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Review

Immunotherapy for Glioma: A compartmental framework for resistance and rational combination design

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ABSTRACT

Diffuse gliomas remain among the least responsive solid tumors to immunotherapy despite a compelling rationale for immune surveillance of infiltrative disease. The clinical record—negative phase III checkpoint blockade trials, limited durability of single-antigen vaccines, and impressive but transient responses to adoptive cellular therapy—suggests that failure is rarely attributable to a single mechanism. We propose that glioma immunotherapy resistance is best understood as a compartmental problem. Effective antitumor immunity must traverse a sequence of spatially and functionally distinct compartments: antigen generation and drainage; T-cell priming in deep cervical lymph nodes, cranial bone marrow, or tertiary lymphoid structures; trafficking through vascular and stromal gateways; and effector persistence within a myeloid-rich, metabolically stressed tumor microenvironment. Each therapeutic class acts with a different compartmental center of gravity. Vaccines amplify priming but do not guarantee tumor access or persistence; checkpoint inhibitors require a pre-existing or newly generated tumor-reactive T-cell pool; adoptive cellular therapies bypass priming but remain vulnerable to antigen heterogeneity and local suppression; and oncolytic or innate immune agonists can create *in situ* inflammatory signals but require compatible trafficking and effector niches. This framework explains why monotherapies have generally underperformed and why effective combinations must be designed to bridge specific blocked compartments rather than simply intensify immune stimulation. It also highlights the importance of tumor state: treatment-naive and treatment-remodeled gliomas may have different dominant immune barriers. Future trials should pair mechanism-matched combinations with biomarkers that report on priming, trafficking, and effector competence.

Introduction

Gliomas remain among the most difficult solid tumors to control with systemic therapy [1]. Despite refinements in surgery, radiotherapy, molecular diagnosis, and supportive care, diffuse gliomas infiltrate beyond radiographically visible disease and almost invariably recur after local therapy. For glioblastoma (GBM), maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide remains the current standard-of-care, but durable disease control is uncommon [2–4]. Lower-grade IDH-mutant astrocytomas and oligodendrogliomas often follow a more indolent course, and mutant IDH inhibitors have altered the therapeutic landscape [5], yet these tumors also remain diffusely infiltrative, capable of progression and malignant transformation. Current guidelines continue to frame glioma management around surgery, radiotherapy, and systemic pharmacotherapy [6].

The appeal of immunotherapy in glioma is intuitive: an effective antitumor immune response could, in principle, recognize infiltrative tumor cells beyond the surgical margin, track evolving tumor subclones, and provide durable surveillance against recurrence [7]. Yet clinical results in gliomas have been far more modest than in melanoma [8], non-small cell lung cancer [9,10], renal cell carcinoma [11,12], and other cancers. This gap cannot be explained simply by invoking the CNS as an immune-privileged compartment. Rather, the CNS contains a complex and dynamic immune landscape in which antigen drainage, meningeal lymphatics, cervical lymph nodes, cerebrospinal fluid immune surveillance, skull bone marrow niches, and tertiary lymphoid structures can all contribute to immune recognition and immune-cell trafficking [13–17]. Brain metastases from immunogenic systemic cancers can also respond to checkpoint blockade, indicating that intracranial location alone does not dictate resistance [18,19].

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Productive antitumor immunity in glioma unfolds across distinct spatial and functional compartments, each of which can become the dominant point of failure [13,14,17,20]. Peripheral priming occurs in the deep cervical lymph nodes, to which glioma-derived antigens drain through glymphatic and meningeal lymphatic pathways [21–23]. Paracerebral priming niches include cranial bone marrow, which can harbor tumor-reactive $CD8^+$ T-cells shared with the tumor and connected to the meninges by direct osseous vascular channels, as well as intratumoral tertiary lymphoid structures in a subset of gliomas that support local antigen presentation and clonal lymphocyte expansion [13,17,24,25]. Trafficking corridors, including specific post-capillary venules and perivascular niches, determine whether primed lymphocytes actually reach the tumor bed [20,26,27]. The tumor core itself is where effector function is either sustained or extinguished by suppressive programs [28–30].

The familiar formulation that glioma immunotherapy fails when antigenicity, access, and a suppressive microenvironment converge [7,31] maps onto this anatomy rather than acting uniformly across the lesion. Antigenicity constraints act on peripheral and paracerebral priming. Here, the available neoepitopes must be both abundant enough and clonally expressed across tumor cells to seed a tumor-reactive T-cell pool. EGFRvIII illustrates this limit. Its subclonal expression and frequent loss under immune pressure undermined monovalent targeting [32,33]. Access constraints act on the trafficking compartment, where vascular anatomy, chemokine gradients, extracellular matrix architecture, and the spatial organization of tumor and immune niches filter which primed cells reach the parenchyma [20,26,27]. Suppression acts overwhelmingly within the effector compartment, where tumor-associated macrophages, microglia, regulatory T cells, dysfunctional dendritic cells, astrocytes, hypoxia, lactate, and tryptophan metabolism together extinguish effector function [7,26,27].

Each immunotherapeutic modality acts most directly at one of these steps. Vaccines depend on peripheral priming and antigen drainage; checkpoint blockade presupposes a primed tumor-reactive T-cell pool; adoptive cellular therapies bypass peripheral priming but still depend on niche accessibility and persistence; oncolytic viruses and innate agonists generate in-situ priming signals at the tumor core; and myeloid- or innate-directed agents act predominantly in the effector compartment. Clinical failure therefore often reflects compartmental mismatch rather than modality-specific weakness. The therapy acts in one compartment while the dominant immune block resides in another (Fig. 1).

These compartmental dependencies have direct therapeutic implications. The most promising future strategies are unlikely to be one-size-fits-all monotherapies, but biomarker-guided combinations that match the dominant immune barrier in each tumor, increasing antigen visibility, improving immune-cell trafficking and persistence, or reversing local immune suppression as the relevant molecular and clinical context dictates. In this review, we use glioma immunobiology as the organizing principle for therapeutic development, arguing that the next generation of glioma immunotherapy must be designed around the compartmental anatomy of antitumor immunity rather than around treatment modality alone.

