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Immunity

Review

# Complex neural-immune interactions shape glioma immunotherapy

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## SUMMARY

Rich neural-immune interactions in the central nervous system (CNS) shape its function and create a unique immunological microenvironment for immunotherapy in CNS malignancies. Far from the now-debunked concept of CNS "immune privilege," it is now understood that unique immunological niches and constant immune surveillance of the brain contribute in multifaceted ways to brain health and robustly influence immunotherapy approaches for CNS cancers. Challenges include immune-suppressive and neurotoxicity-promoting crosstalk between brain, immune, and tumor cells. Developing effective immunotherapies for cancers of the nervous system will require a deeper understanding of these neural-immune-malignant cell interactions. Here, we review progress and challenges in immunotherapy for gliomas of the brain and spinal cord in light of these unique neural-immune interactions and highlight future work needed to optimize promising immunotherapies for gliomas.

## INTRODUCTION

Despite decades of research and significant therapeutic advances in systemic malignancies, effective treatment strategies for high-grade gliomas (HGGs) remain elusive, although incremental progress is being made by the medical and scientific community. Glioblastoma (GBM) is the most common primary brain tumor in adults with a median overall survival (OS) of 15–21 months.[1–3] Primary brain tumors are the most common cancer of childhood and a leading cause of death in children and young adults.[1] Immunotherapy has revolutionized the field of oncology in recent decades leading to significantly improved patient outcomes in systemic solid and liquid tumors.[4,5] However, several challenges occur when applying immunotherapy in the context of central nervous system (CNS) tumors. The immune environment of the CNS is unique with tightly controlled bi-directional interactions between the CNS and immune system that we are only beginning to appreciate.[6] Furthermore, intracranial tumors exploit these specialized immune mechanisms, creating an immunosuppressive tumor environment and inducing systemic immunosuppression,[7–9] which complicates immunotherapy approaches.

Recent scientific advances have led to paradigm shifts in our understanding of CNS immunity. No longer is the CNS viewed as one of sealed-off immune privilege. Instead, we are discovering and understanding the distinct adaptations and interactions of the immune system within the CNS. As a result, standard approaches with proven success in systemic malignancies will likely need to be modified in the CNS to flourish, much like tumor and immune cells themselves adapt in the CNS.[6,10] Initial immunotherapeutic trials for CNS tumors have not been outright successes, but they have shown glimmers of hope in multiple trials across different modalities.[11–14] Correspondingly, these treatments have also revealed new toxicities that are particular to immunotherapeutics in the CNS.[15] As we delve into the complex interplay of the immune system with the brain and learn from patient responses in clinical trials, new treatment strategies and targets will also arise and further invigorate future immunotherapies.

## CNS-IMMUNE ENVIRONMENT

The previously established paradigm of the brain as "immune privileged" has been overturned in recent decades. There is mounting evidence of the crucial role of the immune system for maintaining CNS function and response to pathologic states. Historically, the brain was thought to be immune privileged from early experiments, which showed lack of skin graft rejection in the brain. This lack of immunity was attributed to the absence of lymphatic drainage in the CNS.[16] In recent decades, a lymphatic system of the CNS—also called the glymphatic system to acknowledge the role of glia in CNS lymphatic drainage—was rediscovered[17–20] and provided a key conduit for CNS-immune communication.[21] In addition, studies have clearly demonstrated trafficking of adaptive immune cells into the CNS,[22,23] as well as contribution of peripheral immune cells to CNS repair,[24,25] maintenance,[26,27] and inflammatory responses in the CNS.[28] Indeed, even social behavior and stress coping were found to be regulated by the immune system.[29,30] We are now starting to appreciate the immune landscape of the CNS and the nuanced crosstalk between the two, which is integral to maintaining the intricate function of the CNS.

A wide array of specialized immune cell populations exists in the CNS. Microglia—specialized tissue-resident macrophages—have long been identified as the resident immune cells of the brain

 

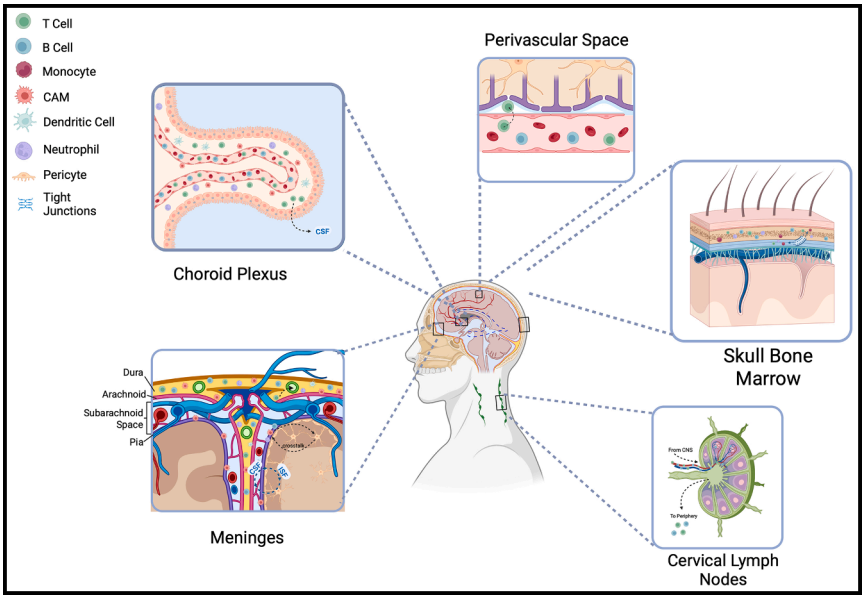


**Figure 1. Brain border immunological niches**

Specialized compartments in the blood-CNS interface that allow trafficking and exchange of peripheral and CNS metabolites and immune cells to facilitate immune surveillance and response. The meninges have diverse immune populations predominated by CAMs with blood vessels in the dura lacking tight junctions allowing connection to the peripheral circulation and play a key role in B cell maturation, immune cell trafficking, and regulation of CNS inflammation. The choroid plexus consists of ependymal cells with tight junctions and fenestrated endothelium to allow tracking of immune cells and cytokines. The perivascular spaces are key for antigen presentation and may allow T cell entry into the CNS. The skull bone marrow allows for bi-directional communication with the CNS and immune surveillance. The CLNs allow for drainage of immune cells from the CNS and interaction with the peripheral immune system. Figure created with BioRender.com.

parenchyma and critical to supporting brain development, including myelination,[31] neural circuit refinement,[32,33] and immune surveillance.[31,34] Now, there is increasing interest and understanding of the unique immunologic compartments at the CNS borders. These immunologic niches at the brain borders contain a diversity of immune cells that far eclipse those of the CNS parenchyma including myeloid cells, lymphoid cells, and dendritic cells.[35] These brain border immunologic niches include structures within the CNS such as the meninges, choroid plexus, perivascular spaces as well as those closely interconnected with the CNS such as the skull bone marrow and cervical lymph nodes (CLNs).[6,36]

The predominant immune cells of these brain borders immunologic niches are CNS-associated macrophages (CAMs) or also called border-associated macrophages (BAMs), which are unique by virtue of their location and molecular signatures that distinguish them from microglia.[37,38] In addition, immune cells in these specialized niches can further influence neuronal function through cytokine signaling.[39,40] The adaptive immune system also contributes to CNS development and function. For example, T cells are required for microglial maturation,[41] play a role in autoimmune diseases,[42] and contribute to memory and behavior.[43,44] Delving into the role of the innate and adaptive immune system in the CNS will transform our understanding of how the brain functions and changes in states of inflammation and disease. These discoveries have led to a paradigm shift in our understanding of the CNS-immune system[6] and pave the road to new immunotherapies.

