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Antibody therapies in glioblastoma: Overcoming micro-environmental barriers

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ABSTRACT

Glioblastoma (GBM) remains the most aggressive adult brain tumor, with median survival largely unchanged over two decades. Antibody-based therapies have shown promise in hematologic and systemic cancers, but translation to GBM has been hindered by the tumor's hostile microenvironment and immune evasion mechanisms. A structured literature search was conducted in PubMed, Scopus, Web of Science, and ClinicalTrials.gov for studies published between 2010 and 2025. Eligible publications included preclinical investigations, clinical trials, and reviews addressing antibody-based therapies, tumor microenvironmental barriers, and computational innovations. Data were synthesized into thematic categories: mechanisms of resistance, antibody-based platforms, nanotechnology-assisted delivery, and artificial intelligence (AI)-driven strategies. Antibody therapeutics including monoclonal antibodies, antibody–drug conjugates, bispecific antibodies, and photoimmunotherapy show potential to enhance tumor targeting and immune activation. Key barriers such as the blood–brain barrier, immunosuppressive cell infiltration, and tumor heterogeneity significantly restrict efficacy. Novel approaches, including AI-enabled antibody design, digital twin modeling, and biomarker-driven patient stratification, offer opportunities to improve precision and overcome resistance. Combination strategies with radiotherapy, vaccines, or adoptive cell therapies further expand therapeutic potential. By reframing antibody therapy through the lens of barrier disarmament and technological integration, this review positions antibody-based approaches as realistic pillars of future GBM management. Strategic innovations in delivery, engineering, and computational modeling may transform antibodies from experimental tools into cornerstone therapies for this lethal malignancy.

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Introduction

The most prevalent and aggressive primary brain cancer in adults, WHO grade 4 glioblastoma (GBM), is characterized by rapid clinical development and poor survival rates (1). Despite advancements in surgery, radiation, and chemotherapy, patients still only have a median lifespan of 12 to 15 months after diagnosis. About 5,000 new instances of GBM are diagnosed annually in Germany, where the disease affects about 6 out of every 100,000 persons. Significant morbidity and death result from its aggressive biology and the invasive nature of surgical therapy (2-4).

GBM is the most malignant adult brain tumor, rapidly

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invasive and recurrent, with median survival below 15 months (5). Two primary categories of antiangiogenic (AA) medicines target the microvasculature of this highly vascular tumor in several new therapies (6-11). These treatments function by either selectively harming the tumor vasculature that already exists or by stopping the development of new blood vessels. Antiangiogenic therapies mostly target the inhibition of vascular endothelial growth factor (VEGF), a crucial protein that stimulates the creation of blood vessels and is widely distributed in gliomas (12, 13). On the other hand, other treatments focus on VEGF receptors (VEGFRs). VEGF improves the permeability of preexisting blood vessels in addition to promoting the development of delicate, leaky micro vessels. According to Vredenburgh *et al.*, this process plays a major role in the vascularization of tumors in gliomas (6). Bevacizumab, which targets VEGF-A, increased progression-free survival to more than double that of previous results in recurrent malignant glioma, according to a phase II study conducted by Vredenburgh *et al.* The contrast-enhancing tumor volume on T1-weighted post-contrast MRI decreased by more than 50% in around two-thirds of patients, indicating a partial response (14). Because the tumor depends on angiogenesis, antiangiogenic treatments that prevent the growth of new blood vessels have been developed (15). These treatments deprive the tumor of oxygen and nutrients that are necessary for its growth by preventing the development of new blood vessels. Early laboratory research and first clinical trials revealed encouraging outcomes for antiangiogenic drugs, especially those that target VEGF and its receptors (16). In individuals with GBM, bevacizumab, a monoclonal antibody against VEGF, has considerably increased progression-free survival and reduced symptoms (17). Nevertheless, early hope has diminished since these treatments sometimes just provide temporary advantages and don't much increase overall survival. GBM tumors often become resistant to antiangiogenic therapy, which limits long-term success and presents a significant clinical management problem (18). Temozolomide is usually used in conjunction with radiation therapy, chemotherapy, and surgery as part of the conventional treatment (19). However, rather than offering a permanent cure, the primary goals of these therapies are to increase survival and enhance quality of life.

Treatment resistance is widespread because GBM tumors often activate alternate angiogenic pathways to avoid antiangiogenic therapy (20). Tumor cells may compensate for the inhibition of VEGF signaling by up-regulating other pro-angiogenic factors, such as angiopoietins, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), in order to sustain blood vessel creation (21). These other mechanisms can override VEGF suppression, allowing blood vessel development to continue and tumor growth to persist even after therapy (22). Furthermore, inhibiting VEGF could inadvertently make GBM cells more invasive and more likely to spread, thereby accelerating the course of the illness (23). Because of their enhanced invasiveness, tumor cells may penetrate adjacent brain tissue, leading to difficult-to-treat recurrences resistant to conventional treatments (24). Hypoxia, or low oxygen levels in the tumor microenvironment, is another important factor that contributes to resistance to antiangiogenic treatments (25). Hypoxia-inducible factors (HIFs) may be activated when antiangiogenic treatment worsens hypoxia by interfering with the tumor's blood supply (26). Several genes that assist tumor cell survival in low oxygen environments, adjust cellular metabolism, and encourage angiogenesis are regulated by HIFs (27). The tumor thus grows more adaptive and resistant to therapy. This resistance is facilitated by hypoxia, which also induces vascular mimicry, a process in which tumor cells form networks resembling vessels. These structures enable the tumor to continue developing even when treatment disrupts the normal blood vessels, allowing blood to circulate within the tumor without affecting normal endothelial cells (28).

Current treatment approaches are being improved to address the complicated nature of GBM due to its many resistance mechanisms. Combination strategies targeting multiple angiogenic pathways simultaneously are being intensively investigated by researchers. To improve therapeutic effectiveness and overcome resistance, there is now growing interest in combining antiangiogenic medicines with conventional treatments such as immunotherapy, radiation, and chemotherapy (18). Through the alignment of medication with each patient's own cancer features, personalized medicine, which customizes therapy based on a tumor's unique molecular profile, offers promise for better outcomes (29). Furthermore, new avenues for intervention are becoming possible as researchers discover new therapeutic targets outside of the conventional angiogenesis routes. At the same time, there is extensive research on the novel use of nanoparticles to improve drug delivery and effectiveness, which might enhance therapeutic impact and precision in GBM therapy (30). Significant obstacles still need to be overcome to overcome GBM resistance to antiangiogenic treatment, despite notable progress. The tumor's complex microenvironment and its highly adaptable, diverse nature require a dynamic, multimodal therapy strategy that adapts as the tumor evolves (31). Examining the intricate processes that underlie GBM resistance to treatment and investigating combination approaches that may successfully combat the tumor's aggressive and resilient characteristics are the goals of this study. In particular, the study offers a thorough analysis of antibody-based therapy strategies for GBM, emphasizing their modes of action, cutting-edge drug delivery systems, and how the tumor microenvironment affects treatment resistance. Additionally, it evaluates current clinical studies and showcases innovative technologies including antibody–drug conjugates and bispecific antibodies. The research concludes by outlining potential future paths to enhance immunotherapy's accuracy, effectiveness, and general success in treating GBM.

Methods

This review was designed as a structured narrative synthesis integrating both conventional and emerging therapeutic approaches for GBM. A comprehensive literature search was performed in PubMed, Scopus, Web of Science, and ClinicalTrials.gov, covering the period 2010-2025. Keywords included combinations of GBM, antibody therapy, antibody–drug conjugates, bispecific antibodies, immunotherapy, tumor microenvironment, blood–brain barrier, artificial intelligence, and digital twins. Only peer-reviewed articles, open-access clinical trial data, and high-impact preclinical studies were included to ensure

reproducibility and translational relevance.

Inclusion criteria emphasized studies addressing therapeutic efficacy, resistance mechanisms, or novel delivery technologies. Exclusion criteria were non-peer-reviewed reports, duplicate records, or publications lacking sufficient methodological detail. Reference management was performed using EndNote and Zotero to eliminate redundancy.

Data were systematically categorized into four domains: (i) microenvironmental barriers and mechanisms of resistance, (ii) antibody-based therapeutic platforms (monoclonal, bispecific, ADCs), (iii) nanotechnology-assisted and photoimmunotherapy strategies, and (iv) computational innovations such as AI-driven antibody design, digital twin simulations, and immune profiling. Figures were redrawn from open-access sources under CC-BY licenses and adapted to highlight mechanistic pathways.

By combining classical immunotherapeutic evidence with emerging AI-enabled approaches, this methodology ensured a forward-looking and novelty-driven synthesis, positioning antibody therapeutics not only as experimental tools but as future pillars in GBM precision medicine.

The glioblastoma transformative ecosystem

Stromal-immune architecture

GBM is recognized to be a very aggressive brain tumor with a poor prognosis and a short life expectancy (5, 31). In an effort to prevent the growth and spread of tumors, antiangiogenic therapies, particularly those that target VEGF, have been utilized to reduce blood flow to the tumors (31). However, immune system modulation has been shown to be a significant contributing factor in the widespread resistance to these therapies (32). The tumor microenvironment (TME) is significantly altered by antiangiogenic therapies, which may affect therapy effectiveness by altering both innate and adaptive immune responses. The TME is significantly impacted by antiangiogenic therapies, which alter both the innate and adaptive immune responses in ways that might compromise the effectiveness of a treatment (33). These therapies may initially help control the abnormal vasculature's form and slow the development of tumor blood vessels. This vascular remodeling may promote immune cell penetration into the tumor and boost the immunological response (34). However, when the body becomes resistant, the tumor's immunological milieu changes dramatically, ultimately promoting tumor growth and survival. These alterations often create an immunosuppressive environment to help the tumor evade immune attack (35).

Immune regulation during antiangiogenic therapy includes changes in myeloid cell populations, which are essential in defining the tumor's immunological landscape and influencing treatment response (36). Therapy-induced hypoxia often draws myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) to the tumor microenvironment, where they help in immune suppression and encourage tumor growth (37). These cells often have immunosuppressive properties that protect the tumor and promote its development, in addition to initially promoting anti-tumor immunity (38). TAMs emit immunosuppressive cytokines like TGF-β and IL-10, which further weaken the immune system's ability to fight the disease, while MDSCs stop T cells from activating and multiplying (39). Furthermore, by intensifying hypoxia, antiangiogenic therapy may stabilize HIFs. Tumor cells create more immunosuppressive molecules, such as PD-L1, as a result of these factors, which wear out T cells and compromise immune surveillance (40). Hypoxia-driven immunosuppression is a major barrier to the efficacy of antiangiogenic therapies because it reduces the immune system's ability to effectively target and eliminate tumor cells (41). The abnormal vasculature of resistant tumors also creates a physical barrier that limits effective immune infiltration and reduces therapeutic effectiveness, sometimes impeding the transfer of immunotherapy medicines and immune cells (42). Additionally, tumors with abnormal blood artery architecture and high interstitial fluid pressure prevent immune cell infiltration and activity, which reduces the overall effectiveness of immune responses and limits the effectiveness of treatment (43). In conclusion, immune modulation is primarily responsible for GBM's resistance to antiangiogenic therapy. This resistance is caused by a variety of factors, such as the recruitment and activation of immunosuppressive myeloid cells, hypoxia-induced production of immune-suppressive molecules like PD-L1, and physical barriers that prevent immune cell infiltration, such as high interstitial pressure and aberrant vasculature. Understanding these pathways is crucial for the development of combination therapies that might overcome resistance and increase the efficacy of antiangiogenic therapy in GBM.

Furthermore, while little research has looked at how surgical resection affects T cell–mediated antitumor immunity in brain tumors, evidence from non-CNS malignancies suggests that surgical trauma may result in an immunosuppressive stress response. Studies have shown elevated levels of damage-associated molecular patterns (DAMPs) after surgery, which may contribute to this immune suppression (44, 45). DAMPs may originate from a number of substances, including components of the extracellular matrix, nuclear or cytosolic proteins, and waste products released after tissue injury or cell stress (46). Certain DAMPs have been shown to raise IL-1β and IL-18 levels, which promote the migration of MDSCs and macrophages to the tumor microenvironment and create an immunosuppressive environment (46, 47).