Glioma immunobiology as the foundation for therapy

Gliomas are not a single immunologic entity, but a group of biologically distinct diseases shaped by developmental lineage, anatomical context, and molecular driver alterations. Modern classification distinguishes IDH-mutant astrocytoma, oligodendroglioma, H3 K27-altered diffuse midline glioma, and IDH-wild-type glioblastoma, each of which differs in antigenic landscape, immune composition, and therapeutic vulnerability [7,28,34]. These subtype-specific differences

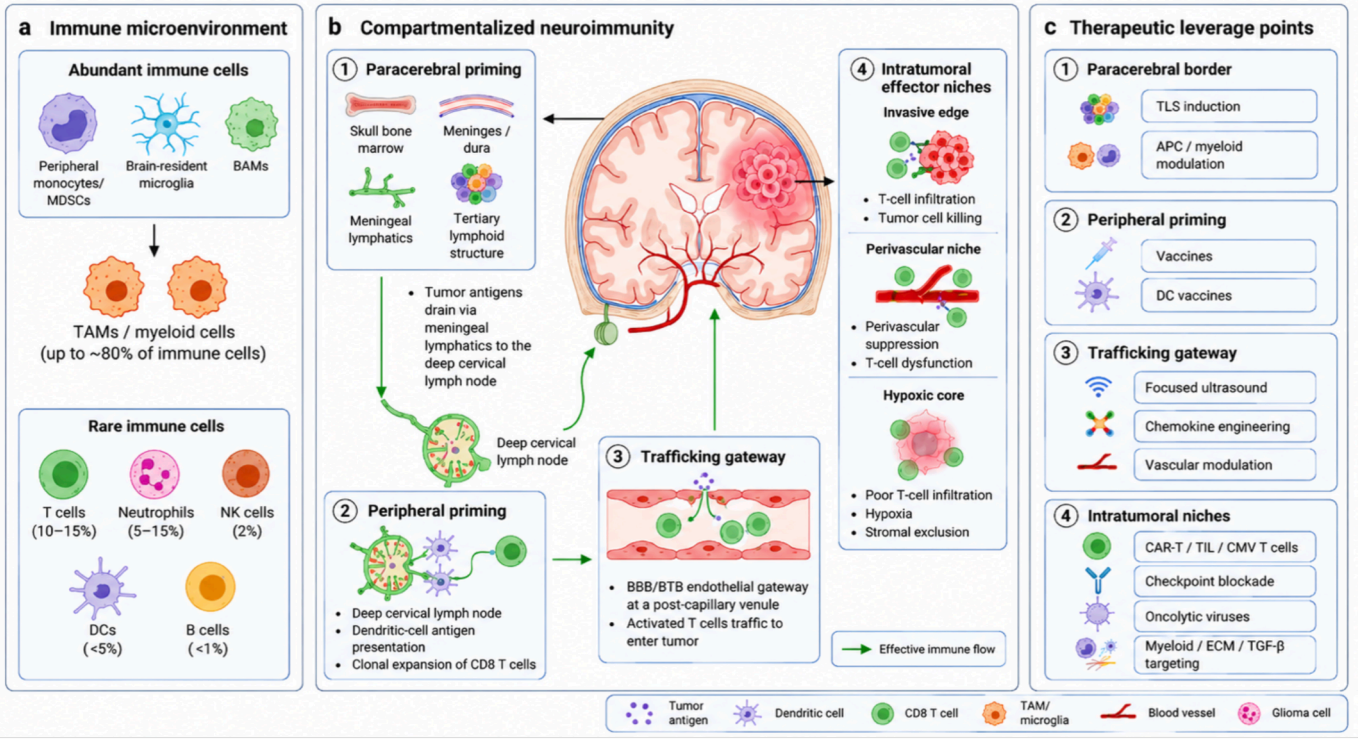

Fig. 1. Compartmentalized neuro-immunity in glioma. (a) The glioma immune microenvironment is predominantly myeloid, with comparatively limited lymphoid infiltration. **(b)** Antitumor immunity in glioma is organized across distinct anatomical and functional compartments, including peripheral priming in the deep cervical lymph node, paracerebral priming at CNS border sites, trafficking through BBB/BTB endothelial gateways, and spatially heterogeneous intratumoral effector niches. Green arrows denote effective immune flow, whereas red dashed arrows denote blockade or mismatch between compartments. **(c)** These compartments define distinct therapeutic leverage points and suggest that immunotherapy failure in glioma may arise not simply from weak immunity, but from mismatch between where immune responses are primed, where they can traffic, and where they are ultimately able to function. Created with BioRender.com.

provide the biological context for immunotherapy design (Table 1). Across these entities, however, several shared features remain central to immunotherapy resistance such as clonal heterogeneity, cellular plasticity, and a microenvironment dominated by myeloid suppression rather than productive lymphocyte-mediated immunity [35].

Myeloid dominance establishes the suppressive effector compartment

The glioma effector compartment is myeloid-rich and often poorly supportive of productive lymphocyte immunity. Tumor-associated macrophages, microglia, and myeloid-derived suppressor cells (MDSCs) are major regulators of immune function in glioma [47–49]. Tumor-associated macrophages and microglia can comprise more than half of the cellular content of the GBM microenvironment and arise from both embryonically derived resident microglia and bone marrow-derived infiltrating macrophages [50]. These populations occupy distinct spatial niches, with infiltrating macrophages enriched in perivascular and necrotic regions and microglia more prominent at the invasive edge, but both contribute to immunosuppression and tumor support [51,52]. Importantly, tumor-associated macrophages do not fit neatly into a simple M1/M2 or "suppressive versus inflammatory" model. Instead, they exist across a range of states shaped by their origin, location, cytokine exposure, metabolic signals, and local niche [52,53]. Some states directly suppress T-cell immunity through checkpoint ligands, immunoregulatory cytokines, arginine metabolism, and chemokine programs. Others may support angiogenesis, hypoxia adaptation, tissue remodeling, tumor invasion, or phagocytosis [49].

MDSCs are also key mediators of immunosuppression in glioma. These cells originate in the bone marrow, where, under normal conditions, myeloid progenitors differentiate into mature macrophages, dendritic cells, or granulocytes. However, signals within the GBM tumor miscroenviornment (TME) disrupt this differentiation process, arresting myeloid development and promoting the expansion of immature, immunosuppressive MDSCs [54]. Traditionally, MDSCs have been divided into two major subsets: polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs) [55]. More recent transcriptomic, proteomic, and functional profiling has refined this framework in GBM, identifying M-MDSCs and early progenitor MDSCs (E-MDSCs) as the dominant tumor-relevant populations. E-MDSCs are enriched in palisading regions adjacent to mesenchymal-like tumor cells, where they are thought to support tumor stemness and growth. These cells can further differentiate into M-MDSCs, which exert potent immunosuppressive effects on both $CD4^+$ and $CD8^+$ T cells [30]. Collectively, these findings underscore the dynamic and highly immunosuppressive microenvironment orchestrated by myeloid cell populations in GBM.

Several convergent pathways sustain this myeloid-driven suppressive program and make it therapeutically actionable. TREM2 signaling promotes protumor myeloid states and has been associated with worse outcomes, while its inhibition shifts myeloid cells toward a more inflammatory phenotype and improves tumor control in preclinical models [56,57]. Tryptophan metabolism through IDO1/2 and TDO2 generates kynurenine, activating AhR-dependent programs that support macrophage polarization, MDSC differentiation, CCR2/CCL2-mediated recruitment, and T-cell suppression [58–60]. AhR inhibition increases MHC class II expression, augments T-cell priming, and improves survival when combined with anti–PD-1 therapy [61].