## BRAIN BORDER IMMUNOLOGIC NICHES—MENINGES, CHOROID PLEXUS, AND PERIVASCULAR SPACES

The CNS has long been known to have specialized protection with unique barriers both physical and chemical such as the meninges, which surround the brain and spinal cord, as well as the blood-brain barrier (BBB). A barrier between the brain and peripheral circulation was hypothesized even in the 19th century when studies of pigment injected into rodents did not extravasate into the brain. However, injected tracers could be found in the leptomeninges, choroid plexus, and perivascular spaces.[45] The BBB, comprising endothelial cells, basement membrane, pericytes, and astrocytes, selectively control trafficking of substances to the CNS.[45] However, at select locations, such as the meninges, choroid plexus, and perivascular spaces, unique specializations at the blood-CNS interface allow increased trafficking of molecules and immune cells, creating specialized compartments for immunosurveillance and response.[45] We will explore these immunologic niches at the brain border and their roles in the CNS-immune interface (Figure 1).

The meninges, composed of three layers—dura mater, arachnoid mater, and pia mater—not only provide physical protection for the brain but also serve as a unique immunologic compartment.[46] The dura mater, the outermost layer, consists of two layers that are largely fused but separate in certain areas to form the dural venous sinuses.[46] Blood vessels in the dura mater lack tight junctions,[45,47] which allows more direct connection to the peripheral circulation. In addition, meningeal lymphatic vessels are present in the dura mater, running alongside venous sinuses. They facilitate the drainage of molecules and antigens from the CNS parenchyma to the CLNs and serve as a conduit to the peripheral immune system system.[48]

Below the dura mater lies the arachnoid mater, which features an outer epithelial layer connected by tight junctions. This layer overlays the subarachnoid space, which is filled with cerebrospinal fluid (CSF) and serves as a critical barrier between the more open vasculature of the dura mater and the CSF.[49] Folds of the arachnoid mater up into the dural venous sinuses, termed arachnoid granulations, facilitate the reabsorption of CSF into the venous blood. The pia mater closely adheres to the brain parenchyma and forms a semipermeable barrier between the CSF and brain parenchyma.[46] According to the glymphatic (glia + lymphatics) theory, one proposed mechanism of CSF and interstitial

fluid (ISF) flow involves arterial pulsations propelling CSF from the subarachnoid space into the brain parenchyma through astroglial aquaporin-4 channels. By convective flow, ISF then drains into the meningeal lymphatics along with metabolites and antigens, eventually reaching the CLNs.[18] MRI imaging studies in humans have also demonstrated visualization of contrast injected into the CSF within the glymphatic system that subsequently traverse to the CLNs.[50] The glymphatic vessels are crucial in CNS-immune surveillance and is required for a full inflammatory response in the CNS.[7,50,51] Ligation of meningeal vessels leads to T cell accumulation and cognitive impairment.[52]

The immune cell population of the meninges is predominantly comprised of CAMs, but there is also a diversity of innate and adaptive immune cells including T cells, NK cells, dendritic cells, and neutrophils.[37] The T cells of the meninges seem to be a key regulator in CNS inflammation and behavior, and IL-4-producing T cells are required for normal cognitive function.[39] Interferon-γ (IFN-γ) production by meningeal T cells can also affect neurons in the prefrontal cortex and mediate social behavior.[29] Additionally, the meninges may also play a role in B cell maturation to protect against autoimmunity in the CNS.[53] Taken together, the meninges represent a unique immunologic niche in the CNS and is a key regulator of neuronal function.

Another specialized immunologic compartment in the CNS is the choroid plexus, which is located within the ventricular system. The choroid plexus has a unique blood-CSF barrier composed of ependymal cells with tight junctions overlying fenestrated endothelium on choroid plexus vessels,[45,54] which regulate passage of immune cells and metabolites between the blood and CSF.[55,56] The immune cells within the choroid plexus are diverse and include lymphocytes, macrophages, neutrophils, dendritic cells, and B cells.[57] Macrophages in the choroid plexus are positioned for vascular surveillance and extend their processes along blood vessel in response to insults.[58] During inflammation, the choroid plexus can release extracellular vesicles that enter the brain and are taken up by astrocytes and microglia, thereby transmitting information about peripheral inflammation to the CNS.[59] Additionally, the choroid plexus serves as a site for T cell trafficking from the periphery into the CNS after injury.[28,60]Thus, the choroid plexus plays a unique role in the CNS by facilitating immune surveillance and trafficking.

Perivascular spaces represent yet another unique immunologic niche in the CNS and may play a key role in antigen drainage and presentation from the CNS.[18] The perivascular space is a compartment that surrounds blood vessels and exists between the basement membrane of the glia limitans and the endothelial basement membrane of blood vessels. This space ultimately disappears when two basement membranes fuse at the level where arterioles become small capillaries.[61] The perivascular space may facilitate drainage of metabolites from the CNS as part of the glymphatic system.[62] In addition, the perivascular space of the postcapillary venule may be a site where T cells can recognize their cognate antigens on macrophages,[63,64] which then allows for T cell activation and entry to CNS parenchyma via migration across the glia limitans.[51,63] There is also evidence that perivascular macrophages can regulate vascular permeability[65] and thus regulate CSF flow, leading to modulation of clearance of cytokines and antigens in the CNS.[66]

## IMMUNOLOGIC NICHES BORDERING THE CNS

While certain specialized niches in the CNS allow for immune cell trafficking, there are also specialized areas closely bordering the CNS, such as the skull bone marrow and CLNs that play unique roles in CNS-immune crosstalk. The skull bone marrow may be a reservoir of myeloid cells including monocytes and neutrophils for the CNS and a source of peripherally derived macrophages in the CNS during inflammation.[67] Microscopic channels in the skull bone marrow traverse the dura and into the venous sinuses, which allow for trafficking of immune cells from the peripheral marrow into the CNS.[68,69] After CNS injury, such as ischemic stroke, there is preferential migration of skull-derived immune cells compared with immune cells from long-bones such as the tibia.[69] Moreover, the communication between the skull bone marrow and CNS is bi-directional. Contrast tracers injected into the CSF can be seen in the skull bone marrow in patients with CSF disorders.[70] CSF can egress to the bone marrow from the dura and may play a role in bone marrow hematopoiesis and immune surveillance of the CNS.[68,70,71] Indeed, this may be a pathway that may be co-opted for spread of systemic malignant cells into the leptomeningeal space leading to leptomeningeal metastatic disease.[72]

The CLNs represent yet another specialized immunologic compartment in close communication with the CNS. Recently re-discovered meningeal lymphatic vessels in the CNS drain directly into the CLNs, which allows peripheral immune cells to recognize CNS-specific antigens.[19,21] Ablation of lymphatic drainage leads to decreased inflammatory response with decreased T cell activation.[21] Peripheral immune surveillance of CNS antigens appears crucial for maintaining brain health as ablation of lymphatic drainage can lead to exacerbation of Alzheimer's disease pathology[73] as well as impairment of the antitumor response to brain tumors.[74] Activated T cells from CLNs may then traffic to the CNS via other brain border niches such as the meninges or choroid plexus.[6] CLN-derived type-1 regulatory T cells (Tr1) can suppress astrocyte activation and decrease inflammation by decreasing recruitment of peripheral immune cells.[75] Thus, CLNs represent a conduit for CNS immunosurveillance and crosstalk between the CNS and peripheral immune system. The immunologic niches at the brain borders represent a unique space, which not only facilitate immune cell trafficking and antigen drainage but also influence neuronal function and response to injury or disease.