Another feature that sets GBM apart is the mechanism by which T cells are trapped in the bone marrow, preventing them from entering the tumor microenvironment or the circulation. This makes it more difficult for the immune system to effectively combat the tumor (48). These occurrences might be caused by the G protein-coupled receptor, the sphingosine-1-phosphate receptor 1 (S1P1), which is expressed on lymphoid and endothelial cells. T cell development in the thymus and the regulation of lymphocyte migration depend on S1P1. When T and B cells express S1P1, they depart from secondary lymphoid organs and enter the peripheral circulation. However, the T cell sequestration observed in GBM is partly due to their retention in the bone marrow, resulting from reduced or absent S1P1 expression (49). In mouse models of GBM, the absence of S1P1 receptors on T cells has been linked to lymphocyte homing to the bone marrow, preventing their circulation and penetration into the tumor site (49).

The observation that human T cells limited to the bone marrow likewise show reduced S1P1 expression compared with those in healthy individuals suggests a

similar mechanism of decreased T cell circulation and tumor infiltration (48). Interestingly, following adoptive transfer, T cells that were altered to express a stable version of S1P1 (S1P1-K1) were able to move to the tumor location without sequestering in the bone marrow. This implies that S1P1 is essential for T cell trafficking and may enhance the efficacy of immunotherapy for GBM (48). S1P1-K1 alone did not significantly improve overall survival, even though it increased T cell infiltration into the central nervous system and restored T cell penetration into the GBM tumor microenvironment. The strong immunosuppressive effects of GBM are most likely the reason for this restricted effect. However, compared to mice treated with S1P1-K1 alone, animals treated with both S1P1-K1 and immune checkpoint inhibition (ICI), such as anti-PD-1 therapy, showed a 50% improvement in long-term survival. According to Chongsathidkiet *et al*., restoring S1P1 surface expression in GBM may increase T cell-mediated immunity as a possible treatment strategy (48).

Both functional and structural barriers

The blood-brain barrier (BBB) protects brain homeostasis by functioning as a highly dynamic and selective interface rather than a passive barrier. Its intricate structure, mainly constructed by brain microvascular endothelial cells (BMECs), which form adherens and tight junctions to maintain barrier integrity, is what gives it its strength. BMECs are distinct from other endothelial cells due to their absence of fenestrations, low levels of caveolar transcytosis and micropinocytosis, and decreased expression of integrin ligands, leukocyte adhesion molecules, and specialized transport systems. Together, these characteristics control immunological cell access and molecular exchange, promoting healthy brain function (50). The brain's interior environment is tightly controlled by BMECs, which carefully regulate the movement of chemicals throughout the vasculature. The Rho GTPase signaling pathway is essential for sustaining this barrier function because it controls the structure and stability of tight junction (TJ) proteins in BMECs, protecting the integrity of the BBB (51). The BBB serves as a selective barrier and is essential for protecting the brain from viruses and toxins, maintaining ionic equilibrium, regulating neurotransmitter levels, facilitating nutrient transport, and eliminating metabolic waste. These roles are maintained by intimate relationships within the neurovascular unit (NVU), where pericytes and astrocytes promote BMEC activity and maintain BBB integrity by contributing structurally and via signaling pathways (50-52).

The transmembrane proteins that make up BMEC tight junctions (TJs) include occludins, claudins, and junctional adhesion molecules (JAMs). These proteins are secured to the actin cytoskeleton by scaffold proteins such as cingulin and Zonula occludens (ZO). Together, these elements preserve the BBB's structural stability and functional integrity by carefully controlling permeability (53). Important BBB constituents occludin, ZO-1, and claudin-5 are highly responsive markers of the permeability of the BBB. Changes in their location or expression often indicate a breakdown in the integrity of the barrier (54). The BBB integrity is significantly influenced by claudins-1, -3, -5, -11, -12, and -25, according to recent research. By functionally interacting with occludin and JAMs and precisely regulating ion permeability, these proteins support the barrier's structural stability and selectivity (54). Occludin and claudins have been shown to create heteropolymers, which might result in dynamic (50), while the claudin-5 protein strengthens the BBB via JAM-A's positive control of C/EBP-α (52).

AJs give structural support, provide an intercellular route connecting neighboring cells, and comprise cadherins, catenins, vinculin, and actinin (55). In order for BMEC junctions to develop and remain intact, VE-cadherin is essential. It maintains the integrity of tight junctions by controlling the expression of the claudin gene by activating Wnt signaling, inhibiting the transcription factor FoxO1, and stabilizing β-catenin via its interaction with the actin cytoskeleton. The BBB's structural cohesiveness and appropriate barrier function are guaranteed by this cooperation (52). When VE-cadherin is lost, the integrity of TJs is compromised, and important junctional proteins, including ZO-1, claudin-1, and claudin-4, are not properly localized. This results in a weaker BBB structure and greater permeability (52). N-cadherin promotes the stability of the fibroblast growth factor receptor (FGFR) and activates important signaling pathways, including MPK/ERK and PI3K, which support cell survival, proliferation, and migration, while E-cadherin strengthens cell–cell adhesion and contributes to tissue cohesiveness (54).

The BBB is further strengthened by the Basement Membrane (BME)(56). Through its interactions with extracellular matrix (ECM) proteins, N-cadherin also aids in the regulation of BBB permeability and structural integrity, supporting signaling, cell adhesion, and barrier stability (54). NVU components bind to the BME via dystroglycan receptors and integrins (56). Cellular structure is maintained by the binding of extracellular α-dystroglycan to BME proteins and the anchoring of this complex to the actin cytoskeleton by transmembrane β-dystroglycan. Additionally, integrins, which are made up of α- and β-subunits, engage with vascular BME components to start intracellular signaling cascades. BMECs, pericytes, and astrocytes produce β1-integrins, which are essential for maintaining the integrity of the BBB. They do this by binding to collagen IV in the BME and regulating claudin-5 production, a crucial tight junction protein (51).

The BBB's regulatory center, the NVU, is composed of many cell types. Because they maintain both structural integrity and dynamic barrier modulation by modulating BBB permeability via calcium (Ca^{2+}) signaling and strengthening TJ continuity in BMECs, astrocytes are crucial components (51). Glial Fibrillary Acidic Protein (GFAP) and Vimentin play a significant role in maintaining the structural integrity of astrocyte end-feet processes (51). However, under adverse conditions, reactive astrogliosis can be triggered, leading to the structural integrity of astrocyte end-feet processes being maintained mainly by vimentin and GFAP (51, 53). By contracting or relaxing blood vessels, pericytes help eliminate harmful chemicals from the brain and regulate cerebral blood flow. The precise regulation of vascular tone at the BBB is enabled by the production of contractile proteins, such as myosin, tropomyosin, and α-smooth muscle actin (α-SMA) (53, 57). Additionally, pericytes release signaling molecules that sustain the structural and functional integrity of BMECs and influence astrocyte polarization toward either neuroprotective or

neurotoxic phenotypes, thereby supporting the overall stability of the BBB (58). Additionally, they alter the angiogenic factors NOTCH 3 and VEGFR and have an impact on cellular functions (58). The expression of TJ proteins in BMECs is believed to be mostly regulated by the Sonic hedgehog (Shh) signaling pathway in pericytes. By activating this process, pericytes may increase the synthesis of proteins such as occludin and claudins, thereby strengthening the BBB's integrity and selective permeability. Altogether, these cellular and molecular components sustain the structural integrity and selective permeability of the BBB. However, in GBM, the same features that protect brain homeostasis also contribute to therapeutic resistance and immune evasion. By restricting the trafficking of lymphocytes and therapeutic antibodies, the BBB limits effective immune surveillance. In parallel, pericytes, astrocytes, and endothelial signaling pathways foster an environment that attracts immunosuppressive cells such as TAMs and MDSCs, while reducing the infiltration of effector T cells. As a result, the BBB does not act in isolation but functions synergistically with tumor-driven immunosuppressive mechanisms to create a dual barrier, physical and immunological, that undermines treatment efficacy. These interlinked processes are summarized in Figure 1, which illustrates how BBB restriction, stromal support, and tumor-induced immune suppression converge to limit antitumor responses in GBM (Figure 1)(51-54).

Although it has been shown that the Spock1 gene affects BBB growth and maintenance, neurons play only a minor role in the BBB (60). It has been shown that in BMECs, neural activity alters the expression of genes linked to circadian rhythm and BBB efflux transporters. By enabling dynamic, activity-dependent modulation of BBB function, this relationship allows barrier permeability to align with physiological cycles and brain demands (61). According to recent research, neurons may strengthen the protective mechanisms of the BBB by encouraging the production of tight junction proteins, including VE-cadherin and claudin-5. Glial cell line-derived neurotrophic factor (GDNF), which fortifies BMEC junctions and maintains barrier integrity, is released by neurons to mediate this action (62). Near neocortical gray matter capillaries are oligodendrocyte precursor cells (OPCs), suggesting a possible function in fostering angiogenesis. In response to HIF activation, OPCs may help control and modify the local vascular network to fulfill the metabolic needs necessary for their differentiation and maturation by secreting Wnt and VEGF (63-65).

Although not direct parts of the NVU, microglia are essential for maintaining homeostasis in the central nervous system (CNS). They contribute to immunological defense, synaptic remodeling, and general neural stability by continuously assessing their environment and regulating neuronal activity (66, 67). M1 or M2 phenotypes may be adopted by microglia in response to environmental stimuli. The pro-inflammatory M1 phenotype supports pathogen protection and immune activation, while the anti-inflammatory M2 phenotype supports tissue healing and inflammation resolution (67). Microglia may maintain the integrity of the BBB in non-inflammatory settings, as shown

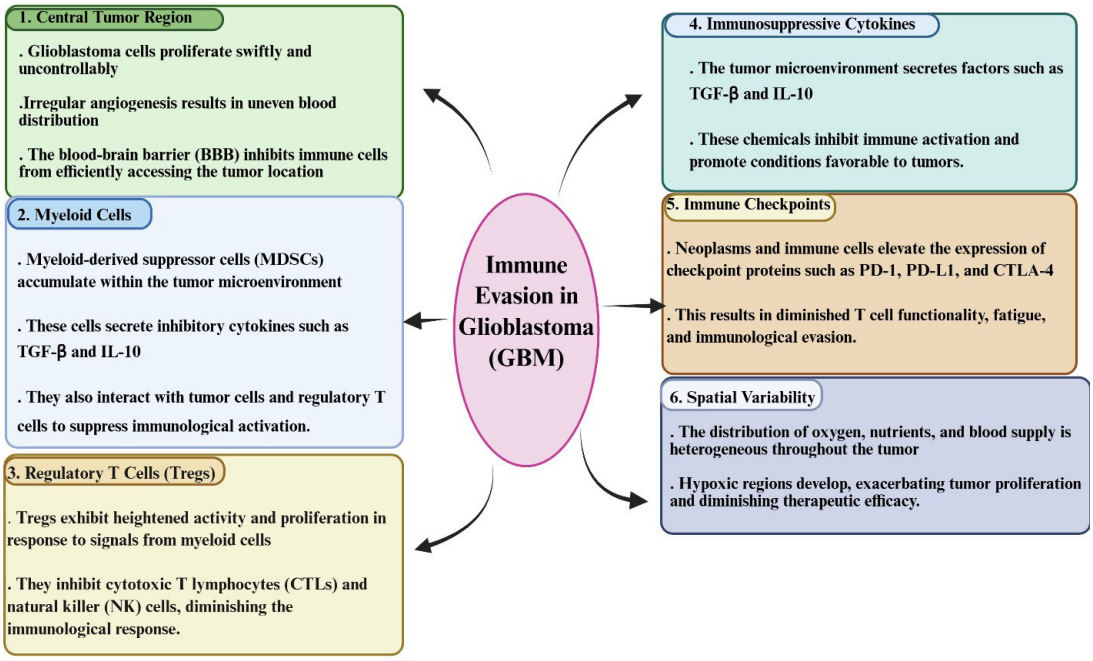

Figure 1. Mechanisms of immune evasion in glioblastoma hinder antitumor response and reduce treatment efficacy
This schematic illustrates the multifactorial mechanisms contributing to immune evasion in GBM, a highly aggressive brain tumor. The central tumor region features rapid cell proliferation, aberrant angiogenesis, and a restrictive BBB, all of which limit immune cell infiltration. MDSCs infiltrate the tumor microenvironment and release immunosuppressive cytokines such as TGF-β and IL-10, inhibiting immune cell activity. These MDSCs also interact with regulatory T cells (Tregs), which are expanded and activated in response to MDSC signaling. Tregs suppress cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, reducing immune-mediated tumor clearance
In addition, the tumor secretes immunosuppressive cytokines (TGF-β, IL-10), further dampening immune activation and promoting tumor progression. The up-regulation of immune checkpoint proteins, such as PD-1, PD-L1, and CTLA-4, on tumor and immune cells leads to T cell exhaustion and immune evasion. Spatial heterogeneity within the tumor, including uneven distribution of oxygen and nutrients, results in hypoxic regions that not only support tumor growth but also confer resistance to therapies
Together, these interconnected factors create an immunosuppressive tumor microenvironment in GBM that impedes immune surveillance and limits the effectiveness of current immunotherapeutic strategies. Understanding these barriers is essential for developing more effective interventions (59)

by *in vitro* co-culture experiments combining mouse BMECs and resting microglia that revealed increased expression of important TJ proteins (68-70). The BBB's structure, function, and gene expression may not be maintained by microglia in healthy brains, according to current research, suggesting that their supporting function may be more pertinent in inflammatory, illness, or damage situations than in physiologically normal circumstances (Table 1)(71).

