TAAs, but a darker purple region indicates antigen loss, evading recognition. CAR T cell trafficking and infiltration, with CAR T cells (blue) in a blood vessel (red) moving toward a dense tumor mass (pink/red), arrows highlighting the infiltration challengeThe immunosuppressive and nutrient-restricted tumor microenvironment, featuring inhibited immune cells (light blue), immunosuppressive cytokines (IL-10, TGFβ, brown dots), and an exhausted CAR T cell (blue, labeled PD1) amid reduced oxygen (↓ O_2) and glucose (↓ Glucose) levels.

growth in preclinical models [172–176]. However, clinical trials are still endeavoring to evaluate their effectiveness and safety in GBM patients.

The use of lipid nanocapsules (LNCs) is another emerging therapeutic approach for inhibiting MDSCs. LNCs loaded with chemotherapy agents have displayed promising results in animal studies, but additional studies are necessary to evaluate their effectiveness in GBM patients [177–181].

Antiangiogenic therapy plays a critical role in addressing tumor hypoxia and supporting immune responses in GBM. These therapies primarily target the VEGF signaling pathway [182]. Among anti-VEGF agents, only bevacizumab has demonstrated efficacy in improving PFS and reducing symptoms such as cerebral edema; however, it has not significantly impacted overall survival [183,184]. Other anti-VEGF therapies have exhibited limited to no efficacy [183]. Another approach involves targeting angiopoietin-2 (Ang-2), which regulates angiogenesis [185]. While animal studies on anti-Ang-2 therapies have shown promise, further research is needed to increase their effectiveness in GBM treatment [186,187].

Hypoxia, a hallmark of GBM, contributes to immunosuppression and treatment resistance [188]. HIFs, particularly HIF-1α and HIF-2α, are crucial mediators of the cellular response to low oxygen levels and targeting them has shown potential in preclinical models [188,189]. HIF-1α plays a central role in GBM therapy by acting as a master regulator of the tumor's response to hypoxia, a key characteristic of GBM that drives angiogenesis, metabolic adaptation, and resistance to treatment. Therapeutic strategies targeting HIF-1α aim to disrupt these processes, thereby inhibiting tumor progression and enhancing treatment efficacy [190]. Preclinical evidence supports this approach, with studies showing that HIF-1α inhibition can induce apoptosis in glioma cells, improve their sensitivity to chemotherapy, and reduce angiogenesis [191]. HIF-2α inhibitor monotherapy has resulted in promising outcomes, but its combination with standard treatments has not significantly improved survival [192,193]. Hyperbaric oxygen therapy is another approach that has shown potential in increasing the sensitivity of tumor cells to chemotherapy and radiotherapy (RT), although further clinical validation is needed [194].

Targeting metabolic pathways in GBM cells can increase T cell infiltration by disrupting the ability of tumors to create an immunosuppressive microenvironment. GBM cells exhibit altered metabolism, such as the Warburg effect, leading to nutrient depletion (such as glucose and tryptophan) which T cells need for survival and function, and the production of inhibitory metabolites such as lactate and kynurenine. By inhibiting these metabolic pathways in GBM cells, the competition for nutrients is reduced, production of immunosuppressive factors decreases, and the TME becomes less acidic and more favorable for T cell activity and infiltration, ultimately promoting a stronger antitumor immune response [195]. Pharmacological inhibition of these pathways has shown potential for increasing T cell-based therapy efficacy [195–198]. Moreover, metabolic ICIs, such as those targeting adenosine and IDO, have shown promising potential in preclinical studies and are currently being evaluated in clinical trials [199,200].

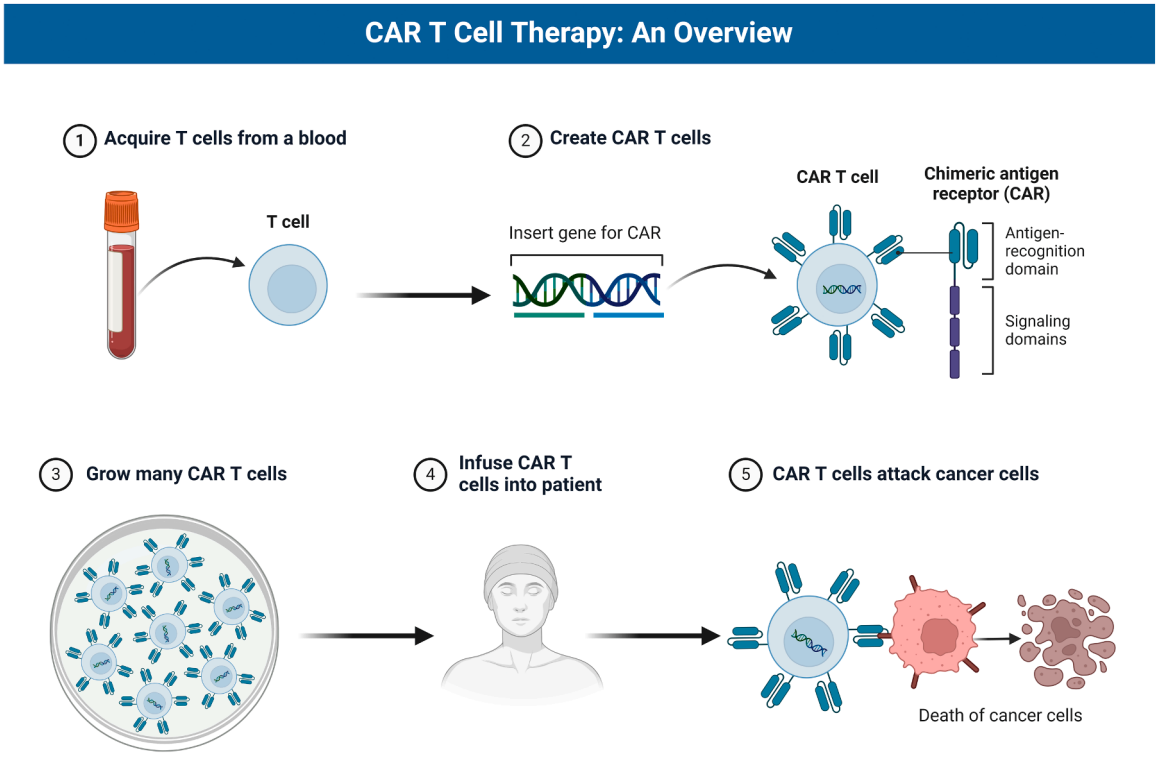


Fig. 3. Generations of CAR T Cell.
This figure illustrates the evolution of CAR T cell designs across five generations, highlighting structural and functional advancements, including the addition of costimulatory domains (CD28, 4–1BB, OX40), IL-12 induction, and IL-2Rβ signaling, to enhance T cell activation, proliferation, and persistence in glioblastoma immunotherapy.