## MICROGLIA

In considering the CNS-immune environment, we also must turn our attention to the CNS parenchyma. Microglia are the resident myeloid cell of the brain parenchyma and play highly specialized roles critical for healthy brain function such as synaptic pruning and regulation of neuronal excitability.[32,33,76] Microglia are derived from yolk sac cells, colonize the brain in early embryonic development, and require colony-stimulating factor 1 (CSF1) or IL-34 for development and maintenance.[77–79] CD4 T cell populations may also have a role in the process of microglial maturation

since absence of T cells in mouse models inhibited transition from fetal to adult states.[41] Microglia populations are stable, self-renewing, and largely independent of peripheral contributions.[80] Numerous distinct subpopulations of microglia exist, with clear regional diversity such as those in white matter representing a distinct population (called axon tract microglia, ATM).[81] Regionally diverse subpopulations exhibit differential dependence on CSF1 and IL-34.[76,82]

Microglia engage in nuanced crosstalk with neurons and astrocytes, with bi-directional modulation of activity and function. Microglial maturation is highly dependent on neuronal interactions, while microglia, in turn, shape neural circuit refinement and regulate developmental myelination.[31,83–85] Neurons and astrocytes synergistically maintain microglial identity via transforming growth factor β2 (TGF-β2) and modulate responses to inflammation by suppressing responses to weak stimuli.[86] Microglia play a key role in neuronal regulation via synaptic remodeling in conjunction with astrocytes, and in maintaining oligodendrocyte progenitor cells and myelination.[87–89] Additionally, astrocytes and microglia coordinate to clear neuronal debris, with astrocytes removing dendritic apoptotic bodies and microglia phagocytosing cell bodies and nuclei.[90] They are also critical to immune surveillance and are constantly sampling their microenvironment so that injury leads to activation and response.[34]

## CNS AND IMMUNE CROSSTALK

Evolutionarily, communication between the immune system and the CNS is essential, as behavioral changes during illness may be adaptive.[40] Cytokines, key mediators of this communication, contribute to neuronal function and can regulate neuronal synapses. For example, neuronal expression of CX3CL1 signals microglia to remove synapses.[91] Cytokines are released by immune cells such as T cells and myeloid cells including microglia, as well as glial cells such as astrocytes and oligodendrocytes.[40] In the CNS, cytokines can influence synaptic plasticity by modulating synaptic long-term potentiation (LTP) and long-term depression (LTD), whose effects vary by developmental stage and regional location.[92] For instance, IL-33 production promotes synaptic pruning in the developing spinal cord, whereas in the adult hippocampus, it supports synapse formation.[93,94]

Proinflammatory cytokines in the CNS such as IL-1, IL-6, and TNFα affect neuronal function and can drive sickness behavior.[40] In mouse models, IL-1 injection induces fever, sickness behavior, and cognitive impairment, which improves with IL-1 blockade.[95,96] Indeed, expression of IL-1 receptor in astrocytes and neurons is necessary to drive behaviors such as decreased food intake and activity in response to administration of IL-1β.[97] IL-6 is another proinflammatory cytokine that acts synergistically with IL-1.[98] TNFα also leads to sickness behavior and increases non-REM sleep, and it may also increase cortical neuronal activity and anxiety behavior.[99,100]

Neuronal signals such as neurotransmitters and neuropeptides can also lead to immune cell changes such as exhaustion.[101] Nociceptive signaling can lead to neuropeptide release such as CGRP, which can lead to decreased cytokine production in macrophages and upregulation of IL-10.[102,103] Mouse models of oral cancer with CGRP knockout showed an increase in infiltration of CD4 and CD8 T cells in the tumor.[104] Stress leading to release of norepinephrine and epinephrine can lead to increased recruitment of immunosuppressive cells such as Tregs and prevent effective immune responses.[101,105,106] Mouse models of pancreatic and colorectal cancer deficient in serotonin showed increase in CD8 T cells, expression of PD-L1 on cancer cells and improved tumor control.[107]

## TUMOR BIOLOGY AND THE IMMUNE SYSTEM

The CNS-immune interface is both bi-directional and closely intertwined to tightly control any inflammatory response within the brain. Thus, the CNS-immune environment is unique and further altered in the presence of tumor biology. Tumor-associated macrophages (TAMs) in brain tumors are comprised of both peripheral infiltrating macrophages as well as microglia; in GBM, 85% of TAMS are peripheral macrophages and 15% are resident microglia.[108] In contrast, for H3K27M-altered diffuse midline glioma (DMG), the majority of myeloid cells are microglia.[109] There is also a spatial difference in tumor-associated immune cell composition, with microglia found in perinecrotic and tumor-leading edge regions, while infiltrating macrophages are found in perivascular regions.[110,111] TAMs may also exhibit different activation and immunosuppressive profiles depending on their location and present different opportunities for targeting strategies.[112,113] Microglia may be more prevalent in newly diagnosed GBM versus more prevalent peripheral infiltrating macrophages in recurrent tumors.[114] TAMs also appear to suppress T cell proliferation and contribute overall to a more immunosuppressive tumor immune microenvironment (TIME) with tumors themselves leveraging existing immunosuppressive mechanisms for immune evasion.[114,115] Indeed, different tumor types may display different immune composition and higher-grade tumors may have increased macrophages compared with microglia.[116] As a result, strategies targeting the TIME have become abundant. CSF1R inhibitors to deplete myeloid cells can potentially reset the microglial phenotype[117] leading to a survival advantage in mouse models.[117,118] However just targeting the tumor immune microenvironment in isolation has not been successful, but it is a common strategy paired with immunotherapies.[118] In addition, immunotherapy strategies may change the CNS-immune environment itself, leading to further complexities.[119]

As we begin to understand the interconnected nature of the peripheral and CNS-immune environments, we must not neglect consideration of the immune system as a whole and its interplay with the nervous system, CNS tumors, and tumor-induced nervous system dysfunction. Patients with newly diagnosed GBM were found to have lymphopenia even prior to treatment initiation.[120] Indeed, intracranial malignancies can lead to sequestration of naive T cells in the bone marrow and resulting systemic immunosuppression,[8] which might relate to the role of the nervous system in regulating T cell trafficking in and out of the bone marrow through adrenergic signaling.[121] Furthermore, GBM may lead to thymic and splenic involution and decreased expression of major histocompatibility complex class II (MHCII).[8,9] Several potential mechanisms may be at play, underscoring the extensive interactions between the nervous system and the immune system. One potential mechanism is upregulation of TGF-β, which can lead to systemic immunosuppression through a decrease in CD4+ T helper cells and lymphopenia[122]

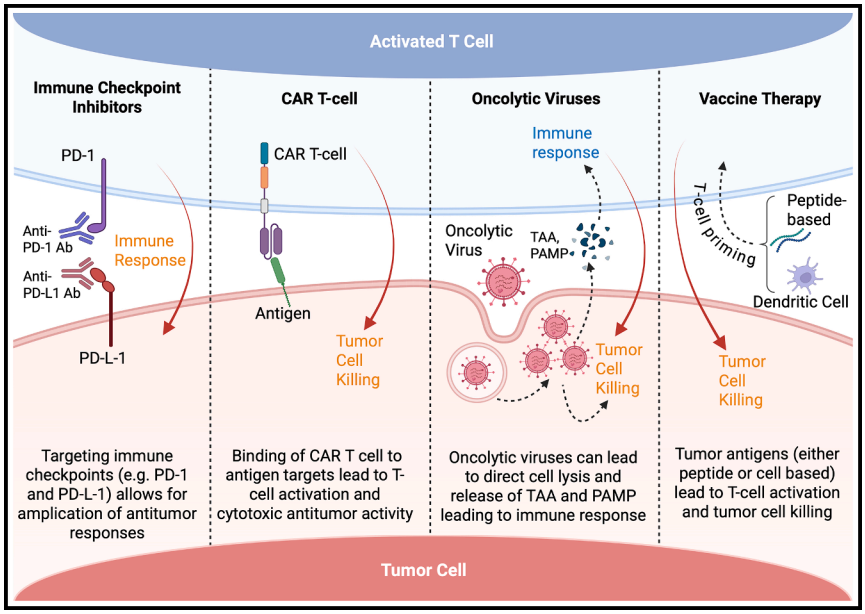


**Figure 2. Immunotherapy strategies for treatment of high-grade gliomas**

Different immunotherapy strategies are being investigated including ICIs, CAR T cell therapy, OVs, and vaccine-based strategies. ICIs target immune checkpoint blockade to amplify the antitumoral immune response. CAR T cell therapy binds to antigens expressed on tumor surfaces leading to T-cell-mediated cytotoxicity. OVs can kill tumor cells via direct lysis and release of tumor-associated antigens (TAAs), and viral pathogen-associated molecular patterns (PAMPs) can also increase antitumoral immune response. Vaccine-based strategies can be peptide based or cell based (e.g., dendritic cell) to prime T cells and lead to tumor killing. Figure created with BioRender.com.

as well as impaired cytotoxic activity of CD8 T cells.[123] While some studies have shown that inhibition of TGF-β may reverse immunosuppression caused by glioma,[124] other studies did not show an effect of TGF-β blockade,[123] such as in the case of T cell sequestration in the bone marrow.[8] Further studies are needed to elucidate the complex mechanisms of systemic immunosuppression in intracranial tumors.