Mechanistic routes of therapy driven by antibodies

Accurately directed tumor attack

A minor, therapy-resistant subpopulation of cancer stem cells (CSCs) propels the onset, maintenance, and recurrence of GBM. CSCs often have elevated levels of CD44 and CD133, which are associated with self-renewal, invasiveness, and suboptimal responses to conventional treatment. CD44 interacts with hyaluronic acid in the extracellular matrix to facilitate adhesion and migration, while CD133 (prominin-1) contributes to the maintenance of an undifferentiated, stem-like phenotype in neural-lineage tumor cells (97).

Antibody-based strategies targeting CSC markers offer a viable approach to combat GBM development. Among them, near-infrared photoimmunotherapy (NIR-PIT) is distinguished by its therapeutic potential. This method combines monoclonal antibodies with a photosensitizer, such as IR700, which binds to tumor-specific antigens. Upon activation by near-infrared light, the photosensitizer elicits immunogenic and necrotic cell death, ensuring spatial and antigen-specific precision that minimizes collateral harm to adjacent healthy tissue (98).

In preclinical GBM models, NIR-PIT targeting CD133 extended survival and significantly inhibited tumor development, underscoring its potential to prevent recurrence by eradicating cancer stem cells. Similar results have been shown in lung, colon, and oral cancer models with CD44-targeted NIR-PIT, resulting in decelerated tumor development and enhanced survival rates. Nonetheless, exclusive targeting of CD44 has not resulted in total tumor eradication, indicating that the incorporation of adjunct medicines may be essential for sustained and thorough management (99).

Table 1. Key cellular and molecular components of the GBM tumor microenvironment are described, with a focus on their distinct functions, possible treatment advantages, related difficulties, and pertinent experimental research results

Component	Type	Key role	Novel insight	Evidence	Main challenge	Translational impact	References
S1P1	GPCR	Regulates T cell egress	Restores CNS infiltration; synergy with ICIs	Adoptive T cell transfer in GBM mice	Limited benefit alone	Increases T cell trafficking, particularly when used with ICIs.	(72, 73)
CCL5 (TAMs)	Chemokine	Promotes GBM invasion	TAM-derived invasion driver	TAM-conditioned media assays	A few selective inhibitors	TAM CCL5 signaling blocking may reduce invasion and aid immunotherapy.	(74, 75)
TREM1	Receptor	Induces TGF-β2, enhances stemness	Links TAMs to invasive GSC traits	TREM1 knockdown studies	Pathway redundancy	Inhibition may lessen the chance of recurrence and inhibit GSC characteristics.	(76)
GPR81	GPCR	Lactate suppresses NF-κB/YAP	Highlights metabolic immune evasion (macrophages/TAMs)	Lactate GPR81 *in vitro*	Off-target metabolic risks	TAM-mediated immune evasion may be reversed by targeting lactate GPR81.	(77, 78)
FOXP3$^+$ Tregs	T cells	Suppress CD8$^+$ responses	Depletion reactivates immunity	Treg depletion + ICI models	Autoimmunity risk	Modifying Tregs may improve checkpoint blockade responses.	(79, 80)
Claudin-5	TJ protein	Maintains BBB integrity	Early marker of BBB disruption	In vivo BBB imaging	Functional overlap with other claudins	Serves as a gauge of potential medication delivery and BBB disruption.	(81, 82)
VE-Cadherin	Adherens protein	Coordinates endothelial junctions via Wnt/β-catenin	Endothelial repair role in GBM vasculature	Murine deletion studies	Compensatory signaling	Aim for better access to treatment and vascular repair	(83, 84)
β1-Integrin	Adhesion receptor	Anchors NVU to ECM	Links ECM stability with BBB function	Integrin inhibition models	Broad physiological roles	Blocking might facilitate penetration and impair the GBM vasculature.	(85)
GFAP	Cytoskeletal protein	Marker of astrogliosis	May distinguish astrocyte states (A1/A2)	Murine stress models	Difficulty separating A1 vs. A2	helpful in differentiating astrocyte subtypes in the course of GBM	(86, 87)
GDNF	Neurotrophic factor	Up-regulates claudin-5 & VE-cadherin	Neurotrophic reinforcement of the BBB	BMEC treatment with GDNF	Complex signaling networks	Possible indicator or target for neuro-oncology's BBB stability	(88)
HIFs	Transcription factors	Drive PD-L1 and hypoxic suppression	Explain hypoxia-driven immune escape	Stable HIF hypoxia models	Multi-pathway effects	Under hypoxia, HIF inhibition may improve immunotherapy.	(89)
Spock1	Neuronal protein	Modulates BBB/TJ expression	Neuronal regulation of the barrier in GBM	Spock1 overexpression	Limited GBM specificity	Potential biomarker for BBB neuronal modulation in GBM	(90)
Wnt (OPCs)	Signaling protein	Supports angiogenesis, vascular remodeling	OPC-derived VEGFA/Wnt contribute under hypoxia	OPC assays + HIF activation	Broad developmental roles	By targeting Wnt generated from OPC, the tumor vasculature may be disrupted	(91, 92)
TGF-β2	Cytokine	Enhances GBM stemness	Connects TAM activation with GSC traits	Cytokine profiling in TREM1+ TAMs	Dual role in repair & immunity	Blocking might increase immunological activation and inhibit CSCs	(93, 94)
JAM-A	TJ protein	Strengthens BBB via C/EBP-α	Identifies new transcriptional axis	JAM-A/C/EBP-α assays	Redundancy with other TJ proteins	Target for adjusting BBB permeability during the administration of treatment	(95, 96)

To improve treatment effectiveness, researchers have investigated dual-targeting techniques. In preclinical trials, the combination of CD44-directed NIR-PIT with checkpoint inhibitors (anti-CTLA-4 or anti-PD-1) or Treg-targeting drugs (anti-CD25) led to complete tumor regression. These strategies not only eradicate CSCs but also rejuvenate antitumor immunity by transforming the immunosuppressive GBM microenvironment (100). Notwithstanding encouraging advancements, considerable obstacles persist. Numerous tumor-associated antigens, including CD44, are concurrently expressed on normal immune cells, such as dendritic cells, which are essential for the activation of cytotoxic T cells. Collateral damage to these cells during photoimmunotherapy may compromise overall antitumor immunity. Consequently, antigen selection must meticulously balance treatment specificity with the maintenance of vital immune processes to guarantee both safety and therapeutic effectiveness (101). In conclusion, NIR-PIT targeting CSC markers presents a precise and unique approach to combat GBM's resistance and recurrence. In addition to eliminating tumor-initiating cells, its incorporation into immune-modulating therapy may help reshape the suppressive microenvironment. Collectively, these results directly address two primary obstacles in GBM therapy: treatment resistance and immune evasion (102, 103). In conclusion, NIR-PIT targeting CSC markers presents a precise and unique approach to combat GBM's resistance and recurrence. In addition to eliminating tumor-initiating cells, its incorporation into immune-modulating therapy may help reshape the suppressive microenvironment (104, 105). Collectively, these results directly address two primary obstacles in GBM therapy: treatment resistance and immune evasion (130, 131). The defining features and molecular hallmarks of GBM stem-like cells (GSCs), which drive tumor initiation and recurrence, are illustrated in Figure 2. This schematic highlights their stemness traits, key markers, and differentiation potential, underscoring why they remain central targets for therapeutic innovation.

Antibody conjugates for intelligent payload delivery

Several FDA-approved medications in recent years have resulted from a crucial therapeutic strategy that uses antibodies' antigen-specific targeting to accurately identify and target diseased cells (106). Antibodies may attach to membrane proteins that tumor cells often overexpress on their exterior domains. The antigen's function may be blocked by this binding, immune-mediated tumor cell death may be triggered, or ADCs may be used to precisely deliver cytotoxic drugs. These are just a few of the ways they might be helpful (106).

One membrane-bound protein that is significantly overexpressed in a particular subtype of gliomas is tissue factor (TF), encoded by the F3 gene and a potential target for antibody-based treatments (106). Although TF is mostly recognized for starting the blood coagulation cascade's rate-limiting phase, it also supports tumor growth and survival by activating important oncogenic pathways,

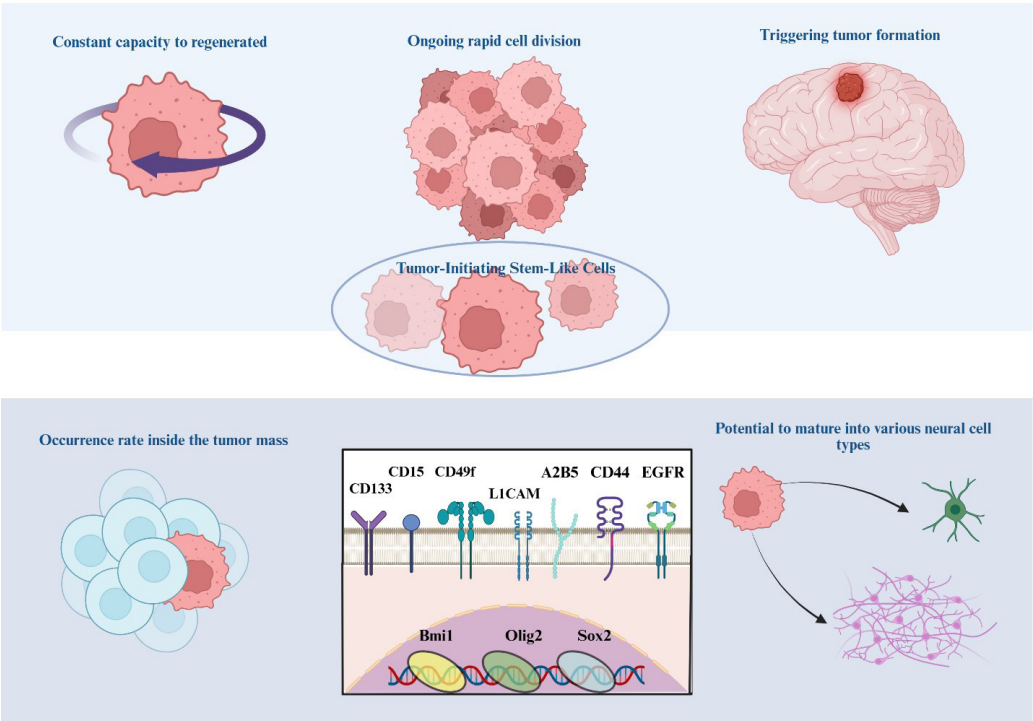

Figure 2. Key functional and molecular traits of glioblastoma stem-like cells are depicted schematically
This schematic illustration outlines the fundamental features and molecular markers of GSCs, a subpopulation of tumor cells responsible for tumor initiation, resistance, and recurrence. The upper panel highlights their defining functional characteristics: sustained self-renewal, persistent proliferation, and the ability to initiate tumor growth in the brain. These properties enable GSCs to continually regenerate and expand the tumor mass. The lower section of the figure depicts additional but non-exclusive attributes of GSCs. On the left, their relative frequency in the tumor microenvironment is illustrated, highlighting their presence within heterogeneous cell populations. The central box shows key surface markers commonly expressed on GSCs, including CD133, CD15, CD49f, L1CAM, A2B5, CD44, and EGFR, which are frequently used for their identification and isolation. Also depicted are stemness-associated transcription factors like Bmi1, Olig2, and Sox2, which regulate GSC maintenance and survival. On the right, the diagram demonstrates the multipotent differentiation potential of GSCs into various neural lineages, such as neurons and glial cells. Together, these features underscore the central role of GSCs in GBM progression and therapeutic resistance, underscoring their importance as critical targets for novel, more effective GBM treatments (104, 105)

including EGFR, ERK, and AKT, which increases tumor aggressiveness (106). To date, the only FDA-approved drug that targets TF is an antibody–drug conjugate (ADC) used for the treatment of recurrent or metastatic cervical cancer named tisotumab vedotin-tftv (TisVed)(106). An intracellularly cleavable linker, a human IgG1 monoclonal antibody that targets extracellular TF, and monomethyl auristatin E (MMAE), a cytotoxic chemical released within the targeted cell to cause cell death, make up this ADC (106). Strong antimitotic MMAE stops cell division by interfering with tubulin polymerization. However, because of its extreme toxicity, it has to be supplied selectively, such as by antibody–drug conjugates, and cannot be used as a stand-alone medication (106). In addition to providing MMAE, TisVed's monoclonal antibody component, tisotumab (Tis), may also help reduce tumors by blocking ERK signaling, adding another therapeutic benefit to targeted medication delivery (106).