Glucose and lactate metabolism similarly reprogram myeloid cells: glycolytic activation and lactate signaling promote IL-10-mediated suppression, while TAM-derived lactate also supports glioma stem-like cells and inhibits cGAS-STING signaling through lactylation-dependent mechanisms [62,63]. These programs are amplified by spatial niche

Table 1
Immunotherapeutic opportunities and barriers across major glioma subtypes. Diffuse gliomas are now classified using integrated molecular features, including IDH-wild-type glioblastoma, IDH-mutant astrocytoma, oligodendroglioma, IDH-mutant and 1p/19q-codeleted, and diffuse midline glioma, H3 K27-altered [34,36]. IDH-wild-type glioblastoma is characterized by substantial spatial and interpatient heterogeneity, a myeloid-enriched and immunosuppressive tumor microenvironment, T-cell dysfunction, and limited durable responses to single-agent immunotherapy [37–39]. Investigated glioblastoma antigen targets include EGFR/EGFRvIII, IL-13Rα2, HER2, EphA2, GD2, B7–H3, and chlorotoxin, but heterogeneous antigen expression and antigen escape support multi-antigen, locoregional, or personalized approaches [40–42]. IDH-mutant astrocytomas and oligodendrogliomas are often less inflamed than IDH-wild-type glioblastoma, in part because the IDH-associated oncometabolite 2-hydroxyglutarate can suppress antitumor immune responses [43]. The shared IDH1 R132H neoepitope provides a rational vaccine target and has been tested clinically using an IDH1 R132H peptide vaccine [44]. Diffuse midline glioma, H3 K27-altered, is defined by the H3 K27 alteration and is limited therapeutically by midline anatomy, pediatric/young adult presentation, and the need for CNS-safe delivery strategies [36,45]. H3K27M-targeted vaccination has shown early clinical feasibility, supporting continued study of mutation-directed immunotherapy in this subtype [45]. In recurrent or heavily treated glioma, prior therapy can select for antigen loss, treatment-resistant tumor states, lymphopenia, T-cell exhaustion, hypoxia/necrosis, and myeloid/stromal remodeling, supporting combination strategies that pair tumor-directed effectors with priming, trafficking, checkpoint, metabolic, vascular, or myeloid-directed interventions [46].

Glioma subtype	Immune context	Antigenic opportunity	Dominant immunotherapy challenge	Rational therapeutic logic
IDH-wild-type glioblastoma	Myeloid-dominant, lymphocyte-poor, spatially heterogeneous, metabolically suppressive.	EGFR alterations, TERT/survivin, personalized neoantigens, splice-derived antigens; surface targets such as IL-13Rα2, HER2, and B7–H3.	Low clonal neoantigen burden, antigen heterogeneity, T-cell exclusion/exhaustion, and myeloid suppression.	Multi-antigen or personalized vaccines; oncolytic virus plus checkpoint blockade; multi-target or bystander-enabled CAR T cells; myeloid/stromal remodeling.
IDH-mutant astrocytoma	Often less inflamed than GBM; immunologically restrained by IDH-associated metabolic programs.	Shared clonal IDH1 R132H neoantigen.	Low immune infiltration, slow disease kinetics, need for durable immune memory, and uncertain timing with IDH inhibition.	IDH1 vaccine strategies combined with approaches that improve priming, trafficking, or reverse IDH-associated suppression.
Oligodendroglioma (IDH-mutant, 1p/19q-codeleted)	Generally indolent clinical course; immune context less clearly defined than GBM.	IDH1 R132H when present; other shared targets less established.	Long natural history complicates endpoints; lower urgency but need for low-toxicity durable strategies.	Preventive or minimal-residual-disease vaccine concepts may be more plausible than highly inflammatory effector therapies.
H3 K27-altered diffuse midline glioma	Anatomically constrained midline disease; pediatric/young adult context; risk from edema and inflammatory toxicity.	H3K27 M shared driver neoantigen; GD2; B7–H3.	Delivery barriers, eloquent anatomy, neurotoxicity, limited surgical tissue, and rapid progression.	Driver vaccines; locoregional CAR T-cell therapy; careful dose escalation and toxicity management; safety-conscious combinations.
Recurrent/highly treated glioma	Treatment-remodeled, lymphopenic, steroid-exposed, antigen-selected, often more hypoxic/necrotic and myeloid-rich.	Residual retained antigens; therapy-induced or noncanonical antigens; recurrent-state targets.	Antigen loss, lymphotoxic injury, terminal exhaustion, and myeloid/stromal remodeling.	Rewiring strategies first: Myeloid, metabolic, or stromal modulation and local immune activation before or with effector therapy.

biology. Hypoxic and perivascular compartments function as organizing centers for myeloid accumulation and reprogramming, with hypoxia favoring MDSC persistence and endothelial-derived IL-6 promoting macrophage polarization through PPARγ–HIF–2α signaling [30,64,65]. Finally, the CD47-SIRPα axis enables tumor cells, including glioma stem-like cells, to evade phagocytic clearance by both microglia and macrophages, and blockade of this pathway restores phagocytosis and improves survival in preclinical models [66–68]. Together, these findings show that the glioma myeloid compartment is not a single suppressive population, but a diverse set of cell states with different origins, locations, and functions. This makes myeloid-directed therapy both important and challenging: effective strategies may need to reprogram specific harmful myeloid states rather than broadly depleting or activating the entire compartment.

T-cell dysfunction spans systemic, trafficking, and intratumoral barriers

If myeloid cells are the engine of immune suppression, T-cell dysfunction is its clearest downstream consequence. In GBM, T-cell impairment begins systemically, before lymphocytes even enter the tumor, and is then compounded by barriers to trafficking, local exhaustion, and diversion into regulatory phenotypes.

A first barrier is reduced peripheral T-cell availability. In treatment-naive patients, naive T cells are sequestered in the bone marrow because of tumor-induced loss of surface S1P1, preventing their circulation and participation in immune responses [69]. Exogenous corticosteroids appear to reinforce this sequestration. Patients with GBM are commonly given corticosteroids such as dexamethasone to control peritumoral edema, and these drugs are broadly immunosuppressive. In preclinical models, corticosteroids induce the chemokine receptor CCR8 on T cells, while bone marrow cells supply its ligands CCL1 and CCL8. This CCR8 signaling retains T cells within the bone marrow and represents a therapeutically targetable retention axis [70]. Non-steroidal factors associated with brain injury also contribute to this systemic immune suppression, underscoring that GBM-associated T-cell dysfunction begins before lymphocytes encounter the tumor microenvironment itself [71].

For the T cells that circulate, entry into the tumor is highly constrained. Effective trafficking requires tethering and firm adhesion at the blood-brain barrier (BBB) endothelium through molecules such as ICAM-1 and VCAM-1, yet these pathways can be suppressed by immunosuppressive cytokines including TGF-β and IL-10 [72]. Beyond the endothelium, the glia limitans and extracellular matrix create a second barrier, where CXCL12, collagen deposition, and other stromal changes retain T cells in perivascular spaces and restrict deeper parenchymal infiltration [72–74].

Even when T cells reach the tumor bed, the myeloid-rich microenvironment drives them toward dysfunction. Tumor-infiltrating lymphocytes display an exhausted phenotype marked by expression of inhibitory receptors including PD-1, TIM-3, and LAG-3. MDSCs promote this exhaustion through Gal-9/TIM-3 and PD-L1/PD-1 interactions, while IL-10 and TGF-β further reinforce loss of effector function [75,76]. TAMs similarly sustain exhaustion through chronic antigenic stimulation and checkpoint signaling [76]. Recent work has refined this picture by distinguishing progenitor-exhausted T cells, which retain reinvigoration potential, from terminally exhausted T cells, which are short-lived and poorly responsive to therapy. Notably, TAMs appear to drive the transition from progenitor to terminal exhaustion, and depletion of TAMs preserves the progenitor-exhausted pool and improves survival when combined with checkpoint blockade in preclinical models [77]. In a tumor where T-cell infiltration is already sparse, preserving this immunotherapy-responsive subset may be as important as increasing absolute T-cell numbers.