Given clear evidence of immunosuppression in both the tumor environment and systemically, a holistic understanding of the immune system and its connection with the CNS needs to be investigated, especially in the setting of malignancy. Within the very specialized immune environment of the CNS, immunotherapy strategies targeting CNS tumors present their own unique challenges. Effective CNS immunotherapy strategies will likely require a deep understanding of both the unique CNS-immune system and the extensive crosstalk between normal brain cells such as neurons, glial cells, immune cells, and brain cancer cells. With these considerations in mind, we will next consider immunotherapies for CNS cancers in detail.

## IMMUNOTHERAPY STRATEGIES FOR HGGs

HGGs are the leading cause of primary brain-tumor-related death in both children and adults. The most common HGG in adults is GBM, and in children is H3K27M-altered DMG, including diffuse intrinsic pontine glioma (DIPG). The median OS for GBM is 14–21 months[2,3] and for DMG is 11–13 months.[125,126] A variety of different immunotherapy strategies are under investigation for HGGs (Figure 2) with more specialized adjustments over time in the unique immune environment of the CNS.

## IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors (ICIs) target inhibitory pathways that modulate immune responses and prevent autoimmunity.[127] These pathways can be utilized by tumors for immune evasion. As a result, targeting these pathways allows for amplification of antitumor immune responses.[127] ICIs have transformed care for systemic cancer and are FDA approved for a variety of targets including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1). PD-1 expression on gliomas is correlated with higher-grade tumors,[128] which makes it an attractive target, and preclinical models have shown promise with improved survival when targeting PD-1.[129] However, the evidence in clinical trials have not been as successful to date.

Multiple clinical trials have examined ICIs in primary brain tumors. While ICI therapy has been shown to be safe in CNS tumors, there is limited benefit except for patients with mismatch repair deficiency.[130] Several large phase 3 trials have examined ICIs for gliomas, such as nivolumab versus standard therapy in newly diagnosed GBM patients, both O6-methylguanine-DNA methyltransferase (MGMT) promotor methylated[131] and unmethylated[132] GBM subgroups, which has not shown survival benefit. In the recurrent setting for GBM, nivolumab versus bevacizumab also did not improve survival.[133] In pediatric CNS tumors, combination nivolumab and ipilimumab therapy similarly did not show benefit.[134]

The lack of ICI efficacy in gliomas is likely multifactorial given high intratumoral heterogeneity[135] and severe T cell dysregulation in the glioma tumor environment,[136,137] which may lead to an inability to respond to ICI therapy. Interestingly, pembrolizumab given prior to surgical intervention was found to confer survival benefit compared with administration in the post-surgical setting.[138] One hypothesis is that surgery may improve T cell priming or inflammatory response compared with use in the adjuvant setting.[139,140] A follow-up study with 25 additional patients showed that pembrolizumab prior to surgery was associated with decreased cancer proliferation genes and upregulation of T cell gene expression.[141] In addition, pembrolizumab given as first line neoadjuvant therapy in newly diagnosed GBM may lead to better response to treatment via increased immune activation and infiltration in the tumor.[142] As a result of this encouraging result, alternative approaches including intracranial administration of ICIs[143] as well as timing and in combination with other therapies are now being explored.[144]

**Table 1. CAR T trials**

| Clinical trial | Tumor antigen | Tumor type | Patients | CAR delivery | Endpoints |
|---|---|---|---|---|---|
| Brown et al.[149] | IL13Rα2 | rHGG | 3 adults | weekly ITu | OS 11 months after relapse |
| Brown et al.[12] | IL13Rα2 | GBM | 1 adult | ITu, then ICV | CR that persisted for 7.5 months |
| Brown et al.[150] | IL13Rα2 | rHGG | 63 adult, 1 patient < 18 years old | arm 1: ITu after biopsy arm 2: ITu after maximal resection arm 3: ICV arm 4: ITu + ICV arm 5: ITu + ICV (new manufacturing, Tn/mem) | no DLTs, SD in 50% (29/58) pts (13 pts > 90 days), median OS 8 months (7.7 months for rGBM),arm 5 median OS 10.2 months |
| O'Rourke et al.[151] | EGFRvIII | rGBM | 10 adults | IV, single dose | no DLTs, median OS ~8 months, 1 patient survived 36 months |
| Goff et al.[152] | EGFRvIII | rGBM | 18 adults | IV, single dose + IL-2 | DLT at highest dose with severe hypoxia, intubation, and death, median OS 6.9 months, PFS 1.3 months |
| Bagley et al.[153,154] | EGFRvIII | nGBM | 7 adults | IV + pembro | no DLTs, median PFS 5.2 months, median OS 11.8 months |
| Bagley et al.[153,154] | EGFRvIII + IL13Rα2 | rGBM | 6 adults | ICV, single dose | DLT in 1 pt at DL2 (anorexia, fatigue, muscle weakness), 3/6 patients at 30% shrinkage, 3/4 patients had SD who had at least 2-month follow-up |
| Choi et al.[155] | EGFRvIII and wild-type EGFR | rGBM | 3 adults | ICV | no DLTs, 1 pt with 60.7% decrease in tumor size for 150 days |
| Ahmed et al.[156] | HER2 | rGBM | 17 patients(14–69 years old) | IV, up to 6 doses if response | no DLTs, median OS 11.1 months after CAR T infusion, 1 patient with PR > 9 months |
| Vitanza et al.[157] | HER2 | CNS tumor (1 anaplastic astrocytoma, 2 ependymoma) | 3 patients (16, 19, and 26 years old) | weekly ICV or ITu | no DLTs, 2 patients with PD, 1 patient with SD |
| Vitanza et al.[158] | B7H3* | DIPG | 3 patients(18, 22, and 10 years old) | weekly ICV | no DLTs,1 patient with IDH-mut, anaplastic astrocytoma had 19.4% decrease in tumor size, 1 patient with PD, 1 patient with SD |
| Vitanza et al.[159] | B7H3* | DIPG | 21 patients (2–22 years old) | ICV | median OS 10.7 month after treatment, 19.8 months from diagnosis |
| Majzner et al.[160] | GD2† | DIPG and spinal DMG | 4 patients (5–25 years old) | IV, then ICV | therapy was well tolerated with no on-target, off-tumor toxicity,3/4 patients had clinical and radiographic benefit |
| Monje et al.[11] | GD2† | DIPG and spinal DMG | 11 patients (4–30 years old) | IV, then ICV | DLT at high dose due to CRS, 1 patient with >90% reduction in tumor volume, 4 patients with major radiographic reduction, 3 patients with minor radiographic reduction, 9 patients with clinical benefit |
| Lin et al.[161] | GD2 | high-grade tumors including DIPG | 11 patients (1–21 yaers old) | IV | 90% with transient improvement of neurologic deficits,2/5 DMG patients with PR |

rHGG, recurrent high-grade glioma; rGBM, recurrent glioblastoma; ITu, intratumoral infusion; ICV, intracerebroventricular infusion; EGFRvIII, epidermal growth factor receptor variant III; HER2, human epidermal growth factor receptor 2; pembro, pembrolizumab; DLT, dose-limiting toxicity; pts, patients; yo, years old; PR, partial response; SD, stable disease; PD, progressive disease; CR, complete response; OS, overall survival; PFS, progression-free survival.
*These two papers describe results from the same B7H3 CAR T trial.
†These two papers describe results from the same GD2 CAR T trial.