By hypermethylating the F3 gene promoter, IDH-mutant (IDHmut) gliomas down-regulate TF, reducing its transcription and therapeutic target potential in these malignancies. In contrast, IDH-wildtype (IDHwt) GBMs usually exhibit significant TF expression (106). This helps explain why IDHmut gliomas are less thrombogenic and aggressive (106). TisVed has not yet been studied in gliomas, despite having been assessed in a variety of carcinoma forms. Interestingly, research has shown that TF expression is more prominent and pervasive in GBM than in cervical cancer, the only cancer type for which TisVed is presently approved by the FDA. This suggests that TisVed has unrealized potential as a treatment for GBM (106). Given these findings, we postulated that TisVed would be a useful treatment for IDH-wildtype GBM, which has high TF expression, but not for IDH-mutant gliomas, which have low TF levels due to promoter methylation.

Immune modulation orchestrated by antibodies

In order to combat tumor heterogeneity and lower the possibility of antigen escape, scientists created CAR-T cells that could target both EGFRvIII and IL13Rα2, two antigens that are often overexpressed in GBM. The safety and effectiveness of intrathecally delivered CAR-T cells that target both antigens were assessed in six patients with recurrent GBM in a Phase 1 clinical study (NCT05168423) (107). The medication demonstrated early biological activity and safety, and its neurotoxic side effects were well controlled. Although some patients' tumors shrank, these alterations did not satisfy the official standards for an objective response. To confirm the therapeutic efficacy of this dual-targeting CAR-T strategy in GBM, further research is needed (107). In another research, a bispecific CAR-T cell that targets IL-13Rα2 and concurrently modulates TGF-β signaling, an immunosuppressive cytokine that is prominent in the GBM microenvironment, was introduced. Through the conversion of TGF-β's suppressive signals into stimulatory ones, these modified CAR-T cells improve T cell infiltration, lower immunosuppressive myeloid populations, and eventually increase survival in preclinical GBM models (108). CART. Bispecific T-cell engagers (BiTEs), which identify EGFR, are secreted concurrently with a CAR that targets EGFRvIII. BiTE cells were designed to combine these two tactics. By tackling the antigen heterogeneity of GBM, this approach allows them to kill both $EGFRvIII^+$ and $EGFR^+$ tumor cells. CART addresses the drawbacks of single-antigen CAR-T strategies. BiTE treatment, which calls on nearby (bystander) T cells to target EGFR-positive tumor cells. These cells were able to eradicate malignancies in mouse models as well as human skin grafts without causing any off-target damage or detectable systemic BiTEs (109). Recently, a tri-modular CAR-T construct, CART-EGFR-IL13Rα2-dnTGFβRII, has been developed by neutralizing TGF-β-driven suppression; this approach aims to counteract the immunosuppressive GBM microenvironment. It decreased TGF-β levels and increased the fitness of neighboring immune cells, as well as T cell proliferation and functional responses. This strategy's safety and therapeutic efficacy in treating GBM were validated by *in vivo* models (110).

BiTEs, fusion proteins that bind T cells and tumor-specific antigens concurrently, may be secreted by genetically modifying macrophages. This allows T cells to attach to tumor cells and promotes precision, targeted immune-mediated tumor elimination (111). In GBM, macrophages were engineered to secrete a bispecific T-cell engager (BiTE) targeting EGFRvIII. This effectively activated T cells and decreased tumor burden in xenograft mice. The anticancer response was significantly enhanced, and tumor growth was totally stopped when these macrophages additionally expressed IL-12. This approach leverages macrophages' natural capacity to enter tumors, providing a potent platform for targeted immunotherapy and improved treatment effectiveness in GBM (112).

Treatment for GBM is increasingly being tailored to the unique genetic and molecular characteristics of each tumor. Using tumor mutational burden (TMB) and tumor-specific neoantigens to create customized vaccines that target particular tumor markers and elicit tailored immune responses is a promising approach (113). TMB is a possible biomarker for the efficacy of immunotherapy since it is often linked to better responses to immune checkpoint inhibitors. To increase anti-tumor immunity in GBM, ongoing clinical studies are investigating the efficacy of customized vaccinations that target neoantigens resulting from each patient's distinct tumor mutations (114). In order to better identify and eliminate tumor cells, these customized vaccinations aim to stimulate the patient's immune system. At the same time, the GBM TME is being more precisely mapped using single-cell RNA sequencing, which reveals the relationships and makeup of immune cells. More individualized immunotherapies may be developed thanks to this thorough screening. Checkpoint inhibitors and tumor-targeted T-cell engagers, such as BiTEs or bispecific antibodies, are a new tactic that aims to increase T-cell activation and infiltration while decreasing the tumor's capacity to elude immune identification (115). A novel family of immunotherapies called CD3 bispecific antibodies binds to both a tumor-specific antigen and CD3 on T cells, rerouting T cells onto GBM tumor cells. In clinical studies, these drugs have shown promising results, providing a focused strategy to increase T cell-mediated cytotoxicity against GBM cells in particular (116). Furthermore, liquid biopsy techniques are being researched as a non-invasive means of monitoring GBM's genetic and immunological alterations in real time. Clinicians may provide more individualized and adaptable therapy by carefully modifying treatment plans in response to the tumor's development and

changing resistance patterns by examining circulating tumor DNA or immunological markers (117). The complicated resistance mechanisms and significant tumor heterogeneity of GBM may be addressed more precisely with personalized therapy. Even though they have significant potential to improve outcomes, further clinical research is needed to refine these strategies and validate their efficacy in larger patient populations. A comprehensive summary of these antibody-based therapeutic approaches, their molecular targets, advantages, and limitations is provided in Table 2.

New developments in antibody-based GBM treatment

GBM checkpoint blockade techniques

The safety, viability, and effects of nivolumab as a neoadjuvant and adjuvant PD-1 blockade in GBM patients were evaluated by Schalper *et al.* in a single-arm phase II experiment (125, 126). One preoperative dosage of nivolumab (3 mg/kg) was administered two weeks before resection, and further doses were given every two weeks until progression or severe toxicity (126). With a median OS of 7.3 months and PFS of 4.1 months, the study showed no discernible overall survival improvement. For more than 28 months, two patients who had gross complete resection, however, were disease-free. T-cell infiltration and receptor diversity increased after therapy, as assessed by tumor analysis, indicating an immunomodulatory effect. Further research on neoadjuvant immune checkpoint suppression in GBM is supported by these results (126).

Neoadjuvant pembrolizumab was tested in 15 patients with recurrent GBM in a single-arm, open-label phase I study by de Groot *et al.* to determine its therapeutic effect as a PD-1 inhibitor (127). After the original Stupp procedure, patients with MRI-confirmed recurrence were recruited. They were given up to two doses of neoadjuvant pembrolizumab on days 21 and 1 before surgery. They were then given further doses every three weeks until the condition worsened or the adverse effects became unbearable (127). The study found that the 6-month PFS rate was 40% and the median PFS was 4.5 months. With an estimated 63% survival rate at 1 year, the median OS was 20.3 months. Immune profiling verified that, even after treatment, the highly immunosuppressive milieu of GBM was characterized by an abundance of CD68-like macrophages and a scarcity of CD4-/CD8- T cells (128). These findings demonstrate the difficulties in obtaining successful immunotherapy responses and the enduring immune resistance in GBM (127).

Though it binds CD80/CD86 more firmly than CD28, CTLA-4, an inhibitory receptor on active T cells, outcompetes CD28 and inhibits T cell activation (129, 130). It may also decrease the expression of CD80/CD86 on the surface of antigen-presenting cells via trans-endocytosis (129). The well-known CTLA-4 blocker ipilimumab restores T cell suppression. Although further confirmation in phase II studies is required, a phase I study that combined ipilimumab and nivolumab with conventional therapy in newly diagnosed GBM revealed a promising median OS of 20.7 months (131). At a 13.7-month follow-up, ipilimumab, nivolumab, and radiation treatment combined produced a comparable overall survival but a shorter median PFS than standard care in newly diagnosed MGMT-unmethylated GBM (132).

Ipilimumab and nivolumab together produced a low mOS of 7.3 months in recurrent GBM (129, 133). Radiotherapy plus ipilimumab and nivolumab together did not clearly outperform nivolumab alone; overall survival was similar, but PFS was worse, underscoring the need for careful assessment of this dual checkpoint approach. Overall, the tumor's limited immunogenicity, low mutational load, and highly immunosuppressive microenvironment restrict T-cell infiltration and activity, which is primarily responsible for the moderate results of immune checkpoint inhibitor monotherapies in GBM. By triggering apoptosis and releasing tumor-associated antigens (TAAs), novel treatments such as tumor-

Table 2. An extensive overview of antibody-driven treatments for glioblastoma (GBM) that addresses important molecular targets, mechanisms of action, therapeutic advantages, present difficulties, and potential future paths for translational research

Mechanism of action	Target(s)	Therapeutic strategy	Advantages	Limitations / challenges	References
Direct tumor targeting (NIR-PIT)	CD44, CD133, CD25, CTLA-4, EGFR	NIR light induces apoptosis via antibody–photosensitizer interaction	Extremely accurate, preserves tissue, and amplifies antigen-specific T cell responses.	Possible risk: co-expression of antigens in healthy immune cells (e.g., dendritic cells).	(118, 119)
Immune checkpoint inhibition	PD-1, CTLA-4, TIGIT, CD73, LGMN, IDO	Blockade of inhibitory receptors reinstates T-cell functionality	Augments immune infiltration and collaborates with metabolic reprogramming	Efficacy is limited by hypoxia, metabolic stress, and tumor heterogeneity	(120)
Antibody-Drug Conjugates (ADCs)	Tissue Factor (TF)	Antibodies convey cytotoxic agents (e.g., MMAE)	Robust tumor eradication with minor systemic damage	Limited clinical evidence specific to GBM; possible off-target effects	(121)
Bispecific antibodies / CAR-T BiTEs	EGFRvIII, IL13Rα2, TGF-β, CD3, CD73	Dual-targeting antibodies and BiTEs stimulate CAR-T and T cells	Mitigates antigen depletion, enlists bystander T cells, and enhances immunological response	Intricate design, preliminary testing, long-term advantages unclear	(122)
Antibody-mediated cell depletion / activation	CD4, CD20, CAIX, TRPV1	Full or fragment antibodies trigger ADCC, CDC, or immune modulation	Adaptable formats with tunable half-life and specificity	Fragment instability, immunogenicity, and clearance mediated by Fc	(123)
Photoimmunotherapy (PDT/PTT with ANCs)	PD-L1, TRPV1, Her2, bacterial antigens	Conjugates of antibodies and nanoparticles allow for tailored phototherapy	Allows for precise tumor ablation, integrates imaging and treatment, and is less invasive	Limited tissue penetration; adjustments to the laser and ANC are necessary	(124)

treating fields (TTF) and laser interstitial thermal therapy (LITT) may provide safer alternatives to chemoradiation, although their mechanisms remain under investigation. Beyond PD-1 and CTLA-4, phase I/II studies are investigating additional immune checkpoints such as TIM-3 (NCT03961971), IDO inhibitors (NCT04047706, NCT02052648), TIGIT (NCT04656535), LAG-3 via relatlimab (NCT02658981, NCT03493932), and CD137 (NCT02658981). The results of GBM studies have been mixed, despite continuous clinical efforts. Long-term therapy effectiveness is diminished, and resistance is fueled by tumor heterogeneity, both within and across individuals. Furthermore, the blood–brain barrier remains a significant impediment to efficient drug delivery, undermining the therapeutic benefit of several systemic medicines (44). Because of the tumor's quick adaptability and varied expression, targeted therapy targeting EGFR or IDH mutations has had little effectiveness in GBM. Anti-PD-1 immunotherapies, such as nivolumab, also work poorly due to the immunosuppressive milieu, low T-cell infiltration, and low mutational burden in GBM. The aggressive, quick-progressing nature of GBM, inadequate biomarker-based classification, and limited trial cohorts are further obstacles (134).