Myeloid cells also amplify suppression indirectly through regulatory T cells. Tregs are essential for physiologic immune tolerance, but in GBM they accumulate in the tumor microenvironment and are associated with worse outcomes [78,79]. TAM-derived CCL2 promotes Treg recruitment, and reduced CCL2 signaling decreases Treg infiltration in experimental models [80]. TGF-β has likewise been implicated in sustaining Treg activity in the tumor bed, providing another point of intersection between myeloid suppression and regulatory lymphocyte expansion [29,81,82]. These findings support a coordinated myeloid–-Treg axis that further limits productive antitumor immunity.

Taken together, T-cell dysfunction in GBM is not simply a paucity of T cells, but an immune response that is constrained at every stage from circulation to infiltration to effector persistence.

NK cells, dendritic cells, neutrophils, and ECM reinforce immune exclusion

Although glioblastoma immunobiology is often framed primarily around T cells and myeloid populations, other components of the tumor microenvironment reinforce the same suppressive architecture. NK cells are rendered dysfunctional despite the intrinsic susceptibility of glioma stem-like cells to NK-mediated killing. αv integrin-dependent activation of TGF-β, impaired NKG2D signaling, and increased inhibitory KIR signaling all contribute to NK-cell hypoactivity [83–86]. Dendritic cells are limited by impaired maturation and antigen presentation, as tumor-conditioned media suppress maturation markers and increase immunosuppressive cytokine production, while TAM-derived IL-10 and TGF-β further weaken antigen presentation [87,88]. Neutrophils can also adopt protumor states that suppress T-cell immunity and promote angiogenesis, tumor growth, and tissue remodeling [89,90].

The extracellular matrix (ECM) provides a further structural barrier to immunity. Tenascin-C-rich glioma matrix impairs T-cell migration and supports mesenchymal glioblastoma proliferation and stemness, linking immune exclusion to tumor aggressiveness [91]. Accordingly, effective immunotherapy will depend not only on activating immune cells but also on enabling their trafficking into the TME, underscoring the ECM as a critical therapeutic target.

Together, these innate, antigen-presenting, and stromal programs show that glioma immune resistance is not reducible to a single missing signal. Even if effector cells are generated, they must enter and function within a tissue environment shaped by innate dysfunction, impaired antigen presentation, and extracellular matrix-mediated exclusion.

Antigenicity in Gliomas

Effective antitumor immunity begins with T-cell recognition of antigenic peptides presented by tumor cells [92]. In gliomas, this first step is constrained by a limited repertoire of immunogenic targets and by intratumoral heterogeneity that undermines both natural immune surveillance and therapeutic targeting [93–95]. Antigens available to the immune system in glioma fall into several broad categories, each with distinct implications for immunotherapy.

Tumor-associated antigens, including survivin, TERT, and wild-type EGFR, are overexpressed self-proteins present across glioma subtypes, but their incomplete tumor specificity and susceptibility to central tolerance can limit immune response magnitude [96–99]. More immunologically distinct are clonal driver neoantigens arising from subtype-defining mutations. IDH1 R132H, present in most IDH-mutant diffuse gliomas, creates a shared MHC class II-presented neoepitope capable of stimulating $CD4^+$ T-cell responses. In humanized-MHC mouse models, IDH1 (R132H) vaccination induces $CD4^+$ T cell-dependent tumor rejection [100]. In the NOA-16 phase I trial, a 20-mer IDH1 (R132H) peptide vaccine produced antigen-specific immune responses in 93.3% of patients, with a two-year progression-free rate of 0.82 among responders [44]. Similar observations with IDH1 (R132H) and H3K27M-directed vaccine strategies suggest that $CD4^+$ T-cell immunity may be mechanistically central, rather than merely supportive, in glioma vaccination.

EGFRvIII illustrates the opposite problem: an immunogenic but heterogeneous and unstable target. Unlike IDH1 R132H or H3K27 M,

EGFRvIII expression is often spatially heterogeneous within GBM. In the phase III ACT IV trial, rindopepimut, a peptide vaccine that targets the EGFRvIII mutation, failed to improve overall survival (OS), and 57–59% of patients lost EGFRvIII expression at recurrence irrespective of treatment arm [101]. Immunohistochemical analysis confirmed that 82% of recurrent tumors lost EGFRvIII expression entirely, underscoring that single-antigen targeting in a heterogeneous tumor creates selection pressure for antigen-negative escape clones. Thus, immunogenicity alone is insufficient when antigen expression is unstable. Durable immune targeting requires recognizable antigens that are also sufficiently clonal, conserved, and retained under therapeutic pressure. Consistent with this, immune checkpoint inhibitor (ICI) response across tumor types correlates more closely with clonal neoantigen burden than with total mutational burden, and the low clonal neoantigen burden typical of GBM may be one further contributor to ICI failure [102–104].

Beyond single-nucleotide variants, noncanonical antigen sources may expand the targetable landscape. Aberrant RNA splicing can generate tumor-specific neojunctions not present in normal tissue. Spatially conserved splice-derived neoantigens, including GNAS and RPL22 neojunctions, have been shown to elicit $CD8^+$ T-cell responses in glioma and other solid tumors and may be present across sampled tumor regions, conferring a form of effective clonality [105–107]. These antigens are particularly attractive in the low-TMB setting of GBM because they may provide shared, tumor-specific targets not captured by conventional DNA mutation-based neoantigen discovery.

Antigen Presentation and T Cell Priming in Gliomas

Even when immunogenic antigens exist, an effective antitumor response requires that they be captured, processed, and presented to naïve T cells in a priming-competent environment. Understanding where glioma antigens are presented, and where tumor-reactive T cells are primed, is therefore central to explaining why immunotherapy fails and how it might be improved. Tumor-derived antigens released in the brain parenchyma do not simply remain local. They drain passively through the glymphatic system into the cerebrospinal fluid (CSF) and subarachnoid space, where they can be captured by meningeal antigen-presenting cells (APCs) [108,109]. These APCs then migrate via dural lymphatic vessels into the deep cervical lymph nodes (dCLNs), the primary peripheral site where tumor-specific naïve T cells can be primed [21]. Pre-clinical studies have demonstrated that in murine GBM models, augmentation of lymphatic dynamics dramatically improved survival in a T cell-dependent manner [110], and that this effect can be abolished by surgical ligation of the dCLNs, establishing the mechanistic necessity of this drainage route [14]. Moreover, tumor antigen-specific T-cell receptor (TCR) clonotypes are detectable in glioma-draining dCLNs, providing human correlative evidence for this pathway [22]. Although soluble antigen may reach these nodes passively, efficient priming appears to depend largely on CCR7-dependent trafficking of antigen-bearing dendritic cells [23].