## ADOPTIVE CELL THERAPIES—CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY

Adoptive T cell therapy strategies have long been of interest in cancer treatment. Early studies examined lymphokine-activated killer (LAK) cells, which were a combination of NK cells and T cells, with NK cells likely the predominant population.[145] While these early studies with LAK cells were well tolerated without significant toxicity, they did not show a survival benefit.[146,147] However, some patients had stable disease or even tumor regressions,[146,148] which prompted continued interest in cell therapies. Iterative advancements have led to a variety of cell therapy strategies such as chimeric antigen receptor (CAR) T cell therapy, tumor-infiltrating lymphocytes (TILs) therapy, T cell receptor (TCR) therapy, and CAR natural killer cell therapy. However, the major focus of adoptive cell therapy in gliomas has been CAR T cell therapy (Table 1).

CAR T cell therapy has revolutionized the treatment of hematologic malignancies with FDA approval of products targeting CD19 and B cell maturation antigen (BCMA).[162] A number of clinical trials have now examined CAR T therapy for HGGs in both adult and pediatric patients targeting different antigens as well as the TIME.

IL13Rα2 was one of the earliest targets in glioma CAR T therapy. It is highly expressed in WHO grade IV gliomas (~58% in GBM)[163] with robust antitumor activity in preclinical models.[164] Initial reports with a 1st generation IL13Rα2 CAR T cells delivered intratumoral infusion showed a median OS of 11 months after relapse.[149] A case report in 2016 with a second generation IL13Rα2 CAR T demonstrated a complete response (CR) in a patient with recurrent GBM that was durable for 7.5 months.[12] Most recently, Brown et al. reported on 65 patients with recurrent HGGs treated on 5 different clinical trial arms with arm 1 receiving intratumoral infusion after biopsy, arm 2 receiving intratumoral infusions after maximal resection, arm 3 receiving intracerebroventricular (ICV) infusions, and arms 4 and 5 receiving combination intratumoral and intracerebroventricular infusions. Arm 5 patients received CAR T cells on a new manufacturing platform using CD62L+-enriched naive, stem cell memory and central memory T cells (Tn/mem).[150] There was no dose-limiting toxicity (DLT), and half of the patients had stable disease (SD) with 2 patients with IDH-mutant gliomas achieving a partial response (PR) and 1 achieving a CR. Investigators found arm 5 with intratumoral + ICV delivery to be the most promising and are currently determining a recommended phase 2 dose (RP2D).

Epidermal growth factor receptor variant III (EGFRvIII) is another attractive target for CAR T therapy for GBM.[165–167] Preclinical studies showed promising tumor reduction.[166] O'Rouke et al. treated 10 adult patients with OS of ~8 months with 1 patient surviving 36 months after recurrence.[151,168] EGFRvIII expression declined in a majority of patients with repeated tissue sampling indicating CAR T activity, but immunosuppressive molecules, such as IDO1, FoxP3, IL-10, PD-L1, and/or TGF-β, were found to be upregulated.[151] Another study with EGFRvIII treated 18 patients with recurrent GBM with lymphodepleting chemotherapy and IL-2 administration.[152] A fatal DLT occurred at the highest dose of $6 \times 10^6$ with hypoxia leading to intubation and patient death. Overall, there did not seem to be survival benefit in the study with median OS of 6.9 months. Given the immunosuppressive TIME found after CAR T treatment,[151] a subsequent trial was conducted with EGFRvIII CAR T in combination with pembrolizumab.[153] However, there was no clear clinical benefit with OS of 11.8 months. As a result, another follow-up study aimed at targeting tumor heterogeneity used a bivalent CAR T against EGFRvIII and IL13Rα2.[154] The initial report treated 6 adults GBM patients with ICV infusions. At least a 30% tumor shrinkage was reported in 3/6 patients with SD seen in 3/4 patients with 2 months of follow-up. Another strategy to optimize anti-EGFRvIII CAR T utilized a second generation EGFRvIII CAR T cell that also secrets a T-cell-engaging antibody molecules against wild-type EGFR (CARv3-TEAM-E),[155] which showed decreased tumor burden in mouse models with heterogeneous EGFR expression.[169] On the initial clinical trial report of 3 patients, 1 patient was reported to have radiographic reduction with disease progression on day 72, 1 patient had tumor reduction that was durable at 150 days, and 1 patient had tumor reduction initially, but recurrence at 1 month. Combination therapy of CAR T with approaches targeting the TIME are still in the nascent stages with data still to fully mature.

Other antigen targets that have been examined in clinical trials include human epidermal growth factor receptor 2 (HER2) and B7H3. HER2 is highly expressed on multiple CNS tumors,[170,171] but clinical trials targeting HER2 have not demonstrated clear benefit. A clinical trial on adult and pediatric patients with recurrent GBM showed a median OS 11.1 months with 1 PR for > 9 months.[156] In pediatric patients, HER2 CAR T therapy was used to treat 3 patients with 1 patient showing SD and 2 with progressive disease (PD).[157] B7H3 is also highly expressed on both pediatric and adult gliomas.[172,173] A trial using B7H3 CAR T therapy in DIPG has showed to be safe[158] with survival of 10.7 months after initiation of treatment and OS of 19.8 months[159] compared with established median survival 11–13 months in DMG.[125,126]

GD2 is a disialoganglioside that is highly expressed in CNS tumors, particularly pediatric gliomas,[172,174] but also in adult GBMs.[175,176] Preclinical models demonstrated robust activity of GD2 CAR T cells in H3K27M-mutant DMG.[174] For DMG, a clinical trial by Majzner et al. in 2022 reported on the initial 4 patients treated with IV followed by ICV GD2-CAR T infusion for patients with biopsy-proven H3K27M-mutant DMG of the pons (DIPG) or spinal cord.[160] One patient did not show a response, but the other 3 patients had both clinical and radiographic benefit following treatment with improvement in clinical symptoms from baseline at 1 month follow-up, including one patient with a >90% reduction in tumor volume. A follow-up study in 2024 reporting on the initial 11 patients[11] reported DLT at the higher IV dose level due to high-grade cytokine release syndrome (CRS). Four patients demonstrated major radiographic reductions ranging from 50% to 100% reduction in tumor volume, with one patient achieving a CR durable for >30 months and ongoing. Another 3 patients also had smaller radiographic reductions, and 9 of the 11 patients had neurologic benefit. Median OS was 20.6 months (17.6 months for patients with DIPG and 31.96 months for patients with spinal cord DMG). Another trial of GD2-CAR T therapy in combination with constitutive interleukin-7 receptor (C7R) expression was also studied in pediatric patients including those with DIPG[161]—albeit at lower doses of CAR T cells than those in

the trial discussed above—and demonstrated transient improvement of neurologic deficits compared with baseline.