5.4. Combination approaches

RT not only eradicates tumor cells but also acts as an immune modulator. It can enhance the immune response by augmenting the expression of MHC molecules and releasing tumor-associated antigens (TAAs) [201–203]. RT has shown potential synergy with ICIs and adoptive cell therapies, such as CAR-T cell therapies [201,204]. Ongoing and future clinical trials are poised to furnish additional insights into refining these composite strategies to optimize patient outcomes.

Combining ICIs with adoptive T cell therapies, specifically CAR-T cells, has demonstrated a synergistic enhancement in antitumor efficacy. ICIs rejuvenate T cells in the immunosuppressive GBM TME, while also improving CAR-T cell function [205,206]. Ongoing clinical trials are investigating combinations of CAR-T cells and ICIs, with initial results showing improved survival rates and immune responses [189,205].

6. Emerging technologies and approaches

The ability of T cells to circulate and interact with inflamed tissues is well characterized [207,208]. In the pathological state, the release of inflammatory cytokines induces the expression of chemokines and adhesion molecules that recruit effector T cells to the CNS [209].

6.1. Nanoparticle-based delivery systems

Nanoparticle-based delivery systems hold significant potential for improving T cell infiltration in GBM treatment [210]. These systems can overcome the BBB, enabling the targeted delivery of T cells directly to the TME. This targeted approach not only improves therapeutic efficacy but also minimizes off-target effects associated with systemic delivery [211]. Immunotherapy, particularly CAR-T cell therapy, holds promise for GBM treatment, but its effectiveness is hindered by the BBB. However, neutrophils can traverse the BBB. Chang et al. demonstrated the potential of leveraging this ability by using CAR neutrophils to deliver TME-responsive nanodrugs, resulting in superior and specific antitumor activity, reduced off-target effects, and increased lifespan in mouse models. Importantly, the authors reported that CAR-T cells neutrophils could deliver more than 20 % of the administered nanodrugs to the tumor mass, whereas only 1 % of the free nanodrugs could be delivered [212].

To increase T cell infiltration and combat therapeutic resistance in GBM, Zhang et al. developed a nanoparticle system that targets both the CD47 and PD-L1 immune checkpoints while delivering a STING agonist. This nanoparticle engages tumor-associated myeloid cells (TAMCs) with GB cells, and a STING activation in TAMCs triggers proinflammatory cytokine production, leading to effector T cell infiltration and activation. By concurrently blocking innate (CD47) and effector (PD-L1) checkpoints while delivering the STING agonist, this approach enhances antitumor immunity and radiation therapy, promoting tumor regression in vivo [213].

Using photothermally activated nanoparticles to generate localized hyperthermia in the tumor is another strategy to overcome physical and immunological barriers that hinder T cell infiltration and function within the GBM microenvironment. This mild heat disrupts the tumor matrix, increases blood flow, and releases tumor-specific antigens, thereby promoting T cell accumulation and enhancing their antitumor response [214]. Another approach uses magnetic nanoclusters conjugated with anti-PD-1 antibodies to facilitate T cell recruitment to the tumor site. Once at the tumor site, the structures disassemble, allowing simultaneous T cell-mediated killing and checkpoint blockade [215].

These findings underscore the significant potential of nanoparticle-based delivery systems to overcome challenges associated with traditional GB therapies and enhance the effectiveness of immunotherapeutic approaches, providing hope for improved treatment outcomes for GB patients.