Beyond the deep cervical lymph nodes, CNS-border and paracerebral niches may also shape glioma immunity. Direct osseous vascular channels connect skull marrow to the dura and provide routes for immune-cell trafficking, while cranial bone marrow from GBM patients can harbor tumor-reactive $CD8^+$ T-cell clonotypes shared with the tumor but absent from distal marrow [13,24,25]. CXCR4-PET imaging of cranial immune enrichment has been associated with improved progression-free survival, suggesting that cranial marrow may represent an extracerebral immune niche adjacent to the tumor [13]. Bone marrow may therefore occupy opposing roles in glioma immunity depending on anatomical context. In intracranial tumors, systemic marrow can act as an immune sink, sequestering naïve T cells through S1P1 loss and limiting the circulating pool available for vaccination or checkpoint blockade [69]. By contrast, it is possible that cranial and vertebral marrow niches serve as CNS-associated immune reservoirs, supported by their anatomic connection to the meninges through specialized osseous vascular channels and by evidence that cranial marrow in GBM can harbor tumor-reactive $CD8^+$ T-cell clonotypes shared with the tumor [13,24,25]. Within the tumor itself, a subset of gliomas develop tertiary lymphoid structures composed of T cells, B cells, and follicular dendritic cells that may support local antigen presentation and clonal lymphocyte expansion independent of the dCLNs [17]. Although the prognostic significance of TLS in glioma remains incompletely characterized, TLS presence predicts ICI response in other solid tumors, raising the possibility that TLS induction could sensitize otherwise cold gliomas to checkpoint blockade [111–113].

Together, these data suggest that glioma antigen presentation is constrained not simply by antigen availability, but by the anatomical routes through which antigen and antigen-presenting cells access priming-competent niches. This priming geography provides the biological context for interpreting immunotherapeutic strategies that seek either to amplify endogenous immunity or bypass it altogether.

Immunotherapeutic Strategies in Gliomas

The major immunotherapeutic strategies under investigation in glioma include checkpoint blockade, vaccines, adoptive cellular therapies, oncolytic viruses, and innate or myeloid-directed approaches, each of which acts at a different point in the antitumor immune circuit (Fig. 2). The following sections review the clinical and mechanistic evidence for each modality.

Immune checkpoint blockade

Checkpoint blockade acts most directly in the effector compartment but is unlikely to succeed unless a tumor-reactive T-cell pool already exists or can be generated through peripheral, CNS-border, or intratumoral priming sites. ICIs have transformed the treatment of many solid tumors. However, their application in gliomas has been largely disappointing. Three large, randomized phase III trials of nivolumab, an anti-PD-1 monoclonal antibody, in GBM (CheckMate 143, CheckMate 498, and CheckMate 548) collectively enrolled over 1600 patients but uniformly failed to meaningfully improve overall survival when compared to the controls [114–116]. In CheckMate 143, nivolumab monotherapy demonstrated no improvement in OS compared with bevacizumab in recurrent GBM (median OS 9.8 vs 10.0 months, respectively) [114]. CheckMate 498 found that nivolumab combined with radiotherapy was inferior to temozolomide plus radiotherapy in newly diagnosed MGMT-unmethylated GBM (median OS 13.4 vs 14.9 months, respectively), and CheckMate 548 showed no benefit of adding nivolumab to standard chemoradiation in MGMT-methylated tumors [115,116].

These failures are consistent with the biology outlined above: GBM has low clonal neoantigen burden, sparse effector T-cell infiltration, severe T-cell exhaustion, and dominant myeloid suppression [117,118]. Even when nivolumab reaches saturating concentrations in resected GBM tissue, compensatory upregulation of alternative checkpoints such as TIGIT and LAG-3 may limit efficacy, supporting combination strategies rather than PD-1 blockade alone [119].

Despite these failures, neoadjuvant ICI administration has yielded more encouraging biological and clinical signals. In a randomized study of 35 patients with recurrent GBM, neoadjuvant pembrolizumab given before surgical resection and continued as adjuvant therapy was associated with upregulation of T cell and IFN-γ signatures, increased tumor-infiltrating lymphocyte (TIL) clonal expansion, and a coordinated decrease in PD-1 expression on peripheral blood T cells [120]. A subsequent single-arm expansion cohort confirmed this transcriptomic signature, characterized by suppression of cell-cycle and proliferation genes alongside upregulation of T cell and interferon programs, and identified it as an independent positive predictor of survival in post hoc analysis [121]. Overall survival in the initial cohort suggested a benefit to neoadjuvant administration of pembrolizumab (median OS 13.7 vs