Current CAR T cell trials for gliomas have not yet demonstrated ground-breaking efficacy paralleling the success of hematologic malignancies, highlighting a need to further elucidate and overcome immunosuppressive CNS tumor environments. However, early trials have demonstrated promising glimmers of therapeutic effect, and the field is investigating ways to augment CAR T therapy, which include consideration of additional antigen targets such as EphA3[177] or even targeting the extracellular matrix of tumor cells.[178] Indeed, another potential mechanism to tailor immunotherapy for the CNS is engineering specialized next-generation CAR T cells. Advancements in CAR T cell engineering are under active investigations, such as multi-specificity and logic-gated CAR T cells to overcome antigen heterogeneity or CAR T cells that can further engage the immune system, such as through delivery of immunostimulatory molecules.[179] In addition, route of delivery for CAR T therapy can also likely be optimized; preclinical studies indicate potential advantages in intracranial delivery,[180,181] which is being implemented in clinical trials. Other alternative strategies, such as nanoparticle delivery of mRNA to induce transient CAR T cell expression, are being explored.[182]

## OTHER ADOPTIVE CELL THERAPY STRATEGIES

Autologous TIL therapy has been successful for melanoma[183] with recent FDA approval of Lifileucel.[184] However, in gliomas, T cells are known to be severely dysregulated and exhausted,[136] leading to difficulty isolating and expanding TILs for primary CNS tumors.[185] In addition, TILs in GBM may have variable proportions of Tregs[186] and would need careful processing to avoid using potentially immunosuppressive populations for treatment. However, TILs can be expanded from glioma tumor tissue,[187] and an early pilot study using TILs for recurrent gliomas showed that treatment was feasible with unclear clinical benefit.[188]

Other adoptive T cell strategies include TCR therapy, which has been shown to be efficacious in synovial sarcoma[189] and is now FDA approved.[190] TCR therapy may be a good strategy for solid tumors given the ability to target intracellular antigens. Preclinical studies of TCR targeting the H3.3 histone mutation in DIPG are being explored and may be another approach.[191]

CAR natural killer (CAR NK) cells are another strategy of interest. NK cells can have cytotoxic activity similar to CD8 T cells without restriction to major histocompatibility complex (MHC).[192] As a result, CAR NK cells can be a potential "off-the-shelf" therapy without requiring patient collection for an autologous infusion. One NK cell line, NK-92, is a source of NK cells, but it requires irradiation since it is derived from a non-Hodgkin lymphoma line to reduce risk of secondary malignancy, which in turn limits *in vivo* expansion.[193] Clinical trials of CAR NK cells have been tested in hematologic and solid tumors with mixed results and persistence.[194–197] CAR NK cells are also being studied in gliomas with one trial investigating NK-92 CAR NK cells for patients with recurrent HER2-positive GBM (NCT03383978) via intracranial delivery. Therapy was well tolerated with no DLTs and no CRS.[198] Five out of 9 patients showed SD with median OS of 31 weeks. Limitations of antigen target, immunosuppressive microenvironment, and tumor resistance mechanisms for CAR T cell therapy in the context of CNS tumors also applies to adoptive cell therapies in general.

## ONCOLYTIC VIRUSES

Oncolytic virus (OV) therapy utilizes engineered replication-competent viruses to selectively target cancer cells without infecting normal tissue leading to antitumor response through direct cell lysis as well as alternation of the TIME.[199] OVs may also elicit additional immune response via release of tumor-associated antigens (TAAs) and viral pathogen-associated molecular patterns (PAMPs) to take advantage of the inherent antiviral mechanisms of the CNS.[199,200] OVs can be based on pathogenic strains such as herpes virus or attenuated strains used for vaccines such as poliovirus.[201]

In Japan, teserpaturev, an HSV-1-based therapy, was conditionally approved for treatment of recurrent GBM via intratumoral infusions.[202] The phase 1/2 trial treated 13 patients with OS 7.3 months and 3 patients surviving >46 months with 1 patient in CR and 1 patient in PR at 2 years.[203] Radiographically, patients were observed to have enlargement of the lesion within 14 days of therapy as well as clearing of contrast-enhancement at the injection site. Biopsy specimens showed destruction of tumor cells, suggesting that radiographic changes may reflect inflammation. The phase 2 trial treated 19 patients with up to 6 infusions, which showed 1 year survival of 84.2% and median OS of 20.2 months,[13] leading to its conditional approval.

Other OV therapies being explored include polio-rhinovirus-based approaches (PVSRIPOs). One trial treated 61 patients with recurrent GBM and showed a higher rate of survival compared with historical controls.[204] Another promising trial of DNX-2401, an adenovirus-based therapy, treated 12 patients with DIPG and demonstrated a median survival of 17.8 months.[205] DNX-2401 may lead to direct tumor lysis as well as improved immunity due to enhancement of tumor-antigen presentation.[206,207]

While OV therapy has generated excitement, especially with the conditional approval of teserpaturev, there are still limitations for its therapeutic efficacy. Barriers include the immunosuppressive environment of the CNS, which is co-opted by intracranial tumors to further decrease inflammation and drive immunosuppression.[9] In addition, T cells are limited and frequently exhausted in gliomas.[136] Delivery itself is a challenge with different strategies being explored to ensure adequate exposure throughout the tumor bed[201] such as convection enhanced delivery[208] or via cell carriers.[209] Checkpoint blockade may also be upregulated with OV therapy,[210] which supports combination therapy with ICIs. An initial clinical trial showed potential benefit in a subset of patients, and indeed, there is evidence that some OV therapies have a more synergetic effect with ICIs than others.[144,211] Indeed, as new viruses are being discovered or produced, there may be new vehicles for OV therapy.[212]

## VACCINE THERAPY

Vaccine-based strategies for gliomas have been investigated using both peptide-based and dendritic-cell-based approaches with either single or multiple antigens.[213] However, despite decades of research, there is only one FDA-approved cancer

vaccine treatment, sipluleucel-T, for castration-resistant prostate cancer. While an initial phase 2 trial with EGFRvIII peptide vaccine showed improved survival of 26 months,[214] no survival benefit was found in a randomized phase 3 trial.[215] Immune escape may be the reason for lack of response since recurrent patients demonstrated loss of EGFRvIII expression.[214] Recently, a peptide vaccine for newly diagnosed GBM, SurVaxM, with adjuvant TMZ showed a median progression-free survival (PFS) of 11.4 months and may be a promising strategy.[216] Dendritic cell vaccines represent another approach where a multitude of tumor antigens are loaded from a variety of sources including tumor cell lines[217] and autologous tumor lysates.[218] An initial phase 3 study with DCVax-L has shown the approach to be safe and may improve survival based on intent to treat analysis.[218] However, study limitations included lack of reporting of PFS, concerns regarding validity of the external control arm and the long length of study enrollment leading to unclear molecular diagnosis.[219] In general with immunotherapies, limitations exist such as dexamethasone use, which leads to T cell response inhibition as well as T cell exhaustion.[185,220]

H3K27M vaccine in adult patients with H3K27M-altered DMG was promising with a cohort of 8 patients treated exhibiting median OS of 12.8 months and 1 patient with CR for >31 months.[14] Responders may have decreased baseline levels of myeloid-derived suppressor cells[221] and increased in H3K27M-reactive TCRs and recruitment of activated B cells in the CSF with $CD4^+$ T cells as the main responder.[222]

Although vaccine-based approaches for glioma are well tolerated, efficacy has not clearly been demonstrated and may require further improvements. Optimization to increase immunogenicity include addition of agents such as IFN-α and polyinosinic:polycytidylic acid (p-I:C) or TLR agonists[223] that may improve dendritic cell efficacy.[224] Combination with another vaccine such as tetanus toxin may boost memory T cell activation.[225] The mRNA vaccine approach is another exciting platform, which may address tumor heterogeneity and target the TIME.[226]

## COMBINATORIAL APPROACHES AND FUTURE DIRECTIONS

Different immunotherapy approaches have all showed glimmers of promise in clinical trials with prolonged survival in a subset of patients in a number of trials.[11–14] However, a resounding success paralleling the results seen with hematologic malignancies have not been occurred. While there are multiple optimizations available for all approaches, interest has also turned toward combinatorial approaches. Combinations of ICIs with OV therapy or vaccine therapy are already being investigated as well as other strategies targeting the TIME.[118,155,161] One interesting proposal is the combination of OV therapy and adoptive cell therapy.[227] In a mouse model, a combination of using EGFRvIII CAR T therapy followed by vesicular stomatitis virus (VSV), showed improved T cell expansion and prolonged survival.[228] Combination therapy could also improve CAR T infiltration and help reprogram the TIME,[229] but conversely, the combination could lead to CAR T attenuation, posited due to overexposure to inflammatory cytokines.[230] As such, unique combinations as well as the sequence of combinatorial approaches still needs investigation.[231] As more therapies become available, potential combinations can also exponentially expand and highlight the need for prediction algorithms to model favorable regimens to be investigated.[232]

Indeed, as we further investigate immunotherapies in the CNS, we are also gaining insights into how the immune environment changes with perturbation and inflammation as well as patient specific factors that may lead to improved response. For example, increased CNS inflammation following GD2 CAR T therapy was reflected in increased CNS cytokines, which may drive response from myeloid cells that further contribute to neurologic toxicity.[11] An understanding of how the CNS tumor immune environment responds to immunotherapy can potentially lead to additional targets and adjunct therapies to strengthen disease response. For instance, constitutive interferon pathway activation is a resistance mechanism in OV therapy[232] and insights into this pathway may further develop a prediction algorithm for patient response.[232] When examining the subset of patients who respond well to immunotherapy, further understanding of individual patient factors would also help enhance any potential response prediction. Differences in the immune environment in genetic profiles of responders to immunotherapy[221,233] as well as innate difference in the immune system, such as sex-specific immune response,[234] require further examination in other to further tailor immunotherapy and augment successful patient responses.