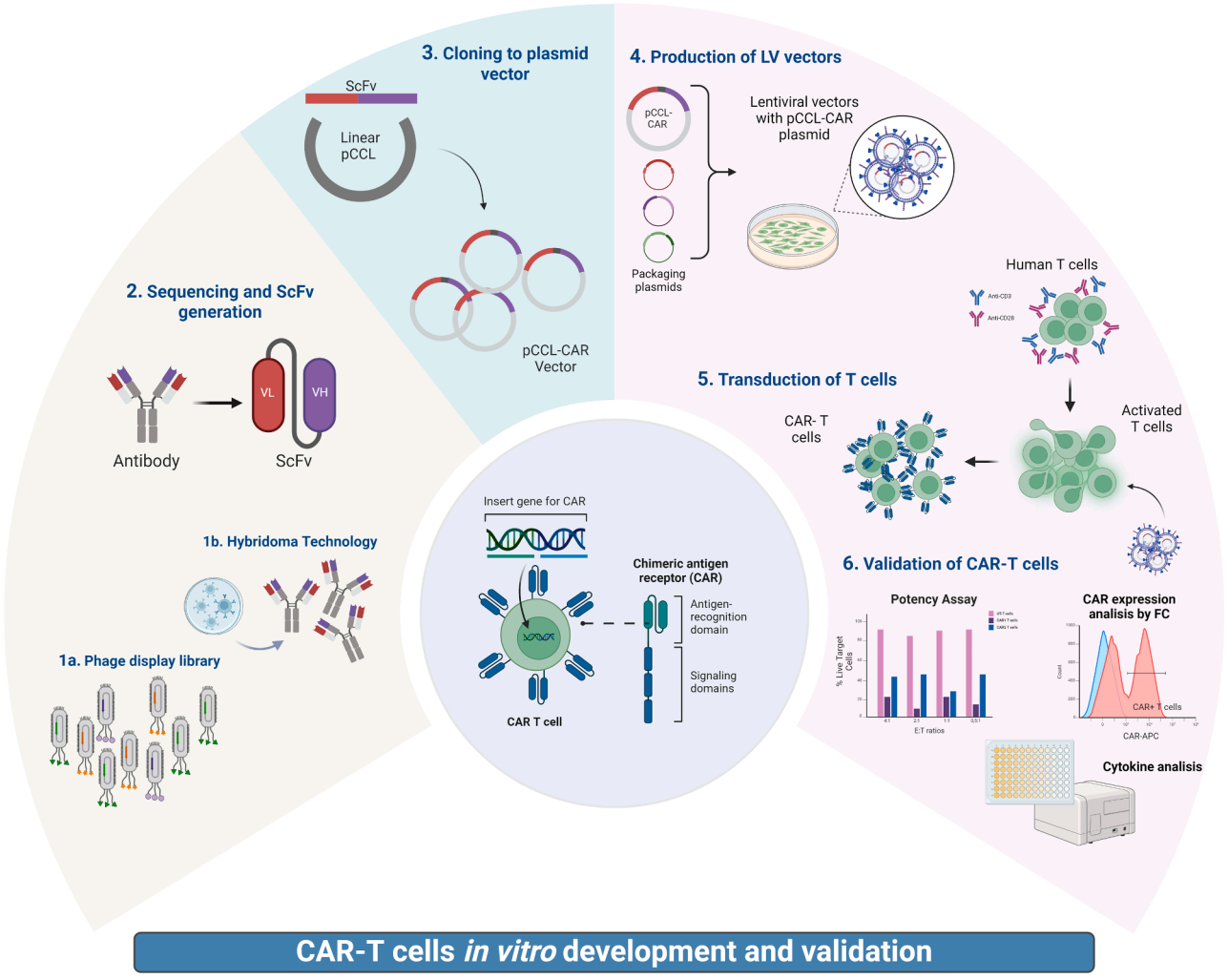


Fig. 4. CAR T cells in vitro development and validation.
The schematic illustrates the sequential steps involved in the in vitro development and validation of CAR T cells, including antibody selection, scFv generation, cloning into plasmids, production of lentiviral vectors, transduction of T cells, and validation through potency and cytokine assays.

6.2. *Gene editing techniques for enhancing T cell function*

CRISPR-based gene editing has emerged as a promising approach for enhancing T cell function in the context of cancer immunotherapy, including GBM. The CRISPR/Cas9 system enables targeted genomic modifications, where clustered regularly interspaced short palindromic repeats (CRISPR) serves as the guide RNA system that directs the Cas9 endonuclease to specific DNA sequences for cutting [216,217]. This allows researchers to develop more effective and safer CAR-T cell therapies. This approach holds promise for improving CAR-T cell persistence, overcoming exhaustion, and enhancing the ability of CAR-T cell to target GBM cells [218].

Research groups have used CRISPR activation (CRISPRa) and CRISPR interference (CRISPRi), which employ modified Cas9 proteins (dCas9) fused to activator or repressor domains to screen for genes involved in T cell cytotoxicity, increasing the tumor-killing ability of CAR-T cells through single or multiple gene editing [219,220]. Sidi Chen's laboratory has developed a hybrid genetic screening system using Sleeping Beauty transposons and CRISPR to identify membrane protein targets in CD8+ *T* cells. This approach has led to the identification of genes such as PDIA3, MGAT5, EMP1, and LAG3, which, when edited, can increase the anti-tumor activity of T cells in GBM models [221]. Another study used CRISPR to eliminate the TLE4 and IKZF2 genes in CAR-T cells, resulting in enhanced anti-GBM activity [222]. Additionally, screening approaches have identified p38 kinase as a crucial regulator of T cell proliferation, memory, and metabolic fitness, suggesting that its inhibition could enhance CAR-T cell persistence and anti-tumor efficacy [223]. These findings demonstrate the potential of gene editing techniques to engineer T cells with improved functionality against GBM, opening new avenues for therapeutic development.

The use of CRISPR/Cas9 technology in CAR-T cells has demonstrated potential for overcoming T-cell exhaustion, thereby improving their resistance to the immunosuppressive TME and enhancing their efficacy as a cancer immunotherapy. T cell exhaustion is a state characterized by dysfunction and reduced responsiveness, leading to impaired anti-tumor capabilities and decreased proliferation. Studies have shown that disrupting immune checkpoints, such as PD-1 receptors in EGFRvIII-CAR-T cells, via CRISPR/Cas9 can increase cytotoxicity and mitigate exhaustion in GBM [224,225]. Importantly, the CRISPR component refers to the RNA guide sequences that direct specificity, whereas Cas9 (or other Cas proteins) is the endonuclease that performs actual DNA cleavage. Together, the CRISPR/Cas9 system enables precise, permanent genomic modifications when combined with cellular DNA repair mechanisms [216,217,226,227].

6.3. *Novel imaging methods for monitoring T cell infiltration*

Novel imaging techniques have revolutionized our ability to study T

cell infiltration in GBM. These methods provide real-time insights into T cell movement and activity, aiding in the evaluation of immunotherapy efficacy. T cell tagging, a noninvasive approach, enables the assessment of T cell migration, expansion, engagement with tumor cells, and overall therapeutic response [228].

One promising approach involves the use of reporter genes, such as HSV1-tk, to track engineered CAR-T cells. One study used [18F]FHBG to successfully track CAR-T cells expressing IL-13 zetakine and HSV-1-tk in patients with recurrent high-grade gliomas. The investigators found that [18F]FHBG accumulation was significantly greater in transfected T cells than in nontransfected cells without affecting cell proliferation or normal brain uptake [229].

In mouse models of GBM, [89Zr]-oxine has been successfully used to label CAR-T cells. This radiotracer enables in vivo tracking of T cell movement and activity, including cytokine production and tumor cytotoxicity. Importantly, [89Zr]-oxine labeling does not appear to impair T cell function or antitumor efficacy [230].

Magnetic particle imaging (MPI) is another emerging technique for T cell tracking. Ferucarbotran-labeled T cells can be visualized in real-time via MPI, providing valuable information about their distribution and persistence within the brain. This approach has been shown to be feasible in mouse models of GBM. Histological analysis confirmed their entry into the brain after intravenous administration. Furthermore, ferucarbotran labeling did not affect T cell activity, including IFN-gamma production [231].

Despite these advancements, challenges remain in T cell tracking within gliomas. Poor trafficking and persistence of T cells within the CNS can hinder accurate monitoring. Additionally, the potential impact of radiotracers on T cell function requires further investigation. Future studies will be essential to optimize T cell tracking methods for clinical application. By addressing these limitations and refining these techniques, researchers can gain a deeper understanding of T cell dynamics in GBM and develop more effective immunotherapies [228].