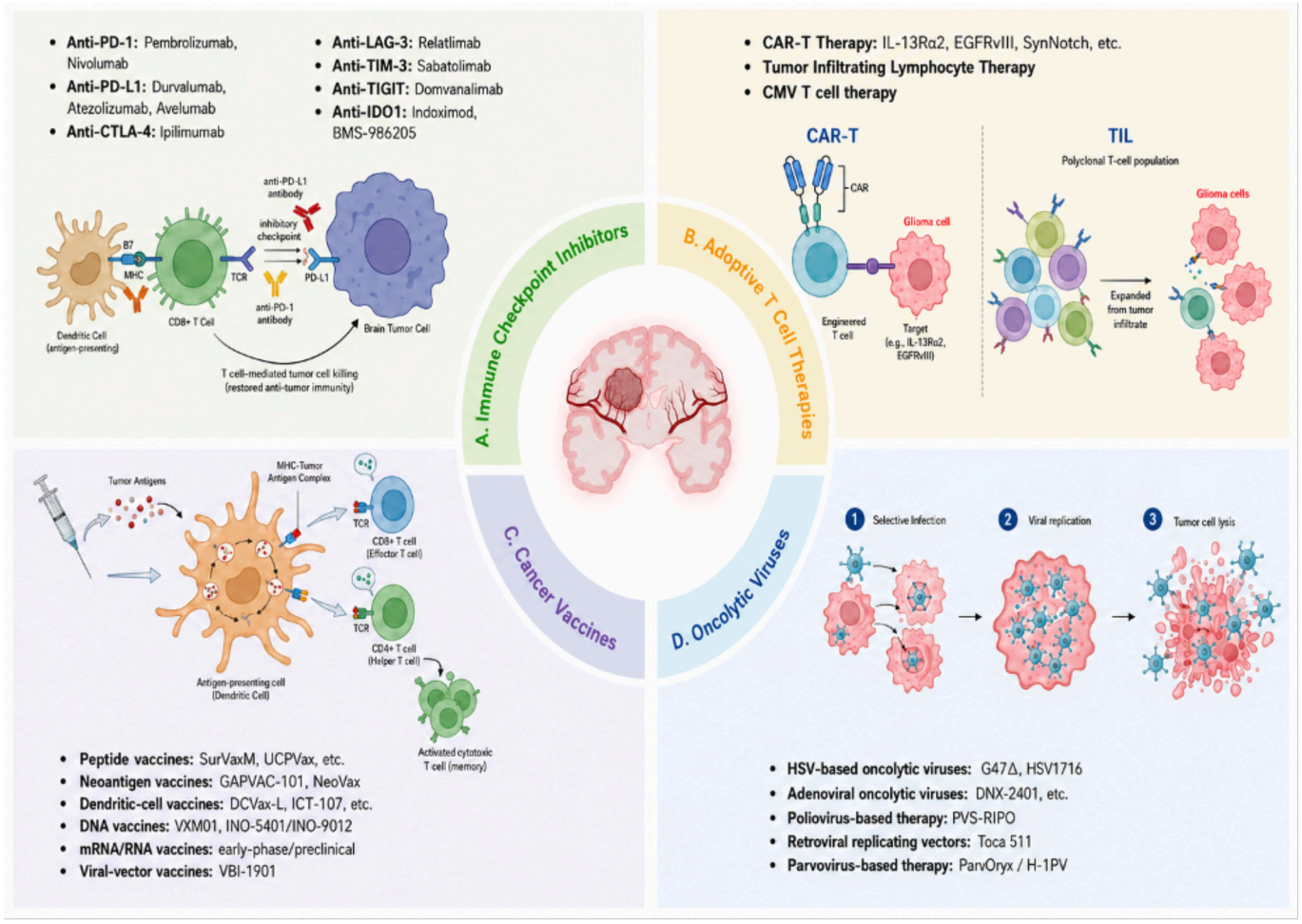

Fig. 2. Overview of immunotherapeutic strategies in glioma. The major immunotherapy modalities under investigation in glioma include **(A)** immune checkpoint inhibition, **(B)** adoptive T-cell therapies, **(C)** cancer vaccines, and **(D)** oncolytic viruses. Representative mechanisms and example agents are shown for each category. Collectively, these strategies seek to overcome the immunosuppressive glioma microenvironment by restoring T-cell activity, introducing or expanding tumor-reactive lymphocytes, priming antitumor immunity, or promoting immunogenic tumor destruction. Created with BioRender.com.

7.5 months, $P = 0.04$), though this benefit was not confirmed in the expansion cohort [120,121]. In a parallel study, 30 GBM patients (27 recurrent, 3 newly diagnosed) were treated with a single presurgical dose of nivolumab [122]. Matched pre- and post-treatment tumor specimens showed significant increases in chemokine transcripts (CXCL10, CCL4) and increased $CD8^+$ T cell infiltration, though no significant survival difference was observed. Together, these studies indicate that the timing of ICI relative to surgery shapes the local immune response, while a durable survival benefit from neoadjuvant single-agent PD-1 blockade remains unproven. More recent data suggest that pairing neoadjuvant PD-1 blockade with a second checkpoint inhibitor may be a more effective strategy, an approach now under active investigation [123].

Vaccines

Vaccines act primarily by generating or amplifying tumor-reactive T cells in peripheral lymphoid compartments. Durable efficacy then requires those cells to traffic to the tumor bed and retain function within the suppressive glioma microenvironment. Among peptide platforms, SurVaxM, a survivin-targeted vaccine, demonstrated a median OS of 25.9 months and a 6-month progression-free survival (PFS) rate of 95.2% in newly diagnosed GBM in a single-arm phase IIa trial, with an ongoing phase IIb study [124]. UCPVax, a telomerase-targeted universal cancer peptide vaccine, elicited de novo immune responses in 97% of patients with unmethylated MGMT GBM, and epitope spreading correlated with improved survival [125]. In contrast, the phase III ACT IV trial of rindopepimut, an EGFRvIII-targeted peptide vaccine, was terminated after showing no difference in OS between vaccine and control arms (median OS 20.1 vs 20.0 months) [101]. This likely reflects the subclonal nature of EGFRvIII expression and the frequency of antigen loss in treated and untreated tumors. Additional peptide-based strategies include IMA950, a multipeptide vaccine targeting multiple GBM-associated antigens that has shown tolerability and immunogenicity in early-phase studies [126,127], and HSPPC-96, an autologous heat-shock protein peptide complex designed to broaden antigenic coverage and potentially mitigate the limitations of single-antigen targeting [128].

Personalized neoantigen vaccines have demonstrated immunogenicity in early-phase GBM trials. The GAPVAC-101 trial combined a shared antigen library with patient-specific neoepitopes, eliciting sustained $CD8^+$ memory and $CD4^+$ Th1 responses [129]. In the NeoVax trial, vaccine-generated T cells were shown to traffic into the intracranial tumor by single-cell TCR analyses, though dexamethasone use blunted immune response [130]. Among dendritic cell platforms, DCVax-L is the most advanced, with a phase III trial reporting a median OS of 19.3 months versus 16.5 months for external controls in newly diagnosed GBM [131]. Other dendritic-cell approaches include ICT-107, which showed safety, immunogenicity, and a modest PFS signal without a clear OS benefit in newly diagnosed GBM [132], and CMV pp65

RNA-pulsed dendritic-cell vaccines, which have demonstrated CMV-specific immune activation and durable disease control in a subset of patients [133–135]. Collectively, these data indicate that vaccine strategies in GBM have demonstrated immunogenicity across multiple platforms but have not yet established definite survival benefits in randomized trials. The failure of rindopepimut highlights the vulnerability of single-antigen approaches to clonal heterogeneity, while personalized and multi-epitope strategies remain in early-phase testing. Whether vaccination can produce durable responses in GBM, either alone or in combination with other immunotherapeutic modalities, remains to be determined by adequately powered randomized studies.

Adoptive cellular therapies

Adoptive cellular therapies can bypass inefficient endogenous priming by placing engineered effectors directly into the tumor or ventricular compartment, but durability remains constrained by antigen heterogeneity, product persistence, trafficking, and local suppression. Early EGFRvIII-directed CAR T-cell studies demonstrated feasibility but were limited by antigen loss and adaptive upregulation of immunosuppressive ligands [33]. Subsequent efforts have expanded to target IL-13Rα2, GD2, HER2, and B7–H3, with delivery route emerging as a critical determinant of efficacy.

IL-13Rα2-directed CAR T cells have shown clinical activity, including a single-patient complete regression after intracranial delivery and a phase I trial in recurrent high-grade glioma in which combined intratumoral and intraventricular delivery was associated with improved survival compared with either route alone [136,137]. In diffuse midline gliomas (DMGs), GD2-targeted CAR T cells have yielded substantial responses. In H3K27M-mutant diffuse midline glioma, GD2-directed CAR T cells produced radiographic and clinical responses in early studies, including a durable complete response in an expanded cohort [138–140]. B7–H3 targeting CAR T cells have similarly demonstrated activity in diffuse intrinsic pontine glioma, with three patients surviving beyond 40 months after repeated intraventricular dosing [141].

A key challenge for CAR T therapy in gliomas is antigen heterogeneity. Multitarget and dual-antigen strategies have been developed to tackle this challenge. Bivalent CAR T cells co-targeting EGFR and IL-13Rα2 have produced rapid radiographic responses in a phase I trial of recurrent GBM [40]. The CARv3-TEAM-E construct, which targets EGFRvIII through its CAR domain while secreting bispecific T-cell-engaging antibody molecules against wild-type EGFR, produced radiographic tumor regression in all three patients treated in the INCIPIENT trial after a single intraventricular infusion, although responses were transient in two patients [142]. Logic-gated approaches, including synNotch circuits designed to improve specificity and preserve less-exhausted T-cell states, have shown enhanced activity in preclinical GBM models [143]. Despite these advances, antigen escape, limited persistence, treatment-related neuroinflammation, cytokine release syndrome, and immune effector cell-associated neurotoxicity syndrome remain significant barriers to safe dose escalation and durable clinical benefit.