## IMMUNOTHERAPY TOXICITIES IN THE CNS

While a number of immunotherapy strategies are being investigated for CNS cancers, with increased experience, we are beginning to understand and manage the range of neurologic toxicities associated with immunotherapies. Given the powerful effects of cytokines and chemokines on the function of normal neural cells, it is not surprising that neurological symptoms and syndromes are a major axis of toxicity in immunotherapy trials for brain tumors. Immunotherapy neurotoxicity can affect any part of the nervous system including both the peripheral and central nervous systems. Neurologic toxicities require prompt recognition and management to avoid potentially severe and devastating neurologic injury.

## NEUROLOGIC TOXICITIES ASSOCIATED WITH ICI THERAPY

With more than a decade of experience since the ICIs were first FDA approved in 2011, a wide range of neurologic immune-related adverse events (irAE-Ns) have been described. In treatments for systemic malignancies, irAE-Ns are rare with incidence of 1%–12%.[235–238] Higher rates can be seen with combination therapy[239] and irAE-Ns are responsible for a higher proportion of fatalities.[240] The peripheral nervous system is more commonly affected than the CNS. irAE-Ns mostly occur within the first 3–6 months after treatment and most common syndromes include neuromuscular junction disorders, encephalitis, vasculitis, meningitis, and polyneuropathy.[241] PD-1 ICIs were more commonly implicated in myasthenic syndromes[241] and CTLA-4 ICIs with meningitis.[242] Management varies by syndrome but generally involves interruption of therapy for lower

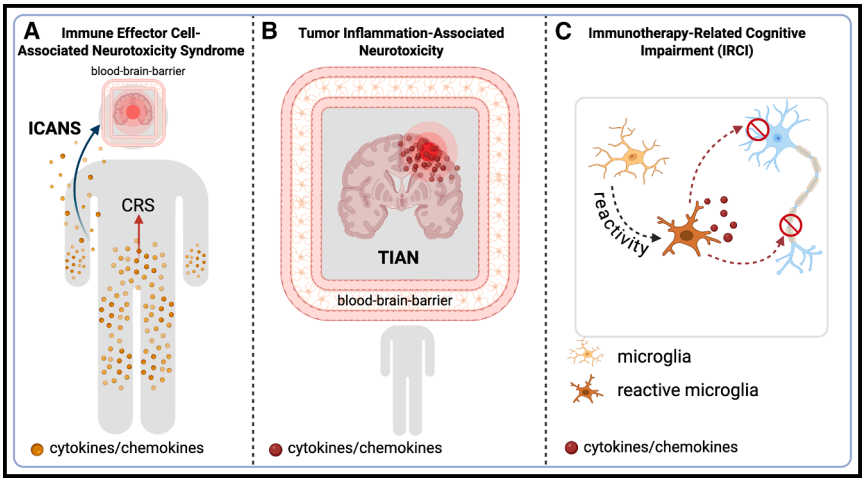


**Figure 3. Types of CAR T neurological toxicity**

(A) Immune-effector-cell-associated neurotoxicity syndrome (ICANS). In the acute period after CAR T cell therapy, systemic CAR T therapy can lead to CRS, which may lead to break down of the BBB and globally elevated cytokines and inflammation in the CNS that manifests as ICANS, although the mechanisms of ICANS remain to be fully understood.

(B) Tumor-inflammation-associated neurotoxicity (TIAN). Intracranial CAR T therapy leads to increased regional inflammation of the tumor and consequent neurological dysfunction in the area of the brain involved by the tumor.

(C) Immunotherapy-related cognitive impairment (IRCI). Long-term cognitive dysfunction following immunotherapy is caused by microglial reactivity that results in loss of subcortical oligodendrocytes and myelin as well as impairment in hippocampal neurogenesis. Figure created with BioRender.com.

grade toxicities and initiation of steroids and additional immunosuppressive regimens for higher-grade toxicities.[243]

ICIs are also used to treat CNS tumors, both primary and metastatic, but toxicities can be more challenging to delineate in patients with baseline neurologic deficits. While ICI therapy is generally tolerated, vasogenic edema can be a rare but fatal complication.[244,245] Phase 3 trials of nivolumab in GBM did not demonstrate survival benefit but did observe neurologic toxicity at 16%–23%[131,132] with common symptoms including headache, dysgeusia, dizziness, cognitive disorder, hemiparesis, and memory impairment. There was one case of fatal vasogenic cerebral edema.[132] In addition, pseudoprogression was also a common challenge,[131] highlighting the difficulty of delineating treatment effect versus disease progression with immunotherapy.

## NEUROLOGIC TOXICITIES OF SYSTEMIC CAR T THERAPY

Along with the therapeutic promise of CAR T therapy, there have been new toxicities that have manifested as well, especially affecting the CNS. CRS with fever, hypoxia, and hypotension and immune-effector-cell-associated neurotoxicity syndrome (ICANS) are well-known side effects of CAR T therapy for hematologic malignancies. ICANS is a syndrome of encephalopathy, headache, tremor, seizure, and somnolence with aphasia as an early and specific finding.[246,247] CRS commonly precedes ICANS, which can start 4–9 days after treatment[246,248] and up to 8 weeks[249] with symptoms commonly resolving within 1–2 weeks. For anti-CD19 CAR T therapy, neurotoxicity ranges from 20%–40% for tisagenlecleucel (tisa-cel)[249,250] and lisocabtagene maraleucel (liso-cel),[251] which have a 4-1BB co-stimulatory domain, versus ~60% for axi-cel[252] and brexu-cel,[253] which have a CD28 co-stimulatory domain.

The underlying mechanism of ICANS remains to be elucidated, but it may be potentially related to break down of the BBB[254] (Figure 3A). During ICANS, markers of astroglial injury such as of S100 calcium-binding protein B (S100b) and glial fibrillary acidic protein (GFAP) have been found to be elevated.[255] Cytokines such as IL-6, IL-10, IFN-γ, and GzB were elevated during peak neurotoxicity. However, IL-6, IL-10, IFN-γ, and GzB were also elevated in the CNS with higher levels of IFN-γ in the serum and similar levels of the other three between serum and CSF compartments, arguing against increased cytokine production in the CNS.[255] Post-mortem studies of brain tissue of patients with ALL treated with anti-CD19 CAR T cell therapy who developed fatal ICANS were found to have cerebral edema, microglial activation, and astrocyte injury without significant malignant or CAR T cells found.[256] However, another case did identify CAR T cells in the CSF and brain tissue but with no CD19 antigen in brain tissue.[257]

Diagnostic criteria and grading have been established for ICANS based on the immune effector cell encephalopathy (ICE) score, level of consciousness, seizures, and concern for increased intracranial pressure/cerebral edema.[258] Seizures are infrequent overall in patients with ICANS but have been found in up to 73% of patients with severe ICANS.[246] Cerebral edema is also a rare but potentially fatal complication of severe ICANS. Management depends on severity and involves corticosteroids, seizure management, and supportive care. Tocilizumab, an IL-6 receptor antagonist, is commonly used for CRS, but its use has not been established for ICANS. Other management strategies such as siltuximab, a direct IL-6 antagonist and anakinra, an IL-1 receptor antagonist[259] are potentially promising strategies.