7. Clinical trials and translation research

7.1. CAR-T cell therapy in GBM and current clinical trials

CAR-T therapy represents an unprecedented advancement in immunotherapy that targets and eliminates cancer cells, particularly in solid tumors including brain tumors such as GBM, offering hope for patients who have exhausted other treatment options [232,233]. The fundamental principle of CAR-T cell therapy involves genetically modifying a patient's T cell to augment the capacity to identify and eliminate cancer cells. This process requires blood extraction, isolation, and genetic modification to express CARs on the outer membrane of T cells. After modification, the patient reintroduces modified T cells, which proliferate and trigger an immune response against malignancies. This individualized strategy improves the precision of the immune response and stimulates long-lasting immunity against cancer recurrence [234,235].

Clinical trials of CAR-T cell therapy have demonstrated mixed results, with some showing complete remission, stable disease, and partial response. The treatment focuses on three main components: recognition, trafficking, and survivability [235]. Studies have shown that anti-GPC3/CAR-T cells effectively suppress and eradicate tumors, while multifunctional RNA-based CAR T cells have strong antiglioma activity [236–238]. The new generation of CAR-T cell immunotherapy is being explored for treating GBM, with a focus on TAAs such as GD2, EGFRvIII, HER2, and IL13Ra2 [239–241].

Key antigens in GBM therapy have revealed potential and challenges. GBM commonly mutates EGFRvIII, which has shown promise in preclinical animal models. However, tumor heterogeneity and compensatory immunosuppressive responses within the TME pose challenges for clinical applications, leading to limited efficacy [240]. IL13Rα2, which is highly expressed in GBM, has been the focus of early clinical trials, which have shown that it is safe and sometimes effective. PET imaging confirmed that T cells were able to move through the body properly. Nonetheless, significant challenges from the immunosuppressive factors present in the TME still exist [242]. HER2 is another antigen that is overexpressed in a substantial proportion of GBMs, with trials indicating durable responses in some patients, including a subset that achieved stable disease for extended periods. However, similar to other targets, the presence of MDSCs and Tregs, along with the upregulation of immune checkpoints such as PD-L1, hinders the efficacy of HER2-directed therapies, dampening the overall immune response [239,240,243].

In the early days of CAR-T cell therapy for GBM, a 2015 pilot study investigated CD8+ CAR-T cells targeting IL13Rα2 in three patients. While intracranial administration was generally safe, all three patients eventually experienced tumor recurrence, even though tumor activity temporarily decreased [244]. Choi BD et al. reported the treatment of three human participants with recurrent GBM using CARv3-TEAM-E T cells. The findings revealed dramatic and rapid radiographic tumor regression after a single intraventricular infusion, which was transient in two of the participants [245]. Recent studies have highlighted the benefits of local and multiple administrations of CAR-T cells for the treatment of brain tumors. Local administration addresses the BBB challenge, while multiple administrations may help mitigate CAR-T cell exhaustion. Additionally, locoregional delivery of CAR-T cells may mitigate poor T cell trafficking and inefficient T cell penetration into tumors [246]. Notably, a patient with multifocal GBM received multiple CAR-T cell infusions, resulting in tumor regression for 7.5 months without significant toxicity [247]. After these first results, Brown et al. performed a phase I trial (NCT02208362) with 65 people who had recurrent high-grade glioma, mostly recurrent GBM. The participants had previously undergone extensive treatments and presented diverse tumor characteristics. The trial explored various administration methods, including locoregional delivery via intratumoral, intraventricular, or dual routes. Overall, the feasibility and tolerability of the treatment were positive; however, one-third of patients experienced Grade 3 toxicities, such as encephalopathy and ataxia. The study established a maximum feasible dose of 200 million CAR-T cells [248].

The future of CAR-T cell therapy is bright, with ongoing research dedicated to enhancing its effectiveness. One promising direction involves the development of next-generation CARs capable of targeting multiple antigens simultaneously [249]. This multitargeting strategy aims to mitigate the risk of tumor escape variants arising from single-target therapies. Additionally, there is increasing interest in integrating CAR-T cell therapy with other treatment modalities, such as ICIs and targeted therapies. These combinations could amplify the overall effectiveness of treatments and extend their applicability to solid tumors [250].

Several therapeutic CAR-T cell treatments have been evaluated for advanced GBM and they target epidermal growth factor receptor variant III (EGFRvIII), (IL)13Rα2 (IL-13Ra2), and ephrin-A2 (Her2), resulting in varied but informative outcomes [251,252]. A prior clinical trial presented encouraging first-in-human evidence supporting the feasibility of the intracranial administration of IL13Rα2-specific CAR-T cells for the treatment of GBM in three patients, which showed good tolerance and manageable temporary brain inflammation [253].

A phase I dose-escalation trial testing the administration of HER2-CAR-modified autologous virus-specific T lymphocytes (VSTs) to patients with progressing GBM has been completed. A safety profile of autologous HER2-CAR VSTs was established in 17 patients with progressing GBM, with no significant side effects. A total of 8 patients exhibited a clinical advantage, with a median overall survival of 11.1 months following T-cell infusion. Additionally, 3 patients remained alive and showed no signs of disease progression during the last follow-up [254].

Another clinical study demonstrated the safety and feasibility of producing CAR-T EGFRvIII cells from 10 patients with recurrent GBM. While there was no observable survival advantage, the intravenous

infusion of cells directly affected the brain tumor and produced antigen-directed effects, resulting in reduced EGFRvIII expression and an inhibitory TME after treatment [241].

The safety and efficacy of CAR-T cells targeting the B7-H3 antigen in patients with recurrent GBM are being investigated in an ongoing experiment led by Zhang. TX103 was injected either intracavally or intraventricularly, with dose escalation to establish the maximum tolerated dose and tumor response. Each patient experienced at least one adverse event, such as cytokine release syndrome, elevated intracranial pressure, headache, epilepsy, reduced consciousness, vomiting, or fever. The 12-month overall survival rate was 83.3 %, with a median survival time of 20.3 months [255].

Using previously validated CD133 CAR-T cells, Shaikh's study aimed to determine whether CAR-T cells from GBM patients showed reduced efficacy compared with those from healthy donors. Compared with controls, patient-derived CAR-T cells demonstrated pretreatment weakness and a reduced survival advantage in autologous, patient-derived CD133-targeting CAR-T cell products. In addition, they developed an "off-the-shelf" allogeneic CD133 CAR-T cell line using CRISPR gene editing technology to address logistical and functional challenges. These findings emphasize the need to reconsider autologous CAR-T cells therapy for GBM and explore allogeneic approaches as potential alternatives [256].