Oncolytic virotherapy and local immune activation

Oncolytic viruses (OVs) address the absence of immunogenic cell death and poor antigen visibility within the TME, a core upstream barrier in GBM immunotherapy. By selectively replicating within and lysing tumor cells, OVs release tumor antigens and pro-inflammatory cytokines, converting immunologically cold tumors to hot. Oncolytic viruses are unusual among glioma immunotherapies in that they can act simultaneously in the tumor core and reconstitute upstream priming signals that engage the dCLN axis. Several platforms have demonstrated clinical activity in glioma.

DNX-2401 (tasadenoturev), a replication-competent oncolytic adenovirus, was associated with survival greater than 3 years in 20% of treated recurrent GBM patients in a phase I trial, with post-treatment biopsies confirming viral replication and $CD8^+$ T cell infiltration [144]. In the CAPTIVE/KEYNOTE-192 phase I/II trial, intratumoral DNX-2401 followed by pembrolizumab produced a 12-month OS of 52.7% in recurrent GBM, with several patients achieving durable responses beyond four years [145]. Oncolytic herpes simplex virus (oHSV) platforms have been particularly active. G207 converted immunologically cold pediatric high-grade gliomas to T cell-infiltrated tumors in a phase I trial [146], and G47Δ (teserpaturev) met its primary endpoint in a phase II study of recurrent GBM with a one-year survival rate of 84.2%, leading to conditional regulatory approval in Japan, the first for any OV in a primary brain tumor [147]. The attenuated poliovirus chimera PVSRIPO achieved a durable survival plateau of 21% at 24 months in recurrent GBM, sustained at 36 months, with mechanistic studies indicating that its primary target is the tumor-associated myeloid compartment via CD155 [148,149].

Myeloid and innate-directed strategies

Given that myeloid cells comprise the majority of the immune infiltrate in gliomas, therapeutic strategies directed at this compartment are increasingly recognized as a viable target. Myeloid- and innate-directed agents act predominantly within the effector compartment, modifying the tissue context in which T cells either function or fail. The CD47-SIRPα antiphagocytic axis is one such target, with preclinical studies showing that brain-resident microglia can mediate antitumor phagocytosis after CD47 blockade [68]. Systemic CD47 blockade carries the risk of hematologic toxicity, prompting the development of locoregional delivery approaches, including oncolytic viruses engineered to express anti-CD47 antibodies [150] and CAR T cells secreting SIRPγ-derived CD47 blockers that eradicate antigen-heterogeneous tumors by co-opting macrophage-mediated bystander killing [151].

CSF1R inhibition has been explored as a strategy to reprogram immunosuppressive TAMs. However, the phase II trial of pexidartinib (PLX3397) in recurrent GBM showed no clinical efficacy despite adequate CNS penetration [152], indicating that macrophage depletion alone is insufficient and that reprogramming toward a pro-inflammatory phenotype may be a more productive approach [153]. Emerging dual-targeting agents, such as SYHA1813 which inhibits both VEGFR and CSF1R, have demonstrated preliminary activity in recurrent high-grade gliomas [154].

Other emerging strategies seek to reprogram suppressive myeloid and antigen-presenting compartments rather than deplete them. CD40 agonism can activate antigen-presenting cells and promote myeloid-dependent antitumor immunity, and early-phase studies are evaluating CD40 agonists in CNS tumors, including sotigalimab/APX005 M in pediatric CNS tumors and the Fc-engineered anti-CD40 agonist 2141-V11 in combination with D2C7-IT for recurrent malignant glioma [155,156]. A distinct approach is transcriptional reprogramming of macrophage states through inhibition of C/EBPβ. Lucicebtide/ST101, a C/EBPβ antagonist, has been reported to shift tumor-associated macrophages toward a more pro-inflammatory phenotype in preclinical models and is being evaluated clinically in glioblastoma [157]. Together, these approaches highlight a broader shift from nonspecific myeloid depletion toward functional reprogramming of suppressive myeloid and antigen-presenting-cell states [157,158].

Innate immune agonists represent a separate avenue. Intracranial STING agonists have produced robust tumor regression in preclinical GBM models, driven primarily by NK cell cytotoxicity and inflammatory macrophage infiltration [159]. Tryptophan catabolism via indoleamine 2,3-dioxygenase is another immunosuppressive pathway exploitable in glioma. A pediatric phase I trial of indoximod demonstrated that responders had significantly longer OS, and single-cell analyses confirmed the emergence of de novo cytotoxic T cell clonotypes [160]. Finally,

IL-21-engineered NK cells have recently shown superior anti-GBM activity relative to IL-15-primed NK cells, with epigenetic reprogramming via CEBPD enhancing long-term cytotoxic fitness [161]. These innate and myeloid-directed strategies are unlikely to succeed as monotherapies but may be critical adjuncts that improve efficacy of adaptive immunotherapies.

Rational combinations

The clinical experience reviewed above suggests that immunotherapy failures in glioma are not simply failures of the modality in isolation, but rather a failure of asking a single therapy to span immune compartments it cannot reach. For example, vaccines generate primed T cells in the deep cervical lymph nodes, but cannot by themselves remodel a suppressive tumor bed. Effective combination strategies in glioma should therefore be designed around compartmental coverage rather than additive intensification.

Bridging priming and effector compartments

One illustrative example of compartmental bridging in clinical glioma immunotherapy is the pairing of intratumoral oncolytic virotherapy with systemic checkpoint blockade. In recurrent glioblastoma, intratumoral DNX-2401 followed by pembrolizumab was associated with a 12-month overall survival rate of 52.7% in the single-arm CAPTIVE/KEYNOTE-192 phase I/II trial, with durable responses sustained beyond four years in a subset of patients [145]. Within the compartmental framework, a plausible interpretation is that DNX-2401 reconstitutes in-situ antigen release and type I interferon signaling, generating primed effectors and engaging draining lymphatics, while concurrent pembrolizumab releases those effectors from PD-1-mediated restraint at the tumor core. Because this trial was single-arm, the relative contribution of each agent cannot be established, although the rationale for engaging both the priming and effector compartments is strong. A conceptually parallel example is controlled IL-12 gene therapy with nivolumab, which established safety, increased intratumoral IFN-γ, and achieved a median overall survival of 16.9 months in the 10-mg veledimex cohort [162]. In both cases, the proposed rationale is that benefit derives less from local cytotoxicity than from reconnecting antigen release, interferon signaling, immune-cell recruitment, and checkpoint release within the same lesion.

The neoadjuvant pembrolizumab experience [120,122] can be read through the same lens, with appropriate caution. Although the survival benefit of neoadjuvant administration is unclear and was not confirmed in a follow-up expansion cohort, surgical resection may transiently reconstitutes a priming signal, releasing antigens into a drainable compartment while the dCLN axis is still intact, and pre-resection PD-1 blockade may allow that priming to occur without immediate effector restraint [121]. Adjuvant-only checkpoint blockade, by contrast, attempts to release a T-cell pool that was never adequately generated. The negative phase III nivolumab trials in newly diagnosed and recurrent GBM [114–116] are consistent with this framework, in that blocking PD-1 in the effector compartment is unlikely to help when the priming compartment has not produced a mobilizable T-cell pool.