Temozolomide, combined with radiation, is the standard therapy for GBM and has not improved much since the majority of investigational medicines fall short of its effectiveness. The need for innovative treatment techniques is highlighted by the fact that clinical progress is still constrained by tumor complexity, challenges in drug delivery, and limited trial designs (134). As shown in Figure 3, these barriers are reinforced by a highly suppressive microenvironment, in which tumor cells, infiltrating macrophages, MDSCs, and regulatory T cells collaborate to exhaust cytotoxic T lymphocytes via checkpoint signaling and immunosuppressive cytokines (133). The figure illustrates how multiple redundant inhibitory pathways, not a single mechanism, converge to block effective antitumor immunity. This explains why most single-agent checkpoint inhibitors have underperformed in GBM and underscores the need for combination strategies that simultaneously dismantle several layers of immune suppression (Figure 3).

Antibody platforms of the future

Immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4, target suppressive pathways that lead to T cell dysfunction, aiming to reinvigorate cytotoxic responses within the GBM microenvironment. CD47/SIRPα blockade was heralded as a potential breakthrough when magrolimab (Hu5F9-G4), the first anti-CD47 antibody, entered clinical trials in 2014. Many people believe that this is the innate immune system's equivalent of PD-1/PD-L1 checkpoint inhibitors (135). With the greatest number of candidates now undergoing phase I clinical studies,

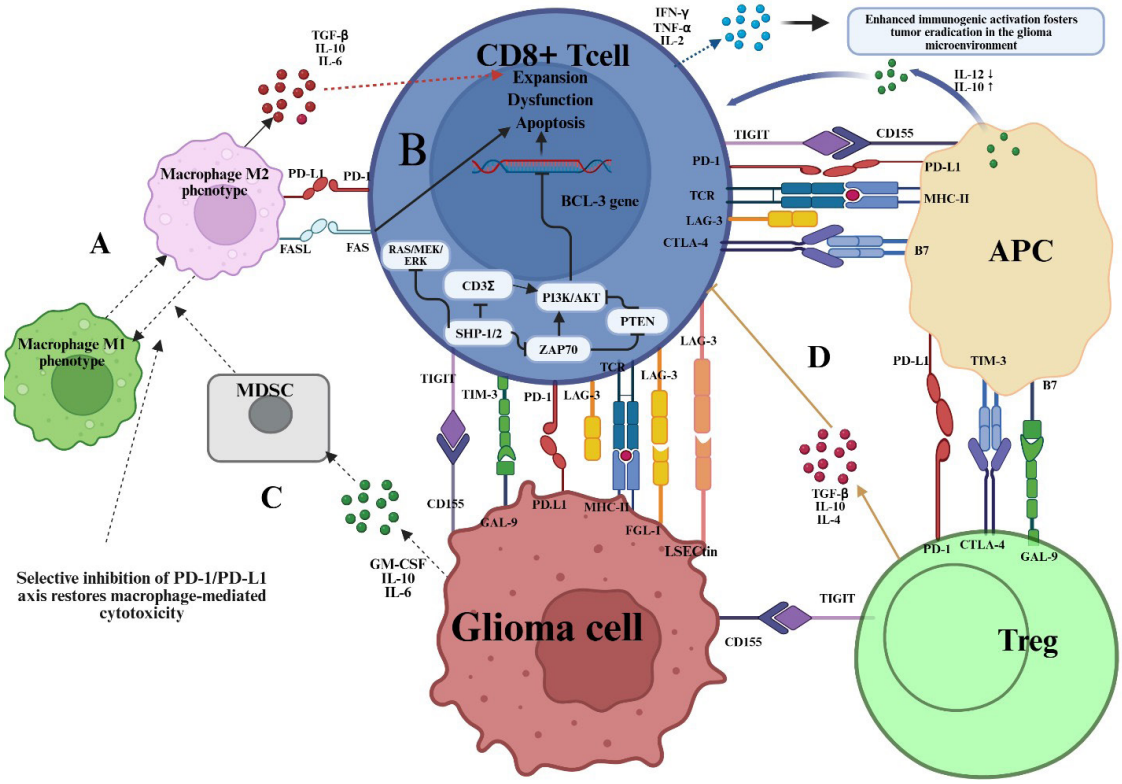

Figure 3. Immune checkpoint signaling and suppressive interactions in glioblastoma microenvironment

A comprehensive schematic of the immunosuppressive microenvironment in GBM, highlighting key immune checkpoint interactions, cellular crosstalk, and modulatory cytokines that influence CD8⁺ T cell dysfunction. Within the tumor milieu, glioma cells express ligands such as PD-L1, GAL-9, FGL-1, and MHC-I, which bind to inhibitory receptors on CD8⁺ T cells, including PD-1, LAG-3, TIGIT, and TIM-3, leading to reduced proliferation, impaired effector function, and apoptosis. Additionally, regulatory T cells (Tregs) and TAMs release suppressive cytokines such as TGF-β, IL-10, and IL-4, further promoting T cell exhaustion. Antigen-presenting cells (APCs) are involved in both immunogenic and tolerogenic responses, depending on the cytokine environment and the expression of ligands such as B7 and MHC-II. The presence of IL-12 and IL-10 from APCs modulates T cell fate toward either activation or suppression. MDSCs and M2 macrophages contribute to immune evasion by releasing cytokines (GM-CSF, IL-6) and engaging FAS–FASL or PD-1 pathways (133). Therapeutic blockade of the PD-1/PD-L1 axis aims to restore macrophage cytotoxicity and T cell responsiveness. This figure integrates multiple immune escape mechanisms operative in GBM and visualizes how checkpoint inhibitors could reverse immune dysfunction and re-establish anti-tumor immunity

Redrawn, adapted, and redesigned by the authors based on an open-access figure from Ref. (133), under a CC-BY license

CD47–SIRPα inhibitors have emerged as the most popular class of anti-TAM treatments in only ten years (136), and have completed phase III clinical testing, making them one of the few classes (137). Despite some recent clinical setbacks, there is still a lot of money being invested in CD47–SIRPα treatments (138). Gilead stopped the phase III ENHANCE-3 study (HR-MDS/AML) from proceeding despite encouraging phase Ib findings of magrolimab with rituximab in lymphoma because of safety issues, including increased mortality, and futility. Due in large part to safety concerns and short treatment windows, even in reliable tumor studies, this led to a wave of CD47 inhibitor program terminations (138). Lemzoparlimab, ZL-1201 (phase II), TQ32928, gentulizumab, SHR-1603, SRF231, and CC-90002 were among the other CD47-targeting interventions that were also canceled (139).

Evorpacept (AXL148), a SIRPα-Fc fusion protein, has shown encouraging phase II/III findings, which have contributed to the continued interest in CD47–SIRPα therapy despite recent failures. When combined with trastuzumab, ramucirumab, and chemotherapy, it increased response rates to 54.8% and provided a median progression-free survival of 15.7 months in patients with HER2-positive advanced gastric and GEJ malignancies (140). The early, dose-limiting on-target toxicities associated with anti-CD47 monoclonal antibodies have also been reduced by novel CD47 decoupling techniques (141). On healthy cells, CD47 is abundantly expressed, particularly on platelets and red blood cells. Serious safety concerns were raised in early studies when severe anemia, thrombocytopenia, and substantial drug loss from off-target binding were discovered (142). Anti-CD47 mAbs may be harmful by binding to phagocyte Fc receptors, triggering ADCC against healthy cells, such as erythrocytes. Early mitigation techniques included mild doses of priming to promote hematopoiesis and remove old red blood cells. Changing the Fc regions from IgG1 to IgG4 to decrease immune activation, improving the specificity of CD47 binding to favor tumor isoforms, and creating molecules like AXL148, a SIRPα-Fc fusion with high CD47 affinity and an inert Fc region, to block the CD47/SIRPα axis without causing ADCC are some of the more recent strategies with better safety profiles (142, 143). Bispecific antibodies such as IBI322 and H×009 that target both CD47 and PD-L1 in patients who have had a lot of pretreatment, the SIRPα-Fc fusion protein Ontorpacept (TTI-621), and previous combination studies using evorpacept (AXL148) are further CD47/SIRPα-targeting therapies that are exhibiting early clinical promise (141). Non-antibody drugs that simultaneously down-regulate SIRPα and rewire macrophages, such as the cyclic peptide VT1021 and the tiny molecule RRx-001, have progressed to phase II/III studies. These findings support the idea that CD47–SIRPα checkpoint modulators are an important class of anti-TAM drugs for the future (141, 144).

Through its action on IL-15 receptors on MDSCs, IL-15 contributes to the transition of the TME from immunosuppressive to pro-inflammatory. Two anti-IL13Rα2 CAR-T cell variants were created by Zannikou *et al.*; one containing IL-15 fused to the CAR (CAR.IL15f) and one secreting IL-15 (CAR.IL15s). *In vivo*, the CAR.IL15f construct decreased bone marrow-derived immunosuppressive cells while increasing $CD3^+$, $CD8^+$ T cells, NK cells, and B cell infiltration and decreasing IL-10, arginase-1, and TGF-β *in vitro* (145, 146).

The potency of bispecific antibodies often surpasses that of monoclonal antibodies. *In vitro*, for example, a CD19×CD3 bispecific single-chain antibody was 100,000 times more effective than rituximab, even at doses lower than 50 pg/ml (147, 148). In comparison to its parent mAb, an EGFRvIII-targeting bispecific antibody demonstrated improved cytotoxicity at a mere 0.01 μg/l. This benefit most likely results from avoiding Fc-dependent processes like CDC and ADCC, which monoclonal antibodies depend on and whose effects wane when immune effector cells are depleted (149).

The capacity of BiTEs to cause serial death by individual T cells is thought to be the reason for their higher potency. Even at low E: T ratios (1:5) and low doses, BiTEs effectively lyse tumor cells by reprogramming T-cell activity to promote prolonged, targeted contacts with numerous tumor cells sequentially (149).

BiTEs aid in combating immunological evasion by activating T cells without requiring MHC presentation. This avoids problems like MHC down-regulation, which often results in tumor escape and antigen loss (150). By engaging the CD3ε component and starting intracellular signaling directly, BiTEs overcome the constraint that native TCRs normally have in detecting certain antigens. BiTEs thus have the ability to activate T cells even in cases when the TCR is specific for an unrelated antigen, expanding their cytotoxic potential beyond that of conventional TAA recognition (151). Third, bispecific antibodies (bsAbs) can potentially activate all $CD3^+$ T cells, including both $CD4^+$ and $CD8^+$ subsets; however, this requires that they bind to CD3 and a tumor-associated/specific antigen (TSA/TAA) simultaneously. This dual-targeting method highlights the antigen-dependent specificity and safety profile of bsAbs by ensuring that T-cell activation and cytotoxicity only occur in the presence of the proper antigen, since no response is seen in antigen-negative cells or tumors (149).

Etevritamab (AMG 596), an EGFRvIII-specific BiTE, was evaluated in a first-in-human, open-label, dose-escalation/expansion trial (NCT03296696) for recurrent or newly diagnosed GBM and malignant glioma. Preclinical data demonstrated effective intracranial tumor suppression and favorable safety, with no observed toxicity in cynomolgus monkeys at doses up to 450 μg/kg/day (150). There were no dose-limiting toxicities (DLTs) found in the first trial cohort of 14 recurrent GBM patients undergoing continuous IV infusion. However, 50% of subjects had significant adverse events (SAEs), which most often manifested as headache and altered consciousness. Two of the eight evaluable patients had stable disease (SD), and one had a partial response (PR). Steady-state serum levels increased dose-proportionately, according to preliminary pharmacokinetic studies (151). In grade IV malignant glioma (NCT04903795), BRiTE, a humanized bispecific scFv that targets EGFRvIII, is scheduled for clinical study. It will be given as a single bolus either at recurrence or after conventional chemoradiotherapy and at least six cycles of temozolomide, either alone or in combination with peripheral T-cell infusion. Following therapy, patients will be monitored for cytokine release syndrome (CRS) for 28 days (149, 151).

According to a preclinical investigation by Iurlaro *et al.*, RO7428731 is a T-cell bispecific antibody (TCB) targeting

EGFRvIII using the 2:1 Crossmab platform (149-151). An open-label, non-randomized study evaluating the safety and tolerability of BRiTE in patients with newly diagnosed GBM is also being conducted. Enrollment for the research, which will be administered as maintenance post-standard-of-care treatment, started in April 2022 and is expected to end in February 2025 (Table 3).

