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Review Article

Immune response recalibration using immune therapy and biomimetic nano-therapy against high-grade gliomas and brain metastases

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ABSTRACT

Although with aggressive standards of care like surgical resection, chemotherapy, and radiation, high-grade gliomas (HGGs) and brain metastases (BM) treatment has remained challenging for more than two decades. However, technological advances in this field and immunotherapeutic strategies have revolutionized the treatment of HGGs and BM. Immunotherapies like immune checkpoint inhibitors, CAR-T targeting, oncolytic virus-based therapy, bispecific antibody treatment, and vaccination approaches, etc., are emerging as promising avenues offering new hope in refining patient's survival benefits. However, selective trafficking across the blood-brain barrier (BBB), immunosuppressive tumor microenvironment (TME), metabolic alteration, and tumor heterogeneity limit the therapeutic efficacy of immunotherapy for HGGs and BM. Furthermore, to address this concern, the NanoBioTechnology-based bioinspired delivery system has been gaining tremendous attention in recent years. With technological advances such as Trojan horse targeting and infusing/camouflaging nanoparticles surface with biological molecules/cells like immunocytes, erythrocytes, platelets, glioma cell lysate and/or integrating these strategies to get hybrid membrane for homotypic recognition. These biomimetic nanotherapy offers advantages over conventional nanoparticles, focusing on greater target specificity, increased circulation stability, higher active loading capacity, BBB permeability (inherent inflammatory chemotaxis of neutrophils), decreased immunogenicity, efficient metabolism-based combinatorial effects, and prevention of tumor recurrence by induction of immunological memory, etc. provide new age of improved immunotherapies outcomes against HGGs and BM. In this review, we emphasize on neuro-immunotherapy and the versatility of these biomimetic nano-delivery strategies for precise targeting of hard-to-treat

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and most lethal HGGs and BM. Moreover, the challenges impeding the clinical translatability of these approaches were addressed to unmet medical needs of brain cancers.

1. Introduction

Brain tumors are a heterogeneous group of neoplasms that originate from the meninges, brain parenchyma, or extracranial sites that have metastasized to the brain. Each tumor type is influenced by different risk factors and represents a unique set of challenges in terms of diagnosis, treatment, and prognosis. The incidence of high-grade gliomas (HGG)has been reported to be approximately 3.21 cases per 100,000 individuals as of 2022. The median overall survival (mOS) for patients with HGG remains around 12–15 months despite aggressive standard treatments [1]. Globally, in 2020, there were about 308,102 new cases and 251,329 deaths due to these tumors. HGG have survival rates varying between 14 and 72 months. Whereas brain metastases (BM), resulting from cancer cells spreading from their primary location, have an incidence rate of 9 %–17 %, with 20 %–40 % of all primary cancer patients eventually developing secondary brain cancer. Lung cancer, breast cancer, and melanomas account for 67 %–80 % of all cases. Each year, an estimated 200,000 to 300,000 people are diagnosed with metastatic cancer. Metastasis exhibits organotropism, with tumors displaying unique dissemination patterns and preferential colonization of specific organs, influenced by factors such as anatomical proximity and the premetastatic niche. The “Seed and Soil” Hypothesis posits bidirectional interactions between tumor cells and the organ microenvironment, mediated by cancer-derived extracellular vesicles (EVs) and genetic alterations. Understanding brain tropism involves overcoming the blood-brain barrier’s (BBB) selectivity, which poses a challenge for cancer cells [2]. The journey to the brain involves complex interactions within the brain microenvironment, including activated microglia and astrocytes. Moreover, the role of the extracellular matrix (ECM) and immune system in facilitating or inhibiting metastasis underscores the multifaceted nature of brain organotropism [3]. Interventions targeting factors such as vascular endothelial growth factor (VEGF) and immune checkpoints (ICs) hold promise in addressing this intricate process, emphasizing the importance of interdisciplinary approaches in combating BM [4].