Anti-BCMA CAR T therapy has been developed for multiple myeloma with idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) reaching FDA approval. A unique neurotoxicity syndrome has been described with anti-BCMA CAR T cell therapy characterized by neurocognitive and movement manifestations with patients developing bradykinesia, hypophonia, micrographia, rigidity, and neurocognitive dysfunction.[260] BCMA expression was found in the neurons and astrocytes of the basal ganglia in post-mortem studies, leading to concern that the syndrome may represent an on-target, off-tumor neurotoxicity. Management strategies with levodopa, intrathecal chemotherapy, anakinra to block IL-1 signaling, and dasatinib to reduce CAR T cell activation did not lead to

significant improvement in symptoms, but protocols decreasing tumor burden and initiation of stringent and early monitoring may have decreased rates of neurotoxicity.[260–262]

## NEUROLOGIC TOXICITIES OF CNS-TUMOR-DIRECTED CAR T THERAPY

Neurologic toxicities in patients with CNS tumors are unique since most patients have pre-existing neurologic deficits. As a result, delineating neurotoxicity, pseudoprogression in the setting of active inflammation, and disease progression can be challenging. In CNS tumor patients, CRS and ICANS appear more common when receiving CAR T treatment as an IV infusion[152,160] rather than ICV.[11] A new neurologic toxicity described that is unique to patients with CNS disease is tumor-inflammation-associated neurotoxicity (TIAN)[15] (Figure 3B). TIAN is characterized as having two types: type 1, which is a result of tumor inflammation and edema leading to the consequences of mechanical space contrainsts including possible obstruction of CSF flow, tissue shifts, and increased intracranial pressure, and type 2, which is due to localized electrophysiological neuronal network dysfunction leading to worsening of pre-existing neurologic symptoms.[15]

Since inflammation occurs directly in the CNS, it is logical that there are unique neurologic manifestations and a distinct syndrome for CAR T therapy directed toward CNS tumors. However, both TIAN and ICANS lead to neurologic manifestations, and distinguishing the two can be difficult but important. Indeed Bagley et al. in their 2024 bivalent CAR T trial,[154] report a combination of both ICANS and TIAN post-treatment. Depending on tumor location, patients may exhibit localized inflammation typical of TIAN but manifest more diffuse neurologic symptoms. This overlap can be especially difficult to resolve when the tumor affects language centers of the brain or in the case of multifocal disease leads to generalized confusion. However, since the underlying mechanisms driving these processes are different, clearly distinguishing between TIAN and ICANS is critical for guiding effective treatment strategies moving forward.

Regardless, the mainstay for both syndromes, especially with moderate to severe toxicity, is corticosteroid therapy. In hematologic malignancies, the effect of dexamethasone on treatment efficacy is still unclear. While there are some studies that show no effect of steroids on treatment response,[252] other studies indicate that higher cumulative doses may be associated with earlier disease progression and shortened survival.[263] In solid tumors, where clinical trials are nascent and there is less overall experience, the effect of corticosteroids is even more unclear. One preclinical study showed that in murine models, lower doses may be better tolerated than high doses, which can potentially impact CAR T activity.[180] Using dexamethasone in the setting of immunotherapy is a blunt weapon for management of neurotoxicity. While effective at suppressing inflammation, how it ultimately affects immune cell populations, especially in the delicate interface of the CNS-immune system, is unanswered and drives the need for more nuanced management of inflammation.

As a result, additional therapies for complications of CAR T therapy in gliomas are being investigated such as anakinra, which targets IL-1R and appears to have CNS penetration when used as an continuous IV infusion.[11,160] Alternative strategies are aimed at modulating the CAR T activity itself, such as dasatinib, which may potentially reversibly inhibit CAR T proliferation and toxicity.[264] However, there are limited other tools, highlighting the need for further management strategies given the immunologically unique environment of the CNS.

## DELAYED NEUROLOGIC EFFECTS OF IMMUNOTHERAPY

As oncologic treatments improve patient survival, correspondingly our interest also turns toward long-term neurologic toxicity. Given evidence that chemotherapy and other systemic immune challenges can lead to persistent microglial reactivity, disruption of neuron-glial interactions important for healthy neural circuit function, and consequent cognitive impairment,[265–268] it stands to reason that immunotherapy leading to direct CNS inflammation may lead to disruption in CNS-immune populations and downstream neurologic toxicities. Immunotherapy for hematologic malignancies are the most mature, and thus, long-term outcomes are starting to appear in terms of neurologic sequelae. Even in the initial CAR T trials, some patients had persistent difficulty with cognitive symptoms including concentration and memory.[269,270] When looking at long-term survivors after systemic CAR T therapy for liquid malignancies, one study reported that 10% had new neurologic findings including vascular events and dementia.[271] On long-term cognitive exams, some studies have shown preserved cognition in patients who are disease free at 2 years,[272] but other studies report small but decreased global cognition a year after treatment that may be correlated with more severe ICANS during treatment.[273] A systematic review found that 40%–50% of patients had cognitive symptoms that were mostly reversible on follow-up, but outcomes were heterogeneous with some studies reporting cognitive decline and others reporting stability or even improved cognition.[274]

Concordant with these emerging reports of long-term cognitive impairment in some patients after immunotherapy, a recent preclinical study has found evidence of cognitive deficits in attention and memory function in mice following tumor-clearing CAR T cell therapy for cancers both within and outside of the CNS, including DIPG, acute lymphoblastic leukemia, and osteosarcoma. The cognitive sequelae observed in this study were accounted for by the tumor-clearing immune response, not by on-target, off-tumor effects of the CAR T cells studied (GD2- and CD19-targeting CAR T cells). As hypothesized, CAR T cell therapy even outside of the CNS results in microglial reactivity, loss of oligodendrocytes and myelin, and impairments in hippocampal neurogenesis[275] (Figure 3C). Microglial reactivity is central to the pathophysiology, as transient microglial depletion rescues the cellular and behavioral pathophysiology.[275] Chemokine signaling emerged as an important molecular mechanism and therapeutic target, highlighting a possible strategy to mitigate long-term effects of CAR T cell therapy on cognitive function.[275]

In addition to the long-term cognitive sequelae,[276] we may anticipate neuropsychiatric symptoms as well, with higher risk for depression[276] and other neuropsychiatric symptoms in the short-term and possibly long-term periods after immunotherapy, given the close links between inflammation and mood. Study of the long-term cognitive and neuropsychiatric outcomes after immunotherapy is an emerging area of inquiry given the novelty

of these therapies. However, as immunotherapies hopefully translate into improved long-term survival, our attention will turn toward elucidating long-term changes in the immunologic system of the CNS and its potential impacts on neurocognitive and neuropsychiatric outcomes.

## CONCLUDING REMARKS

Immunotherapy holds enormous potential for treatment of gliomas, with encouraging early results in clinical trials of CAR T cell therapy and glioma vaccine therapy. CRs in small numbers of HGG patients treated with CAR T cell therapy or glioma vaccine therapy demonstrate that immunotherapies have the potential to be curative for these seemingly intractable cancers. What sets these patients apart from those who experience less beneficial responses is an area of intense ongoing investigation. However, it is clear that optimizing immunotherapies for malignancies of the CNS will require appreciation for and modulation of the unique immunological features of the brain and brain borders, the typically immune-suppressive neural influences on immune cell function, and the powerful immunological signaling effects on nervous system function. Combination therapy strategies—potent immunotherapeutic approaches together with targeting mechanisms that restrain immunotherapy efficacy and durability—will be necessary to achieve complete, durable responses for the majority of HGG patients. Given the extensive crosstalk between neurons, immune cells, and gliomas (for review, see Mancusi and Monje[277]), developing effective combination immunotherapy strategies for cancers of the nervous system will require a deeper understanding of neuro-immunology and neuroscience.

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