Methods for getting past the GBM microenvironmental obstacles

Methods for crossing the blood-brain barrier

Hynynen *et al.* proposed using microbubbles in an animal model of an ultrasound-treated region (169). To promote direct and indirect interactions with the vascular endothelium and induce microbubble cavitation, acoustic radiation forces were thought to aid BBB penetration (170). Temporary BBB permeability may be made possible by vessel stretching, which may temporarily damage intercellular junctions or alter the production of barrier-forming proteins (169). The mechanical pump effect, which is caused by fluid changes brought on by arterial pulsation, may improve microbubble-mediated medication delivery to the brain parenchyma (169).

By focusing energy on a specific focal point, Focused Ultrasound (FUS) enables therapeutic action rather than imaging, unlike conventional ultrasound, which scans large regions and collects echo signals (169).

Overexposure to energy may cause cell death, brain hemorrhage, glial inflammation, and edema (169). One recognized impact of FUS-activated microbubbles (MBs) is sterile inflammation; however, this effect depends on MB dosage and acoustic pressure. The BBB can be safely opened

Table 3. Key molecular targets, mechanisms of action, therapeutic forms, and obstacles to clinical translation are highlighted in this overview of antibody-based treatments for glioblastoma (GBM)

Agent	Target	Class	Key findings	Remaining barrier	References
Depatuximab mafodotin	EGFR/EGFRvIII	ADC (MMAF)	First ADC in GBM phase III; preclinical tumor regression but no OS benefit (INTELLANCE-1)	Preclinical–clinical translation gap	(152)
AMG 595	EGFRvIII	ADC (DM1)	Tumor-specific targeting; limited patient responses (early trial)	Low efficacy; no further studies	(115)
D2C7-IT	EGFR+EGFRvIII	Dual immunotoxin (PE)	Dual WT+mutant EGFR coverage; promising early-phase activity	Immunogenicity and toxin safety concerns	(153, 154)
EGFR(V)-EDV-Dox	EGFR (scFv)	Minicell nanocarrier	First bacterial minicell drug system; transient PFS gain (NCT02766699)	Weak overall benefit	(155, 156)
C225-ILs-Dox	EGFR	Liposomal ADC	Liposome–doxorubicin conjugate; targeted delivery tested in pilot studies	Small cohorts; dosing inconsistency	(157)
Cetuximab	EGFR	Chimeric mAb	First anti-EGFR mAb in GBM; safe but no OS improvement	Poor CNS penetration	(158)
Panitumumab	EGFR	Fully human mAb	Fully human EGFR blocker; phase II terminated for lack of effect	Ineffective in GBM	(159, 160)
Nimotuzumab	EGFR	Humanized mAb	Low-toxicity profile; mixed and inconclusive phase III results	Conflicting trial outcomes	(161)
Sym004	EGFR (dual epitope)	Dual mAb cocktail	Two-epitope blockade did not improve relapse survival	No superiority to SOC	(162)
GC1118	EGFR	High-affinity mAb	Engineered for stronger binding; an early-phase Korean trial is ongoing	Clinical benefit unproven	(163)
Nivolumab	PD-1	ICI (mAb)	First PD-1 tested in GBM; Checkmate 143 showed T-cell activation but no OS gain.	Immunosuppressive TME	(131)
Pembrolizumab	PD-1	ICI (mAb)	Tested in KEYNOTE combos (e.g., vaccines); modest immune activity	Short-lived responses	(164)
Ipilimumab	CTLA-4	ICI (mAb)	First CTLA-4 blockade in GBM; no added benefit in combos	Ineffective alone or in combination	(131)
Magrolimab	CD47	Macrophage checkpoint mAb	First-in-class CD47 inhibitor; blocked "don't eat me" signal, but toxicity observed	High safety risk	(165, 166)
Evorpacept (AXL148)	CD47 (SIRPα fusion)	Fc-silent fusion	Designed to reduce Fc toxicity; safer profile in early trials	GBM efficacy not yet proven	(135)
AMG 596 (Etevritamab)	EGFRvIII	BiTE (EGFRvIII×CD3)	First EGFRvIII BiTE; safe, moderate responses (NCT03296696)	Continuous infusion required	(147)
BRiTE	EGFRvIII	BiTE (bi-scFv)	Bolus BiTE with T-cell infusion; still early	Safety and benefit have not been established	(167)
RO7428731	EGFRvIII	CrossMab bispecific	Novel 2:1 CrossMab design; ongoing phase I (NCT04049513)	Clinical efficacy unknown	(168)

by low pressure, whereas high pressure increases NF-κB activation and distributes pro-inflammatory markers, including FCGR1 and CCLs (171, 172). The astrocyte response, characterized by higher GFAP levels, and microglia activation, shown by enhanced Iba1 expression, are usually restricted in scope and occur quickly after FUS. These cellular responses are short-lived and do not cause structural alterations or chronic inflammation in brain tissue (173). Interestingly, within 48 hours after injection, anti-inflammatory A2 astrocytes increase in tandem with microglial elevation, suggesting a prompt, system-wide immune response targeted at healing (174). Surprisingly, up to two weeks after sonication, astrocytic and microglial activity continued, associated with continuous alterations in gene expression (174).

To generate mechanical waves up to 7 MHz, a piezoelectric transducer with a fixed aperture and focal length is needed (173, 174). The energy absorbed by the surrounding tissues increases with wave frequency. The promotion of improved membrane permeability and effective nanodrug transport occurs when tissue temperatures stay below 55 ˚C. The effects change from therapeutic to cytotoxic when this heat threshold is exceeded, since this triggers planned cell death and causes coagulative necrosis (175). In order to obtain a wider medication dissemination in tissue than injection alone, convection-enhanced delivery (CED) combines one or more local injections with positive pressure (176). The invasive nature of GBM necessitates extensive medication penetration in brain tissue to target distant tumor sites. Better distribution, however, would increase the risk of toxicity; therefore, tumor selectivity is crucial. Consequently, research attention is shifting to CED trials that utilize targeted therapeutics, such as oncolytic viruses and nanoparticles (175). According to Desjardins *et al*., intratumoral RVSRIPO, a polio/rhinovirus hybrid that targets tumor and dendritic cells specifically and lacks neurovirulence, is safe (177). Phase II studies were supported by these preliminary results (177). Additionally, CED is being investigated for local cell therapy delivery. Although CAR-T cells can pass the BBB and are successful in non-CNS malignancies, they have not yet shown clinical effectiveness in GBM (178). As a result, Atik *et al*. suggested using local CAR-T cell delivery in GBM (179). Animals like sharks and camelids produce tiny, single-domain antibodies called nanobodies, which are around 15 kDa in size. Raymond Hammers' group at Vrije Universiteit Brussel made the first identification in 1993 in camelids (180). Camelids produce both typical IgGs and special heavy-chain-only (light-chain-deficient) antibodies. These hefty chains' changeable domains are called nanobodies. Because of their hydrophilic amino acid substitutions, nanobodies exhibit better tissue penetration, faster clearance, and greater stability than conventional antibodies. They maintain a high binding affinity in the nano/picomolar range even though they only have three CDRs (compared to six in complete antibodies) (181). With a strong affinity, the nanobodies' expanded CDR3 loop may enter deep or obscure antigen locations. They may bind multifunctional epitopes, interfere with disease processes, and inhibit certain receptor responses as a result (181). C1qNb75 is a nanobody that targets C1q and prevents activation of the classical complement pathway (CP). Blocking the IgG binding site on C1q is the suggested mode of action (180, 181).

Despite not yet being authorized as stand-alone treatments, nanobodies are perfect for CAR-T design due to their tiny size, special ability to attach to hidden epitopes, and ease of manufacture. Li *et al*. used dromedary camel phage libraries to create CAR-T cells that target B7-H3 using nanobody technology. IL-2 and anti-CD3/CD28 beads were used to stimulate human PBMCs after the nanobody's insertion into a CAR construct. Triple-negative breast, lung, pancreatic, and neuroblastoma cell lines were all successfully eliminated by these CAR-T cells. Strong anticancer effects were also seen in mouse models of pancreatic cancer (182). The antigen-recognition domain of CAR-T cells is one of its most crucial elements (182). IgV, which antibody 8H9 targets, and IgC are the two epitope areas of B7-H3. According to Li *et al*., in PDAC and neuroblastoma models, CAR-T cells that targeted the IgC domain outperformed those that targeted the IgV domain. Their results demonstrate the significance of epitope selection for the effectiveness of CAR-T cells.

Because of the complexity of the BBB and EPR effect, traditional nanoparticles have had little effectiveness in treating brain malignancies. Ligands that target BBB receptors may be coated on nanoparticles to improve brain delivery. Apolipoprotein receptors, such as LDL-R and LRP, which are both expressed on the brain endothelium, are often used to enhance lipid-based NP uptake and promote transcytosis (176-178). A peptide from the Kunitz domain of aprotinin, angiopep-2, binds firmly to LRP1 and promotes transcytosis across the BBB. It has been connected to several medications, such as ANG1005, a combination of angiopep-2 and three paclitaxel units, which has shown promising outcomes in a phase II study for breast cancer's recurrent brain metastases (183). Organic and inorganic nanoparticles are now associated with angiopep-2 to improve the transport of chemotherapy drugs, such as doxorubicin, across the BBB (184, 185).

LDL-R and LRP1 bind to ApoE, a crucial lipid transporter in VLDL/LDL. PEG or polysorbate 80-coated nanoparticles can passively bind ApoE in the bloodstream, facilitating receptor-mediated BBB transcytosis (186). The effectiveness of nanoparticles' BBB penetration may be further increased by directly coating them with ApoE or its peptide fragments (186). In malignancies, ApoE-coated polymer NPs that transport granzyme B (ApoE-PS-GrB) and CpG oligonucleotides (ApoE-PS-CpG) activate dendritic cells and cause immunogenic cell death. Usually, intracranial injection or CED is used to administer them since systemic distribution is inefficient. According to the findings, systemic injection could become feasible if BBB penetration is enabled (187). The work emphasizes how sophisticated nanoparticles can be engineered to deliver drugs to the brain's safe haven. To help move iron ions across the BBB, the iron-transport protein transferrin attaches itself to transferrin receptor 1 (TfR1)(188). Transferrin-coated NPs compete with high blood levels of transferrin for TfR1 binding. TfR1-targeting peptides, like as T7 and T12, are employed to get around this and improve BBB transport (188). By targeting non-ligand locations on TfR1, monoclonal antibodies (like OX26 and RVS10) and fragments circumvent transferrin competition. Preclinical research indicates that in GBM mouse models, these peptide- or antibody-tagged NPs improve brain medication delivery and prolong life (189).

BBB transport has also been investigated using solute carrier proteins. NPs may nonetheless start internalization and transcytosis into the brain by adhering to these carriers, even though they are usually too big for direct carrier-mediated absorption (190). A prospective target for the administration of nanoparticles is GLUT1, a key glucose transporter that is highly expressed on BBB endothelial cells, roughly 100 times higher than TfR. (189, 190). GLUT1 may be used by NPs treated with 2-deoxy-D-glucose to improve paclitaxel accumulation and delivery in brain tumors (188, 189). BBB crossing by carriers is made possible by GSH transporters. Doxorubicin was effectively administered to the brain via GSH-conjugated PEGylated liposomes (GSH-Doxil) in preclinical mice (188, 190). There is a need for more optimization since it is yet unknown what processes determine whether ligand-conjugated NPs undergo lysosomal or transcytosis breakdown (189).

By carrying both tumor-specific and BBB-targeting ligands, nanoparticles are improving medication delivery to brain malignancies while reducing adverse effects. They are strong at transporting a variety of treatments in addition to surface functionalization. But problems still exist: NPs continue to have poor pharmacokinetics, quick clearance, and instability, particularly when they are adorned with peptides that are readily broken down. The secret to bettering GBM therapies is optimization (191). A protein corona may develop when serum proteins are drawn to proteins, peptides, or other ligands on NPs. This corona may inhibit target binding, shorten circulation time, and alter NP behavior (191). In fact, protein corona development *in vivo* has a significant impact on nanoparticle behavior (191). It's still challenging to balance ligand density and affinity; although increased density increases receptor binding, it may also have unintended consequences or impede BBB transcytosis by saturating receptors (188). Although it may trap cargo in endosomes, a stronger ligand affinity increases NP absorption (190). A suggested tactic to increase endosomal escape and enhance payload release is pH-sensitive ligand cleavage (192).