Bridging the trafficking compartment

A separate class of combinations addresses access rather than priming or effector function. The phase I/II trial of repeated blood–brain barrier opening with an implantable ultrasound device and carboplatin administration demonstrated that the BBB-opening endpoint was met in 90% of emitters on MRI and that the regimen could be delivered repeatedly without dose-limiting toxicity [163]. Such platforms do not directly address antigenicity or effector dysfunction, but they enable agents that act in the tumor compartment to actually reach it. Combinations that pair access-modifying technologies with primed T-cell pools, such as ultrasound-mediated BBB opening together with a vaccine or with TIL-derived therapy, represent a logical but largely untested avenue for future therapeutic intervention.

Remodeling the effector compartment

Where the dominant block lies in the effector compartment, the most promising combinations pair checkpoint blockade with interventions that reprogram suppressive myeloid and stromal biology. Myeloid-specific KDM6B inhibition enhances antigen presentation, interferon response, and phagocytosis and sensitizes glioblastoma to PD-1 blockade in preclinical models [164]. Siglec-9 has been identified as a macrophage immune checkpoint whose targeting enhances anti–PD-1/PD-L1 efficacy [165]. Anti-CXCR4 plus anti–PD-1 modulates the glioma microenvironment in mouse models [166], and disruption of the CLOCK–OLFML3–HIF1α–LGMN–CD162 and TFPI2–CD51–STAT6 axes activates T-cell responses and synergizes with PD-1 blockade [167, 168]. These combinations remain largely preclinical, and translating them will require pharmacodynamic biomarkers that report on myeloid state in patient tumors rather than on systemic exposure.

Therapeutic sequence determines which compartments remain accessible

Rational combinations must be designed not only around which compartments are blocked, but also around the sequence in which those compartments can be productively engaged. A vaccine or oncolytic virus may need to precede checkpoint blockade if inadequate priming is the limiting barrier. Myeloid or stromal reprogramming may need to precede adoptive cellular therapy if effector collapse in the tumor bed is dominant. BBB opening may need to precede systemic delivery of agents that otherwise fail to reach the tumor compartment. Conversely, after chemoradiation, corticosteroid exposure, lymphopenia, and antigen loss, the same sequence may no longer be biologically available. Thus, the field needs not only rational combinations, but rationally ordered combinations.

These sequencing questions are especially important because compartmental targets are not static. The immune anatomy that supports priming, trafficking, and effector function in a treatment-naive glioma is meaningfully different from the anatomy that remains after maximal safe resection, six weeks of chemoradiotherapy, prolonged corticosteroid exposure, and clonal selection by alkylator therapy. Two clinically relevant states can therefore be distinguished. In a native-tumor priming state, the intact lesion still serves as an antigen source, the dCLN drainage axis is largely intact, and cranial bone marrow niches may remain immunologically available; the goal is to generate or amplify tumor-reactive immunity before exhaustion and antigen loss become entrenched. In a treatment-remodeled rewiring state, the same anatomical compartments remain present but their function has been altered: lymphopenia compromises peripheral priming, corticosteroids blunt activation, hypoxia and necrosis reorganize the trafficking compartment, and clonal selection narrows the antigenic landscape. The same combination that productively engages two compartments in a treatment-naive tumor may engage only one after first-line therapy, or perhaps none at all.

Toward a compartmental design framework

We propose three combination strategies for use in clinical trials using this compartmental framework, each defined by which compartments it bridges. A *prime-and-release* strategy pairs an agent that generates or amplifies antigen presentation in the priming compartment, such as vaccination, oncolytic virotherapy, lymphatic enhancement, or surgical-window antigen release, with checkpoint blockade in the effector compartment. A *bypass-and-sustain* strategy pairs locoregionally delivered CAR T-cell or TCR-engineered therapy, which deposits effectors directly into the tumor compartment, with interventions that

sustain their function *in situ* — local cytokine delivery, myeloid reprogramming, or metabolic support. A *target-and-unmask* strategy is particularly relevant in IDH-mutant glioma, where mutant IDH inhibition could be combined with vaccination or checkpoint modulation to pair clonal antigen recognition with reversal of tumor-intrinsic immune suppression. In each case, the combination's logic is compartmental: the goal is not maximal immune stimulation, but coverage of the specific compartments in which the dominant block resides at the relevant point in the disease course.

This framework also has implications for biomarker development. The diagnostics required are not additional measures of the tumor itself, but measures of the compartments through which immunity must pass: CSF and dCLN-derived TCR clonotyping to assess peripheral priming, CXCR4-PET or analogous imaging to assess cranial bone marrow engagement [13], TLS scoring on resection tissue to identify ectopic priming sites [17], and pharmacodynamic readouts of myeloid state to assess the effector compartment. Trials that incorporate these compartment-specific endpoints, rather than relying on tumor PD-L1 or TMB alone, are the ones most likely to show whether a given combination is doing what its design intends.

Conclusions

Immunotherapy for glioma has encountered a disease that disrupts antitumor immunity at multiple sequential levels. Antigenicity is often limited or heterogeneous, endogenous priming is inefficient, access to the CNS tumor bed is spatially constrained, and immune effectors that do arrive encounter a profoundly suppressive microenvironment dominated by myeloid cells, stromal barriers, metabolic stress, and adaptive resistance programs. These failures cannot be explained simply by intracranial location or by immune privilege. Instead, glioma immunotherapy is best understood as a problem of compartmental mismatch: therapies act in one immune compartment while the dominant barrier lies in another, and the relevant compartment may shift as the tumor evolves from a treatment-naive to a treatment-remodeled state.

This framework helps reconcile the mixed clinical experience across checkpoint blockade, vaccines, adoptive cellular therapy, oncolytic viruses, and myeloid-directed strategies. Checkpoint blockade is unlikely to succeed when the priming compartment is ineffective. Likewise, vaccines are unlikely to succeed when trafficking and effector persistence remain unsolved. Adoptive cellular therapies can bypass endogenous priming but remain vulnerable to antigen heterogeneity and suppressive tumor niches and myeloid- or niche-directed therapies are unlikely to produce durable benefit without a tumor-reactive effector population. The implication is that rational combinations should not simply add immune agents together, but should connect otherwise disconnected steps in the antitumor immune circuit.

The path forward will therefore require biomarker-guided, state-aware combinations that align therapy with both where the immune block resides and when that compartment is therapeutically accessible. In the native-tumor priming state, interventions may be most effective when they enhance antigen release, drainage, and T-cell priming. In the treatment-remodeled rewiring state, effective therapy may require active remodeling of myeloid, metabolic, stromal, and trafficking barriers before effector cells can function. The next advance in glioma immunotherapy may therefore be conceptual as much as technical, moving toward the design of therapies matched to the anatomy, timing, and evolving immune ecology of each tumor.

Author Contribution

George Nageeb: Conceptualization, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization.

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Justin Liu: Investigation, Writing – Review & Editing.

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Michael Lim: Conceptualization, Supervision, Writing – Review & Editing.

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Animal and Human Studies Experimental Approval Board

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