Bispecific T cell engagers (BiTEs) have been suggested as a possible solution for antigen escape. Integrating EGFR-directed BiTEs, which attach T cells to cancerous cells, into EGFRvIII-CAR-T cells creates a dual-targeted platform to inhibit the escape of antigens. The production of EGFR-targeted BiTEs by CAR-T cells has minimal toxicity and antitumor efficacy against diverse tumors, indicating a promising path for GBM research in the future [257]. Table 2 summarizes recent clinical trial studies regarding T cell infiltration in GBM.

7.2. Challenges in translating preclinical findings to clinical practice

Several preclinical studies have employed mouse models that may not completely mimic the biology of human GBM. Interspecies variations in immune system activity and tumor biology can result in incorrect findings when results are applied to human patients [258–261].

The primary obstacle hindering CAR-T cells therapy for GBM is heterogeneity in GBM, which poses challenges in developing CAR-based approaches that can effectively target all clonal populations, despite very promising results [262]. Although this strategy needs more verification, adjustments to reduce tumor antigen escape and address antigenic heterogeneity could offer a viable method for the successful use of CAR-T cell therapy in the treatment of GBM [263].

Another obstacle is that GBM has a very diverse microenvironment that can inhibit the activation of T cells. Factors such as the existence of immunosuppressive cells (such as Tregs and MDSCs and the release of immunosuppressive cytokines (such as IL-10 and TGF-β) can inhibit the infiltration and functional activity of T cells [264,265].

In addition, GBM cells frequently employ strategies to avoid being detected by the immune system, such as reducing the expression of MHC molecules or producing immunological checkpoint proteins (e.g., PD-L1) [262,266]. A diverse strategy is needed to address these issues, including the advancement of preclinical models, enhanced trial designs, and a more thorough comprehension of the tumorimmune interactions in GBM. Various strategies for addressing T cell infiltration in GBM patients are summarized in Table 3.

8. Discussion

8.1. Personalized approaches based on patient-specific factors

Personalized approaches targeting T cell infiltration in GBM have drawn significant attention because of the immunosuppressive TME and poor prognosis. Owing to the heterogeneity of GBM, strategies should consider patient-specific characteristics such as the tumor's genetic profile, immunological landscape, and expression of immune checkpoints [267]. For example, recent research has emphasized the tumor mutational burden (TMB) as a possible predictive factor for ICI response. Patients with higher TMB may develop more neoantigens, which can improve the T cell infiltration and increase the efficacy of ICIs such nivolumab and pembrolizumab [268]. Furthermore, stratification of patients on the basis of the expression of molecular markers can improve outcomes since varied expression of CTLA-4 and PD-L1 has been associated with different response rates to immunotherapies [269]. Moreover, innovative personalized vaccines including vaccines based on neoantigens using via sequencing technologies, offer new avenues for increasing tumor infiltration [270,271]. These approaches highlight the importance of customizing immunotherapies on the basis of patient-specific profiles to effectively overcome the challenges of GBM and improve clinical outcomes.

8.2. Combining T cell infiltration strategies with other immunotherapies

Combining T cell infiltration strategies with other immunotherapies offers a viable approach to address the obstacles that GBM presents. A) One of the multifaceted approaches involves combining ICIs (e.g., anti-PD-1/PD-L1 inhibitors) with agents (e.g., CXCR4 antagonists) that increase T cell trafficking and persistence by disrupting chemokine gradients limiting T cell entry [272]. B) Combining oncolytic viruses such as adenoviruses with anti-PD-1 therapy as another strategy. This process results in increased T cell infiltration in GBM models [273]. C) The combination of CAR-T cells with BiTE or ICIs has been shown to amplify responses through the targeting of several immunosuppressive pathways [274]. These combined approaches represent synergistic effects to overcome the immune resistance that is specific to GBM, thus increasing the overall effectiveness of therapies.

8.3. Addressing potential side effects and toxicities

While novel therapeutic approaches offer promising outcomes, they are often associated with significant adverse effects, such as irAEs and off-target toxicities, which can reduce their usefulness in clinical settings. Each immunotherapy strategy brings its own balance of strengths and weaknesses. ICIs are generally safe, but on their own they have delivered only limited benefits in GBM. CAR-T cells can target tumors with greater precision, yet their effects so far have been short-lived and sometimes complicated by safety concerns. Combination approaches, for example, pairing ICIs with chemokine modulators or oncolytic viruses, look more promising, as they may better balance safety, specificity, and efficacy. Still, most of these combined strategies are only beginning to be tested, reminding us that careful trial design will be essential to turn early promise into meaningful outcomes for patients.

A few approaches have been suggested to reduce these events, including: (1) Careful selection of immunotherapies to avoid overlapping toxicities and side effects. (2) Balancing the dose of corticosteroids to minimize their impact on the antitumor response. (3) Producing next-generation CAR-T cells greater specificity for tumor cells than for normal tissues to reduce off-target effects [189]. (4) Localized delivery methods (e.g., convection-enhanced delivery or intratumoral injections) that reduce systemic exposure and related toxicity [275]. (5) Real-time monitoring of patient responses and toxicity profiles via biomarkers allows for personalized modifications to treatment plans, promoting a balance between safety and efficacy. As a result, addressing these issues is crucial for the safe and effective application of immunotherapies.

8.4. Improving clinical trial design for GBM immunotherapy

Finally, designing robust and effective clinical trials for enhancing T cell infiltration in GBM requires careful consideration of several key factors to ensure reliable and meaningful outcomes [276]. First,

Table 2
Clinical trial studies regarding T cell infiltration in glioblastoma (Part 1).