Immunosuppressive microenvironmental reprogramming

Often referred to as CD115 or macrophage colony-stimulating factor receptor, CSF1R is a crucial regulator of the differentiation, upkeep, and function of macrophages and microglia. For them to survive in physiological settings, constant CSF1R signaling is essential (193). On the other hand, this route often promotes immunosuppressive TAMs in the tumor environment (194). As a result, investigations on a variety of malignancies have shown that CSF1R inhibition reduces TAM activity and improves immune responses as a result of blocking the pathway (195). To stop its signaling and change tumor-supportive macrophages into a more pro-inflammatory, anti-tumor phenotype, a variety of anti-CSF1R treatments, including small-molecule inhibitors and monoclonal antibodies, have been created (196). However, a CSF1R inhibitor clinical study did not improve survival in individuals with recurrent gliomas (195). There are probably two primary causes of this treatment failure. First, CSF1R inhibition has different effects on different tissues and disease states, leading to either repolarization or macrophage depletion. CSF1R inhibition reduces the number of macrophages that guard against graft-versus-host disease (GvHD), which exacerbates the condition in allogeneic stem cell transplantation (197). Similarly, CSF1R inhibitors may eradicate more than 99 percent of microglia in healthy adult brains. Through CSF1R-mediated pathways, microglia rapidly repopulate when therapy ends (197). TAMs exhibit distinct behavior; PDGF-driven GBMs can maintain TAM survival in the face of CSF1R inhibition, which renders them impervious to depletion (198). TAM preservation during CSF1R suppression is aided by GBM-derived cytokines such as GM-CSF, IFN-γ, and CXCL10. In PDGF-driven glioma mouse models, TAMs experience phenotypic changes toward an M1-like profile, boosting anti-tumor activity and longevity even while depletion is unsuccessful (198). Interestingly, this reaction varies depending on the kind of glioma. Unlike PDGF-driven models, where TAMs survive depletion but change phenotype, CSF1R inhibition efficiently depletes TAMs, particularly microglia, in Gl261 murine gliomas (197). Similar to what is shown in Gl261 glioma models, this is consistent with results in liver and mammary malignancies, where CSF1R inhibition initially depletes TAMs before having anti-tumor effects (195, 197). CSF1R inhibition in the 005GSC glioma model resulted in a negligible decrease in TAM and actually reduced the efficacy of immune checkpoint inhibitors in conjunction with oncolytic virotherapy (199). Future research must elucidate tumor-specific response mechanisms since CSF1R inhibition has different effects on different glioma models and therapy combinations. Resistance is another major cause of treatment failure; TAMs may evade CSF1R blockade by producing factors that maintain their survival and function, such as insulin-like growth factor 1 (IGF1)(200). Therapeutic effects are improved by dual inhibition of IGF1R and CSF1R, indicating that this is a potential approach for clinical trials. Immunotherapy has transformed oncology and has the potential to cure GBM by using the body's immune system to combat cancer (201). The immune system, mainly via NK cells, is essential in identifying and eliminating newly developing cancer cells in normal physiology (201) and T cells (202). In the tumor microenvironment, macrophages more often adopt a pro-tumorigenic function, albeit they may have limited tumor-killing effects (203, 204). Immune cells eradicate cancer in a variety of ways; however, some cancer cells avoid detection by changing their phenotypic, inhibiting immune responses, and reorganizing the extracellular matrix. Restoring immune cells is the goal of immunotherapy in order to overcome this resistance. But the success rate varies depending on the kind of tumor. Due to its hostile TME and limited immune cell penetration, GBM, for example, is regarded as an immunoevasive cold tumor (205). To lessen immune cell identification and binding, GBM adjusts by altering surface receptors, which aids in immune evasion (205), Additionally, GBM suppresses anti-tumor immunity by reprogramming immune cells such as neutrophils and microglia into protumor genic states (205), Additionally, it attracts immune cells that inhibit the immune system, such as Tregs, which reduce immunological responses and increase tolerance to tumors (205) and suppressor cells produced from MDSCs (206), which release cytokines that inhibit the immune system, including TGFβ, IL-10, and IL-35 (206). Together, these processes enhance immunosuppressive signals and restrict the entrance of tumor-killing immune cells, resulting in a hostile TME in GBM. Deciphering the mechanisms behind this immunosuppression is essential to enhancing immune infiltration (205, 206).

Combining antibodies and complementary modalities synergistically

Combining vaccination strategies with immune checkpoint inhibitors

Single therapy is unsuccessful for GBM because of its complexity and heterogeneity. Researchers are now investigating combination strategies combining immunotherapies with other immune-based techniques and traditional treatments. Immune checkpoint inhibitors (ICIs) in combination with CAR-T cells, cancer vaccines, and oncolytic viruses such as AdVs and PVSRIPO, a modified poliovirus-rhinovirus chimera with anticancer properties, are promising strategies (207, 208). Investigations into these combo tactics are ongoing. Notably, preclinical models have shown the possibility for a cure when an IL-12-expressing oncolytic herpes simplex virus (oHSV) is combined with anti-PD-1 and anti-CTLA-4 checkpoint inhibitors (209). The coordinated activity of macrophages and CD4/CD8 T cells may account for the efficacy of this multitherapy method. Pembrolizumab IV after intertumoral DNX-2401 produced a 52.7% 12-month survival rate and a 10.4% response rate in a phase 1/2 study for recurrent GBM. Three out of 49 patients notably lived for more than five years (209).

A helpful part of combination immunotherapies for GBM, radiotherapy is intrinsically immunogenic and can rewire the immunosuppressive TME (210). A lot of research is being done on the combination of immunotherapy and radiation. Although the full significance of these modifications remains unknown, it has been shown that radiation alters the behavior of TAM and microglia in gliomas (211). Optimizing combination therapy requires understanding how radiation affects immune responses. On the other hand, conventional chemotherapy limits the effectiveness of immunotherapy by causing immunosuppression and lymphopenia in GBM patients. In order to improve the results of immune-based therapy, alternative conventional therapies must be developed (211). A single axis, such as a single antigen or immunological checkpoint protein, seems to be insufficiently targeted (211).

Using oncolytic viral platforms to harness antibodies

When used with ICIs, oncolytic viruses may increase the expression of immune checkpoint molecules (such as PD-1/PD-L1 and NKG2A/HLA-E) on tumor and immune cells, creating additional targets and potential for synergy to improve treatment outcomes (212,213). Because ICI-activated T cells may increase antiviral responses and clear OVs too early, decreasing effectiveness, combining OVs with ICIs requires careful planning. To maximize tumor killing and prevent premature OV removal, timing and administration sequence are critical (214).

Combining antibodies with NK and CAR-T cell therapies

CAR T cell therapy is the most advanced and sophisticated gene-modified cell treatment for cancer (215, 216). T cells modified to express chimeric antigen receptors (CARs) are adopted and transferred as part of CAR T cell therapy. These receptors enable MHC-independent tumor detection and activation by combining T cell activation domains with an antibody-derived antigen-binding domain (215, 216). The promise of CAR T cell treatment in targeted cancer immunotherapy has been highlighted by its impressive clinical performance, particularly in B cell malignancies. Two patients with chronic lymphocytic leukemia who had treatment in 2010 were successfully cured with no relapses to date, thanks to CAR T therapy, which resulted in long-term remission (217). In some nations, CAR T cell therapy has been authorized for the treatment of leukemia and lymphoma (217).

Unlike T cells, NK cells are innate immune effectors that may destroy tumor cells directly without first sensitizing them. Given that studies have shown tumor regression in solid tumors, including GBM, this makes them attractive for GBM treatment (218). This section examines the advancements, challenges, and potential of CAR-engineered, allogeneic, and autologous NK cell therapy. By using MHC-independent methods, NK cells eradicate cancer without the need for priming or previous antigen exposure (219). In order to initiate tumor apoptosis via caspase pathways, activated NK cells produce granzymes, perforin, and IFN-γ in addition to expressing death ligands including TRAIL and FASL. They also need CD16a (FcγRIIIA) to mediate ADCC. In addition to killing directly, NK cells interact with and mature dendritic cells to improve tumor antigen presentation and T cell activation, therefore modifying the adaptive immune system (218). Dendritic cells (DCs) increase the cytotoxicity of NK cells in exchange (218). Clinical data demonstrate that NK cells efficiently target mature GBM cells, enhancing their potential as a treatment (218), suggesting that NK cell-mediated death may affect the stem cells linked to GBM (218). To restore NK cytotoxicity and reactivate key receptors such as NKG2D and CD16, which are often inhibited in the GBM microenvironment, a potential approach combines TGF-β inhibitors with NK cell therapy (220). Strong tumor control was achieved in a patient-derived orthotopic GBM mouse model by completely reversing glioma stem cell (GSC)-induced NK dysfunction through inhibition of αv integrin, TGF-β, or TGFBR2 on allogeneic NK cells. The αv integrin/TGF-β axis is a crucial target for improving NK cell-based GBM treatment, according to these results (221). In solid tumors, combining checkpoint inhibitors (anti-PD-1, CTLA-4, LAG3, TIGIT) with CAR cell therapy may improve treatment success by tackling immune resistance (222). Preclinical research indicates that NK cells may be able to reverse the immunosuppression brought on by GBM when combined with histone deacetylase inhibitors (HDACi) or antibodies that target GBM. By raising NKG2D ligand expression, HDACi improve tumor visibility and NK cell activity and recognition (222). Pretreatment with the proteasome inhibitor bortezomib remarkably improves survival in animal models by enhancing NK cell death of GBM via NKG2D and TRAIL pathways (222).

Improving concurrent vs sequential treatment approaches

When combining antibody-based treatments with ICIs, vaccinations, CAR-T/NK cells, or oncolytic viruses, the timing of treatment—whether sequential (stepwise) or contemporaneous (simultaneous)—is critical in GBM therapy (223). Each strategy has unique benefits and difficulties, and they are currently being studied in preclinical and clinical contexts (223). To improve responsiveness to subsequent ICIs, sequential treatment may stimulate the TME. For example, using oncolytic viruses initially increases antigen exposure and PD-L1 expression. But if

ICIs are administered too soon, they can cause the virus to be cleared by the immune system, which would decrease their effectiveness (223).

Because of overlapping or competing processes, concurrent medication increases the risk of toxicity and immune-related side effects even while it might enhance immune responses via synergy (e.g., ICIs with CAR-T or NK cells)(224, 225). For GBM immunotherapy to be more effective, less toxic, and to provide better results, the timing and sequence of combination treatments must be optimized. These therapeutic dynamics are being intensively investigated in ongoing studies (Table 4)(225).

Ongoing difficulties and important restrictions

There are significant obstacles to antibody treatments for GBM, namely the tumor's high antigen diversity. Although GBM cells vary greatly, many of them lack essential targets like EGFR or EGFRvIII. Consequently, immunological escape occurs, wherein non-targeted cells survive and evade immune assault (59). As tumors change or reduce their target antigens, antibody treatments for GBM become less effective over time. Another obstacle is limited access of immune cells to the brain. Even when the BBB is broken, the TME, which is home to Tregs, TAMs, and MDSCs, inhibits immunological activation and T-cell activity (59). Due to both external forces and internal alterations (such as EMT and checkpoint upregulation), GBM often develops resistance to antibody therapies. Through alternative growth or immune-escape pathways, tumors evade treatment, and T cells wear down. The longevity of ICIs and monoclonal antibodies is restricted by these parameters. Furthermore, neurotoxicity and immune-related adverse events (irAEs) are examples of severe side effects that might result after medication (235). Immune activity close to the brain may result in severe conditions, including encephalitis, meningitis, or edema. Steroid management of these impairs immunity, which lowers the efficacy of immunotherapy. Conventional GBM therapies, such as temozolomide and radiation therapy, exacerbate this by inducing systemic immunosuppression and lymphopenia (236). Therapy using antibodies is hampered by these contradictory outcomes. Immunotherapy and immune-supportive treatment must be combined, and multimodal approaches must be used to overcome tumor resistance and maintain immune function in order to overcome them (235, 236).

Prospects for the future

The future of GBM antibody treatments depends on interdisciplinary innovation. Despite persistent challenges, including tumor heterogeneity and immune suppression, key techniques include leveraging AI for therapy design and patient selection, developing sophisticated antibody formats, customizing antibodies to tumor genomes, and using liquid biopsies for biomarker tracking and treatment monitoring.