HGGs, present treatment challenges due to their infiltrative nature, complex microenvironment phenotypes, and resistance mechanisms, compounded by the BBB. Conversely, BMs’ aggressiveness stems from a process where cancer cells detach from the primary site, circulate via the bloodstream, and colonize and proliferate in the central nervous system (CNS). The unique physiology, metabolic constraints, and distinctive biological processes of BMs suggest inherent differences and evolution compared to primary tumors. The BBB’s role in metastatic tumors remains speculative, potentially shielding some tumor cells from therapeutics and creating a sanctuary site. This phenomenon, coupled with the brain’s microenvironment, complicates treatment by promoting tumor cell survival, growth, and therapy resistance. Understanding the sequential mechanisms and brain microenvironment structure driving the metastatic cascade and fostering tumor survival, growth, and resistance is crucial for developing more effective targeted therapies [5]. Furthermore, survival rates of HGGs and BMs vary, with median survival for brain tumors like gliomas ranging from 20 %−75 % depending on the grade of the glioma. However, HGGs have a survival rate of less than 10 %. The success rate of cure is low, with most patients succumbing to local disease progression or distant brain tumor recurrence. Despite these challenges, advancements in treatment strategies, aim to extend life and maintain quality of life as long as possible. However, for HGGs despite having a multimodal treatment approach encompassing surgery, radiation therapy, and chemotherapy, yield only partial and transient responses. Chemotherapy and radiation therapy, while enhancing survival rates, are limited by high tumor relapse, treatment-related toxicity, therapy resistance, and continuous neurological decline. Emerging HGG treatments include targeted therapies such as small molecule inhibitors against irregular kinase signaling and chromatin regulators. However, their clinical effectiveness is typically limited due to the convergence of kinase signaling networks and epigenetic regulators, which often collaborate to enhance drug resistance [6]. Novel modalities like tumor treating fields (TTF), utilizing alternating electric fields for therapy delivery, have been examined for safety and efficacy, but issues related to study design and treatment cost remain undefined yet [7]. Bevacizumab (Avastin®), a humanized monoclonal antibody targeting the VEGF protein, has demonstrated substantial radiographic response (pseudo response), enhanced progression-free survival (PFS), and reduced corticosteroid need in patients with recurrent glioblastoma (rGBM). Despite these benefits, bevacizumab did not extend overall survival (OS) in a recent phase III trial.

Moreover, the TME in HGGs and BM’s is characterized by molecular diversity and immunosuppression, respectively, significantly influencing therapeutic response and prognosis. The TME is shaped by interactions between glioma cells and surrounding healthy cells, promoting oncogenic activities and glioma stem cell (GSC) formation [8]. On the other hand, the TME in BM from other cancers (e.g. melanoma) exhibits a higher proportion of monocyte-derived macrophages (MDMs), lymphocytes and neutrophils [9]. So, immunotherapies, such as chimeric antigen receptor-T cell (CAR-T) targeting specific tumor antigens (EGFR/EGFRvIII, IL13Rα2, B7-H3), have shown safety and disease-modifying activity in treating brain tumors, including glioblastoma (GBM)

[10]. Programmed death-ligand-1 (PD-1/PD-L1) inhibitors (camrelizumab, durvalumab, nivolumab, pembrolizumab, atezolizumab) block the PD-1/PD-L1 pathway, which is crucial for glioma progression, but their effectiveness in improving the prognosis remains controversial [11]. Dendritic cell vaccines (DCVs) have demonstrated improved survival in patients with HGGs and have been used in combination with Hyp-PDT by triggering a shift toward immunostimulation in the immune contexture of the brain [12]. Building upon this concept, immune system recalibration using biomimetic nanoparticles (BNPs) emerges as a promising technique in the fight against HGGs and BMs. This cutting-edge approach aims to recalibrate the immune system by harnessing the unique attributes of BNPs to specifically target and combat malignant HGG and BM. The novelty of this therapy lies in its biomimetic nature, enhancing the body's innate defenses against these formidable forms of brain cancers by mimicking biological systems [13]. Collectively, this approach will pave the way for novel treatment modalities, thereby improving prognosis and, ultimately, survival rates for patients afflicted with primary brain tumors and BM.