NCT identifier	NCT00730613 [217]	NCT01109095 [218]	NCT02209376 [219]	NCT05241392[220]	Not applicable (preclinical study)[221]	Not applicable (preclinical study)[222]	NCT02208362[257]	NCT02208362[258]
Survival outcomes	Not reported	- Median overall survival: 11.1 months from first T-cell infusion - Median overall survival: 24.5 months from diagnosis	- One patient had residual stable disease for over 18 months - Detailed survival outcomes not provided for all patients	- 12-month overall survival rate: 83.3 % (95 % CI: 58.3 %100 %) - Median overall survival: 20.3 months (95% CI: 20.3not reach)	Reduced survival advantage noted for autologous patient-derived CAR-T compared to controls (specific data not provided)	Complete and durable responses in all mice treated with CART-EGFRvIII.BiTE-EGFR cells	Not specifically mentioned, but clinical response continued for 7.5 months after initiation of CAR T-cell therapy	- Median overall survival for all patients: 7.7 months - Median overall survival for arm 5 (dual ICT/ICV delivery with optimized manufacturing): 10.2 months
Side effects	- Grade 3 headaches (1 patient) - Grade 3 neurologic event including shuffling gait and tongue deviation (1 patient)	Generally well-tolerated; 2 patients had grade 2 seizures and/or headaches possibly related to infusion	- No EGFR-directed toxicity - No systemic cytokine release syndrome - Three patients experienced clinically significant neurologic events (seizure, altered mental status, neurologic decline)	Cytokine release syndrome, increased intracranial pressure, headache, epilepsy, decreased level of consciousness, vomiting, and pyrexia (mostly grade 1–2, with three grade-3 events)	N/A	No detectable toxicity reported in animal models	No toxic effects of grade 3 or higher; Grade 1 or 2 events included headaches, fatigue, myalgia, and olfactory auras	- Most common: fatigue, headache, and hypertension - Grade 3+: one grade 3 encephalopathy and one grade 3 ataxia with probable attribution to CAR-T cells - Two patients experienced transient grade 4 cerebral edema
Key findings	- Feasibility of manufacturing sufficient autologous CAR T cells demonstrated - Intracranial delivery well-tolerated with manageable temporary CNS inflammation - Evidence for transient anti-glioma responses in 2 of 3 patients - Reduced IL13Rα2 expression in tumor tissue after treatment in one patient - Increased tumor necrotic volume at T cell administration site in another patient	- No dose-limiting toxicity observed - HER2-CAR VSTs detected in peripheral blood for up to 12 months - 1 partial response, 7 stable disease, 8 disease progression - 3 patients with stable disease alive without progression at 24–29 months follow-up	- Manufacturing and infusion of CART-EGFRvIII cells are feasible and safe - No evidence of off-tumor toxicity or cytokine release syndrome - Detectable transient expansion of CART-EGFRvIII cells in peripheral blood - Trafficking of CART-EGFRvIII cells to regions of active GBM - Antigen decrease in 5 of 7 patients with post-infusion tissue analysis - Increased expression of inhibitory molecules and infiltration by regulatory T cells in tumor microenvironment after infusion	- No dose-limiting toxicity or CAR-T treatment-related death - Significant increases in cytokines (IL-6 and IFN-γ) and elevated CAR gene copy numbers in cerebrospinal fluid - Minimal elevations in peripheral blood - Two patients achieved partial and complete responses	- Patient-derived CAR-Ts showed pre-treatment exhaustion - Reduced survival advantage in autologous, patient-derived CD133-targeting CAR-T cell products - Transcriptomic analysis showed decreased T cell and lymphocyte activation genes in GBM patient-derived T-cells - Allogeneic TCR-knockout CAR-T cells showed comparable pre-clinical efficacy to autologous models	- CART.BiTE cells eliminated heterogeneous tumors in mouse models of glioblastoma - BiTE-EGFR was locally effective but not detected systemically after intracranial delivery - CART.BiTE cells did not result in toxicity against human skin grafts in vivo	Regression of all intracranial and spinal tumors; complete response sustained for 7.5 months	- Locoregional CAR-T cell administration was feasible and well tolerated - No dose-limiting toxicities across all arms - Stable disease or better achieved in 50% (29/58) of patients - Two partial responses, one complete response, and a second complete response after additional CAR-T cycles
Administration method	Intracranial delivery via catheter/reservoir system	Intravenous infusion	Single dose, intravenous infusion	Intracavity and/or intraventricularly via an Ommaya reservoir	N/A	Intraventricular delivery of CAR-T cells	Intracranial delivery: intracavitary infusions into resected tumor cavity, followed by	Locoregional delivery: intratumoral (ICT), intraventricular (ICV), and dual ICT/ICV

(*continued on next page*)

Table 2 (*continued*)