Customizing antibody therapy based on genomic information

Customized therapy is necessary because of the molecular variety of GBM, including EGFRvIII, IDH mutations, and TERT alterations. Neoantigens and targets are revealed by mapping tumors and immunological settings using techniques like spatial transcriptomics and single-cell RNA-seq. This motivates personalized treatments such as vaccinations and bispecific antibodies. Enhancing patient selection, genomic markers such as TMB also help predict response to ICIs and T cell-engaging antibodies (149, 237, 238).

Cutting edge developments in antibody engineering

Beyond conventional monoclonals, antibody therapeutics

Table 4. Summarizes novel treatments for glioblastoma (GBM), emphasizing their mechanisms of action, benefits, drawbacks, and current clinical trial developments

Strategy	Mechanism	Pros	Cons	Evidence	References
FUS+MB	Cavitation opens the BBB	Non-invasive; enhances drug uptake	Inflammation, bleeding, transient BBB loss	Preclinical+phase I	(226)
CED	Pressure-driven intertumoral infusion	Direct reach to the infiltrative tumor	Neurotoxicity: the drug must be highly specific	Phase I/II (e.g., RVSRIPO)	(227, 228)
Nanobodies	Single-domain antibody fragments	High specificity; BBB permeable; low immunogenicity	Complex production; not yet in GBM trials	Preclinical only	(229)
Receptor-Mediated NPs	Ligand-decorated nanoparticles use transcytosis	High tumor accumulation; payload flexibility	Protein corona; clearance; receptor competition	Preclinical+early clinical (ANG1005, ApoE, TfR1, GSH)	(230)
CSF1R Inhibition	Blocks TAM/microglia signaling	Reprograms or reduces TAMs	Subtype variability; IGF1-mediated resistance	Failed recurrent GBM trial; preclinical benefit	(231)
ICIs+Vaccines	ICIs with vaccines/oncolytic viruses	Synergy: better T-cell infiltration	Short durability; complex logistics	Phase I/II (pembro+DNX-2401; 12-mo OS ≈ 53%)	(232)
Antibody+Oncolytic Viruses	Viruses expose targets; ICIs block escape	Boosts lysis+immune activation	Virus may be cleared too early; dosing critical	Ongoing trials	(233)
Antibody+CAR-T/NK	Abs enhance CAR-T/NK targeting	Dual mechanism; combinable with ICIs	TME suppression, cytokine storm risk, heterogeneity	Early/preclinical in GBM; CAR-T approved in blood cancers	(234)
Sequential vs. Concurrent	Optimized scheduling of therapies	Synergy, if timed well	Concurrent ↑ toxicity; sequencing complex	Preclinical+early clinical	(18)

now come in bispecific, trispecific, and nanobody-based forms. At low ratios, bispecifics increase cytotoxicity by connecting tumor antigens to T lymphocytes ($CD3^+$). Trispecifics combat tumor heterogeneity by targeting several antigens. GBM may benefit from nanobodies because of their tiny size and high brain penetration. It is also possible to combine these formats with poisons or nanomaterials to increase accuracy and reduce adverse effects (239-241).

AI-powered antibody development and accurate patient stratification

By enabling rapid design and prediction, artificial intelligence and machine learning are transforming antibody therapy. They optimize immune functions, antibody structures, and binding while using multi-omics data to pinpoint targets and assign patients to appropriate therapies. AI helps guide individualized, adaptive therapeutic strategies by simulating treatment responses and predicting resistance (242).

Using liquid biopsy to find biomarkers and track them in real time

Using ctDNA, vesicles, and immunological transcripts, liquid biopsies provide non-invasive, real-time monitoring of GBM development and response to therapy. Tracking indicators such as EGFRvIII and PD-L1 aids in early resistance detection and treatment modification. By making prompt, data-driven judgments, this strategy promotes individualized, flexible therapy that improves long-term results (243, 244).

AI as a therapeutic strategy in GBM

Artificial intelligence (AI) is rapidly evolving from a supportive tool into a therapeutic enabler in GBM, capable of reshaping tumor biology, guiding immune responses, and personalizing treatments in real time.

AI-driven cellular reprogramming

A pioneering direction uses machine learning to identify "fate-determining" transcriptional programs that can reprogram GBM cells into antigen-presenting dendritic cells (DCs). This bypasses the blood–brain barrier and converts malignant cells into immune activators from within the tumor microenvironment. In preclinical GBM models, AI-guided reprogramming improved survival by nearly 75%, demonstrating that AI can directly induce tumor-to-immune transformation rather than relying solely on external drugs (245).

AI-powered antibody and drug design

Generative deep learning architectures, such as graph neural networks and transformer-based protein language models, can be used to design bispecific antibodies and antibody–drug conjugates (ADCs) tailored to GBM's heterogeneous antigen landscape. Unlike conventional trial-and-error design, AI rapidly predicts antigen–antibody binding affinities, optimizes linker chemistry, and reduces off-target toxicity. These computationally engineered antibodies can then be validated in silico before clinical translation, accelerating drug discovery while reducing costs (246).

Digital twins for precision therapy

AI-enabled "digital twin" models of GBM patients integrate radiomics, multi-omics, and clinical history to simulate therapeutic responses in silico. This allows physicians to test different immunotherapy, ADC, or checkpoint blockade combinations virtually before applying them in patients. Early models show potential for predicting resistance pathways, therapy failure points, and the optimal timing for combined modalities. This represents a shift from static treatment planning to dynamic, adaptive immunotherapy (247).

AI for non-invasive immune profiling

Radio genomic AI approaches now predict not only tumor mutations (e.g., IDH, and MGMT methylation) but also immune signatures of the GBM microenvironment, including T-cell infiltration, TAM polarization, and checkpoint expression patterns. By linking MRI features with immune phenotypes, AI can stratify patients for antibody-based or checkpoint therapies without invasive tissue biopsies, enabling real-time therapeutic decision-making (248).

Future synergies: AI and immunotherapy integration

AI's predictive power extends to synergistic design of combination therapies. For example, AI-guided mapping of hypoxia-inducible pathways can suggest where anti-PD-1 treatment should be paired with HIF inhibitors (249). Similarly, reinforcement learning algorithms can optimize dosing schedules for checkpoint inhibitors or ADCs to maximize tumor killing while minimizing immune exhaustion. The ultimate frontier is AI-enabled closed-loop immunotherapy systems, adaptive platforms where real-time tumor and immune data are continuously analyzed, and treatment is automatically adjusted (250, 251).

Discussion

As summarized in Table 5, antibody-based therapeutics for GBM reveal a spectrum of advantages, limitations, and future directions that collectively illustrate both the promise and the persistent barriers in this field. Direct tumor targeting with NIR-photoimmunotherapy (NIR-PIT) demonstrates the highest spatial precision, capable of eradicating GSCs and inducing immunogenic cell death. However, its reliance on near-infrared penetration and the risk of collateral damage to immune cells underscore the need for ongoing innovations, such as dual-antigen targeting and up-conversion probes, to advance this platform toward intraoperative precision medicine. Immune checkpoint inhibition, widely validated in melanoma and lung cancer, remains constrained in GBM by hypoxia, low mutational load, and an immune-excluded microenvironment. The table highlights how dual or triple checkpoint blockade, alongside metabolic reprogramming, may partially overcome these hurdles, with future directions pointing toward BBB-penetrant engineered antibodies and biomarker-guided stratification using single-cell and spatial transcriptomics.

ADCs are positioned as highly potent, selective cytotoxic delivery systems, yet their GBM application is hindered by intertumoral heterogeneity and sparse trial evidence. Innovations such as nanobody-based ADCs and hypoxia-sensitive linkers may mitigate these weaknesses, while dual-payload ADCs combining cytotoxic and immune-stimulatory cargos offer a transformative future outlook. Similarly, bispecific antibodies and BiTE/CAR-T hybrids

Table 5. Antibody-based therapeutic strategies in glioblastoma (GBM) for each method, advantages and disadvantages are listed, and strategies are compared

Strategy	Advantages	Disadvantages	Innovations	Future outlook	Compare	References
NIR-PIT	Precise CSC kill; spares tissue; immunogenic death	NIR depth limit; off-target immune damage	Dual-antigen PIT; combo with ICIs/Treg depletion	Deep-penetrating probes; intra-op image-guided PIT	More precise than ADCs; better CSC targeting, but limited by light penetration	(252)
ICIs (PD-1, CTLA-4, TIGIT, etc.)	Validated in other cancers; restores T cells; synergizes with chemo/rad	Weak in GBM (low TMB, hypoxia); immune toxicity	Dual/triple blockade; HIF-1α/LGMN inhibition; metabolic reprogramming	BBB-penetrant ICIs; omics-guided stratification; liquid biopsy dosing	Safer and systemic vs others, but weakest in GBM monotherapy	(253, 254)
ADCs	Potent, selective; less systemic toxicity	Sparse GBM trials; heterogeneity; leakage risk	Hypoxia-cleavable linkers; nanobody ADCs	Dual-payload ADCs; patient-specific tailoring	Stronger tumor kills than NIR-PIT but less selective; heterogeneity is a major barrier	(255, 256)
Bispecifics / BiTEs	Tackle antigen escape; recruit T cells	Complex design; cytokine storm risk	Tri-modular CAR-T; macrophage BiTE IL-12	Off-the-shelf bispecifics; Notch-regulated release	More immune activation than ICIs; more versatile than ADCs, but less mature clinically	(257, 258)
Depletion / Activation	Flexible formats; ADCC/CDC; tunable PK	Fc clearance; fragment instability; immunogenicity	Fab′ NP conjugates; optogenetic hybrids	Switchable antibodies; metabolic checkpoint combos	More adaptable than ADCs, but less advanced clinically; best as combo therapy	(259, 260)
Photoimmunotherapy (PDT/PTT)	Theranostic; minimally invasive; precise ablation	Shallow penetration; tech-heavy	Photodynamic priming; PD-L1 liposomes	Up-conversion NP systems; multimodal intra-op use	More versatile than NIR-PIT; best when combined with other immunotherapies	(261)

address antigen escape and broaden immune engagement, though their complexity and associated toxicity risks remain substantial. Their evolution toward "off-the-shelf" bispecifics and synthetic Notch-controlled secretion reflects a clear trajectory toward scalable, precision immunotherapy. Finally, antibody-mediated activation/depletion and antibody–nanoconjugate-based photoimmunotherapy highlight flexibility and theragnostic integration, respectively. Both approaches remain technically constrained, but the emergence of switchable antibodies and multimodal intraoperative workflows suggests tangible routes to clinical translation.

In summary, the comparative framework presented in Table 5 emphasizes that no single antibody strategy is sufficient in isolation. Instead, future progress will depend on rationally designed combinations that integrate antibody engineering, BBB-penetrant delivery, and biomarker-driven patient selection to dismantle the multifaceted barriers of GBM.

Conclusion

GBM remains among the most intractable tumors in neuro-oncology, owing to its rapid progression, extensive heterogeneity, and profoundly immunosuppressive microenvironment. Despite success in other cancers, monoclonal antibody (mAb) therapies have so far failed to deliver meaningful clinical benefits in GBM. The key reasons are clear: the blood–brain barrier (BBB) prevents adequate drug penetration, tumor cells evade immune recognition through antigenic escape, and overlapping immunosuppressive networks blunt therapeutic efficacy. To overcome these barriers, several innovations stand out as realistic game changers. First, next-generation antibody formats, including bispecific antibodies, nanobodies, and antibody–drug conjugates, offer the potential to engage multiple targets and reduce immune escape simultaneously. Second, novel delivery technologies such as nanoparticle carriers, focused ultrasound, and convection-enhanced delivery can improve BBB penetration and ensure sufficient drug exposure at the tumor site. Third, the use of artificial intelligence–driven antibody design and patient-specific biomarker profiling will accelerate the creation of tailored therapeutics and enable dynamic, personalized treatment strategies. Moving forward, progress will depend on a combination of approaches that integrate antibody therapy with checkpoint inhibitors, radiotherapy, or chemotherapy to generate synergistic immune activation while dismantling resistance pathways. Research funding should prioritize strategies that unite innovative antibody formats with BBB-penetrating delivery platforms and AI-guided personalization. If these fronts converge, antibody-based therapies could finally transition from experimental promise to durable clinical benefit in GBM.

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Authors' Contributions

MF D conceived the review framework, coordinated manuscript preparation, and ensured conceptual integrity.

FA M and A S contributed to the study design and thematic structuring. SR J and AS C conducted literature analysis, data synthesis, and initial drafting. A G and L M revised the mechanistic and translational sections. HN S, A S, and ZH A performed reference curation, figure adaptation, and table design. M A and A K refined the structure, edited scientific accuracy, and finalized the manuscript. RA S provided expert review, critical insights, and final approval. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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