NCT identifier	NCT00730613 [217]	NCT01109095 [218]	NCT02209376 [219]	NCT05241392[220]	Not applicable (preclinical study)[221]	Not applicable (preclinical study)[222]	NCT02208362[257]	NCT02208362[258]
							intraventricular infusions	
Patients	3 patients with recurrent glioblastoma (GBM)	17 patients (10 adults, 7 children) with progressive HER2-positive glioblastoma	10 patients with recurrent glioblastoma (GBM) expressing EGFRvIII	Patients with recurrent GBM, aged 18 to 75, with B7-H3 expression $\geq$ 30 %	Glioblastoma (GBM) patients (for T-cell extraction)	Not applicable (mouse models used)	One patient with recurrent multifocal glioblastoma	65 patients with recurrent high-grade glioma (majority being recurrent glioblastoma)
Combination partner	N/A	None (monotherapy)	N/A	N/A	N/A	N/A	N/A	N/A
Compounds	Autologous IL13(E13Y)-zetakine CD8+ CTL (CAR T cells)	HER2-specific chimeric antigen receptor (CAR)–modified virus-specific T cells (VSTs)	Autologous T cells modified with EGFRvIII-directed CAR	TX103 (B7-H3 targeting CAR-T cells)	CD133-targeting CAR-T cells	CART-EGFRvIII.BiTE-EGFR cells	IL13BBζ–CAR T cells	IL-13Rα2-targeted CAR-T cells
Therapy	Chimeric Antigen Receptor (CAR) T cell therapy	Adoptive cell therapy	CAR T-cell therapy	CAR-T cell therapy	CAR-T cell therapy	CAR-T cells secreting bispecific T-cell engagers (BiTEs)	Chimeric antigen receptor (CAR) T-cell therapy	CAR-T cell therapy
Target	IL13Rα2	HER2-positive glioblastoma	EGFRvIII (Epidermal Growth Factor Receptor variant III)	B7-H3	CD133	EGFRvIII and EGFR	IL13Rα2 (interleukin-13 receptor alpha 2)	IL-13Rα2
Study type	First-in-human pilot safety and feasibility trial	Open-label, dose-escalation	First-in-human study	Open, single-arm, "3 + 3″ dose-escalation and multiple-dose study	Preclinical research	Preclinical (animal studies)	Clinical trial	Single-center, nonrandomized, five-arm, dose-escalation
Clinical phase of study (status)	Phase I (Completed)	Phase 1 (Completed)	Phase 1 (Completed)	Phase not specified (Ongoing)	Preclinical	Preclinical	Phase 1	Phase 1 (Completed)
NCT identifier	NCT01454596	NCT04185038	NCT04214392	NCT03726515	NCT03423992	NCT05627323		
Survival outcomes	- Median overall survival was 6.9 months, with a range of 2.8–10 months - two patients survived over a year	Not fully reported yet; preliminary evidence of tumor regression and immune activation	- Evaluating time to progression, overall survival - and disease response (RANO criteria)	- Median PFS: 5.2 months - Median OS: 11.8 months	Overall survival ranging from 86 to 181 days	Not reported (study is ongoing)		
Side effects	- Severe hypoxia in two patients, one resulting in death - transient hematologic toxicities from chemotherapy	Grade 3–4 adverse events observed, cytokine release syndrome, neurological effects	To be evaluated (focus on safety and tolerability)	Rash, liver injury, kidney injury	- Grade 2 cytokine release syndrome in two patients - Pulmonary edema in two patients - No neurotoxicity or other organ toxicity reported	Not reported (safety is the primary endpoint of the study)		
Key findings	- No clinically meaningful effect in recurrent glioblastoma - only one patient remained progression-free at 12.5 months - limited persistence of CAR T-cells	- Preliminary bioactivity and safety - CAR T-cell persistence in CSF and serum - local immune activation in CNS	- Preclinical studies showed robust anti-tumor activity and significantly increased survival	- Safe but minimal efficacy, no dose-limiting toxicities observed, decrease in EGFRvIII in 6/7 patients	- CAR T-cells expanded in peripheral blood and persisted for >4 weeks - One patient achieved SD, two patients reported PD - Transient clinical efficacy observed	Study is ongoing; no findings reported yet		
Administration Method	Intravenous infusion of autologous CAR-T cells post lymphodepleting chemotherapy	Locoregional infusion via CNS catheter	Intratumoral (ICT) injection, dual delivery via ICT and intraventricular (ICV) catheters	Peripheral infusion	Intravenous infusion	Intracranial (intracavitary and intraventricular) administrations		

(*continued on next page*)

Table 2 (*continued*)

NCT identifier	NCT00730613 [217]	NCT01109095 [218]	NCT02209376 [219]	NCT05241392[220]	Not applicable (preclinical study)[221]	Not applicable (preclinical study)[222]	NCT02208362[257]	NCT02208362[258]
Patients	18	Children and young adults with recurrent/ refractory CNS tumors or DIPG	MMP2+ recurrent or progressive glioblastoma (GBM) patients	7	3 patients with recurrent EphA2-positive glioblastoma	Adult subjects with MMP2+ recurrent or progressive GBM after standard therapy		
Combination partner	N/A	N/A	N/A	Pembrolizumab	Lymphodepletion regimen (Fludarabine and Cyclophosphamide)	N/A		
Compounds	Anti-EGFRvIII CAR T-cells	Autologous CD4+ and CD8+ *T* cells expressing a B7-H3-specific CAR and EGFRt	CLTX-CAR T cells	CAR T-EGFRvIII cells	EphA2-redirected CAR T-cells	CHM 1101 (CLTX-directed CAR T-cells)		
Therapy	CAR-T Cell Therapy	CAR T-cell therapy	CLTX-CAR T cell therapy utilizing chlorotoxin tumor-targeting domain	CAR T-Cell therapy + pembrolizumab	CAR T-cell therapy	CAR T-cell therapy		
Target	EGFRvIII	B7-H3 (CD276)	Matrix metalloprotease 2 (MMP-2)	EGFRvIII	EphA2	MMP2+ recurrent or progressive glioblastoma		
Study type	Clinical trial	Clinical Trial	Single-center safety and maximum tolerated dose (MTD) finding study	Single-center, single-arm, open-label	Single-arm, dose-escalation pilot trial	Multicenter study		
clinical phase of study (status)	Phase I (Pilot)	Phase I	Phase 1	Phase 1	Phase I (First-in-human trial)	Phase 1b (Recruitment ongoing)		
Author/Year	Goff et al.,2019	Nicholas A. Vitanza et al., 2023	Behnam Badie et al., 2021	Bagley SJ et al., 2024	Lin et al., 2021	Jason Blair Litten, et al., 2023		
DOI	10.1097/ CJI.0000000000000267	10.1158/2159-8290.CD-22-0750	10.1200/ JCO.2021.39.15_suppl. TPS2662	10.1038/s43018-023-00709-6	10.3389/ fonc.2021.694941	10.1200/ JCO.2023.41.16_suppl. TPS2086		

Table 3
Various strategy of T Cell infiltration in glioblastoma.

Strategy	Mechanism	Technique/Approach
Modifying the BBB	Disrupting BBB integrity	Focused ultrasound Acoustic cavitation Osmotic disruption (e.g., mannitol)
	Enhancing transport across BBB	Nanocarriers (liposomes, solid lipid nanoparticles, etc.)
Enhancing T cell trafficking	Upregulating adhesion molecules	ALCAM upregulation
	Targeting chemokine receptors	Engineering CAR-T cells to express CXCR3, CXCR4
	Targeting tumor-specific receptors	Targeting IL-13Rα2 Targeting EGFRvIII
	Increasing inflammatory cytokines	CCL2-CCR4/CCR and CCL5-CCR5 axis stimulation
Altering glioblastoma microenvironment	Targeting immunosuppressive factors	Immune checkpoint inhibitors (anti-PD-1/PD-L1) Targeting Tregs Targeting MDSCs and TAMs (CSF-1R inhibitors)
	Inhibiting angiogenesis	Anti-VEGF therapies (Bevacizumab)
	Addressing hypoxia	Targeting hypoxia-inducible factors (HIFs) Hyperbaric oxygen therapy
	Targeting metabolic pathways	Inhibiting glycolysis or glutaminolysis Pharmacological inhibition of metabolic pathways
	Targeting metabolic checkpoints	Inhibitors targeting adenosine and IDO
Combination approaches	Combining multiple strategies	Radiotherapy + immunotherapy ICIs + adoptive T cell therapies
Nanoparticle-based delivery	Enhancing immune response	Liposomal nanoparticles
	Enhancing T cell migration	Conjugated CAR-T cells and pexidartinib-containing liposomes
	Increasing T-cell infiltration	Allomelanin nanoparticles delivering immune checkpoint inhibitor
	Enhancing T cell infiltration	Angiopep-2 and IP10-EGFRvIIIscFv fusion protein-modified nanoparticles Cationic lipid nanoparticles Phosphorus dendrimer nano-complexes
	Targeted delivery across BBB	CAR neutrophil-mediated nanodrug delivery
	Multi-targeting immune modulation	Nanoparticle system targeting CD47, PD-L1, and delivering STING agonist
	Localized hyperthermia	Photothermally activated nanoparticles
	T cell recruitment and checkpoint blockade	Magnetic nanoclusters conjugated with anti-PD-1 antibodies
Gene editing techniques	Enhancing T cell function	CRISPR-based editing (e.g., targeting PDIA3, MGAT5, EMP1, LAG3) CRISPR-based editing (eliminate the TLE4 and IKZF2 genes in CAR-T cells)
	Enhancing CAR-T cell persistence and anti-tumor efficacy	Inhibition p38 kinase
	Overcoming T cell exhaustion	Disrupting immune checkpoints in CAR-T cells

considering the heterogeneous nature of tumors, trial designs must account for genetic variations and molecular characteristics. As we mentioned, stratification on the basis of biomarkers can help identify patients who are more likely to benefit from specific T cell-based therapies. Second, the use of advanced biopsy methods and imaging techniques is critical for precisely assessing T cell infiltration and understanding the TME, which might reveal insights into the effectiveness of therapies. Third, adaptive trial designs can increase flexibility and efficiency by enabling adjustments to dosing, combination therapies, and patient selection criteria on the basis of new interim results or when new data become available.

This study has some limitations. Most current delivery methods have clear drawbacks. Systemic routes rarely cross the BBB, while local techniques like intratumoral injection or convection-enhanced delivery are invasive and hard to apply consistently. Newer tools such as nanoparticles or focused ultrasound look promising, but they are still early-stage and unproven in large trials. These gaps remind us that finding safe and reliable ways to bring therapies directly into GBM remains a major challenge. The conclusions are based on existing studies, which can sometimes be influenced by publication bias or incomplete data. The quality of the studies varies, and this can lead to inconsistencies, especially when studies with differing results are included. Additionally, the review mainly focuses on immunotherapy strategies, which means that other emerging therapies or combination approaches may not be fully explored. Since the review only includes published studies, it may miss valuable insights from ongoing or unpublished research, which could provide new perspectives on treating GBM and improving T cell therapies.

9. Future direction

Although many barriers remain, the potential of these approaches is clear: even small improvements in T-cell therapies could bring meaningful survival and better quality of life for patients with GBM. Yet important gaps persist we still lack reliable biomarkers, a full understanding of T-cell exhaustion, and long-term clinical data. Progress in T-cell therapies for GBM is likely to come from smarter combinations rather than single breakthroughs. Advances in imaging, biomarkers, and engineered CAR-T cells will gradually move from experimental to early clinical practice. Most importantly, closer collaboration between researchers and clinicians may finally turn today's hopeful concepts into real options that improve both survival and quality of life for patients. When we think about what "success" should mean for GBM immunotherapy, it is clear that survival alone cannot tell the whole story. Of course, overall survival and PFS remain critical endpoints, but patients and families also care deeply about what those months or years of life look like. Preserving quality of life, maintaining independence, cognitive function, and the ability to engage in daily activities, must be measured alongside traditional survival metrics. At the same time, biological markers are essential to show that therapies are working in the way they are intended. Evidence of sustained T-cell infiltration, persistence, and functional activity in the tumor can provide confidence that an immune therapy is truly altering the disease process, not just delaying it. By combining clinical outcomes, patient-reported measures, and biological readouts, future trials can offer a fuller and more meaningful picture of therapeutic success. Researchers are addressing these challenges through adaptive trial designs, advanced imaging and biopsy tools, and close collaboration across disciplines. Looking ahead, gene-editing tools such as CRISPR-Cas9 open exciting opportunities to make T-cell therapies more powerful and durable. With CRISPR, scientists can turn off "brakes" like PD-1, adjust metabolic pathways to keep T cells from tiring too quickly, or even design synthetic switches that help these cells stay active inside the tumor. Although most of these approaches are still in the lab, they represent one of the most promising frontiers for the future of GBM immunotherapy. By acknowledging both the promise and the obstacles, we aim to give readers not only a clearer scientific view

but also a sense of the urgent human drive to turn these strategies into real therapies.

10. Conclusion

While GBM presents formidable challenges to T cell-based immunotherapy, understanding these challenges at mechanistic levels provides clear paths forward. The convergence of multiple technological advances from sophisticated CAR-T cell engineering to innovative nanoparticle delivery systems represents a paradigm shift from traditional cytotoxic approaches to precision immunotherapy. Success will require addressing multiple barriers simultaneously through rational combinations that target physical barriers, immunosuppressive factors, and metabolic challenges. In simple terms, the obstacles that stop T cells from reaching and fighting GBM can be thought of as three layers. First, there are physical barriers, the protective walls of the brain (BBB/BTB) and a dense extracellular matrix, that keep immune cells out. Second, the immunological barriers: suppressive cells and signals in the TME that weaken and exhaust T cells. Finally, the tumor's own tricks and metabolic challenges, like hiding antigens, creating hypoxia, or releasing adenosine, which make the environment hostile for T cells. Overcoming just one of these walls is rarely enough; real progress will come from strategies that tackle all three at the same time.

GBM surrounds itself with strong immune brakes. TGF-β and IL-10 silence T-cell activity, while PD-L1 pushes them into exhaustion. On top of this, Tregs and MDSCs actively suppress immune responses, reinforced by M2 macrophages. Together, these signals and cells create a hostile microenvironment that T cells alone cannot overcome without targeted intervention. With continued innovation in trial design, biomarker development, and combination strategies, the transformation of GBM from a uniformly fatal disease to a treatable condition is becoming increasingly achievable, offering hope to patients who currently face limited therapeutic options.

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No datasets were generated or analyzed during the current study.

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Not applicable.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no competing interests.

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