2. Immune landscape of brain tumors and BM

2.1. *Immune microenvironment in HGG*

In the exploration of immunosuppression, immune cells emerge as key protagonists. The immune microenvironment of HGG (e.g. GBM), is composed of various innate and adaptive immune cells. Microglia and perivascular macrophages, the resident immune cells of the brain, play multifaceted roles in HGGs. Their contributions extend from promoting tumor progression through intricate signaling pathways to fostering an immunosuppression, allowing the tumor to thrive [14]. These cells can be co-opted by GBM cells to create an immunosuppressive environment that supports tumor growth. Concurrently, tumor-associated myeloid cells, glioma-associated macrophages/microglia (GAMs), and tumor cells activated brain resident cells (astrocytes) facilitate a cold environment within the tumor by secreting immunosuppressive cytokines such as interleukin (IL) −10, transforming growth factor-β (TGF-β), tumor necrosis factor (TNF) and interferons (IFNs), etc. thereby aiding tumor evasion [15]. The adaptive and innate immune systems join the TME through antigen-presenting cells (APCs) and dendritic cells (DCs). Their involvement in recognizing tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) is a crucial link between the innate and adaptive arms of immunity. Cytotoxic T lymphocytes (CTLs), a key component of the adaptive immune system, are responsible for targeting and destroying cancer cells. However, GBM can evade CTL detection and attack through several mechanisms, including the upregulation of ICs proteins such as PD-1, PD-L1 and cytotoxic T-lymphocyte protein 4 (CTLA-4). However, this collaboration proves to be a double-edged sword, as the tumor manipulates these cells to promote immune tolerance, thus shaping the immunosuppressive environment of HGG.

Additionally, regulatory T cells (Tregs) play a pivotal role in the TME by infiltrating the area and employing their suppressive capabilities to inhibit the responses of effector T cells. The recruitment and activation of Tregs significantly contribute to the immune escape mechanisms observed in HGG, creating a favorable environment for tumor progression. However, the situation is further complicated by the presence of ICs. For instance, PD-1 and CTLA-4 engage with their respective ligands PD-L1 and CD80/CD86 on cancer and immune cells, leading to T cell exhaustion and facilitating immune evasion [16]. Meanwhile, cluster of differentiation 47 (CD47) acts as a "don't eat me" signal, providing additional protection for cancer cells against phagocytosis and reinforcing the immunosuppressive environment within the TME. Notably, the VEGF inhibitors, while primarily associated with angiogenesis, play a distinctive role in reversing the immunosuppressive environment in recurrent gliomas by targeting PD-L1 [15]. As the complexity escalates, indoleamine 2,3-dioxygenase (IDO), expressed by tumor and immune cells, serves as a master regulator of immune tolerance. By depleting tryptophan and producing immunosuppressive metabolites, IDO creates a hostile environment for effector T cells, allowing the tumor to evade immune surveillance and thrive.

Interestingly, the complex microenvironment of HGGs not only comprises immunosuppressive cells but also contain various specialized niches that significantly contribute to disease progression and therapeutic resistance (Fig. 1). These niches include the perivascular niche, hypoxic niche, invasive niche and metabolic niche, each with its unique characteristics and impact on tumor behavior. The perivascular niche, a specialized microenvironment surrounding blood vessels, plays a crucial role in tumor progression by creating an immunosuppressive milieu conducive to tumor growth and immune evasion. It involves factors like TNF-α, IL-8, insulin-like growth factor 1 (IGF1), and IL-6 which suppress antitumor immune responses and promote tumor-associated inflammation. These molecules contribute to the suppression of antitumor immune responses and the promotion of tumor-associated inflammation. Moreover, the abundance of GAMs within the perivascular niche exacerbates immunosuppression through the secretion of VEGF and PDL1 [17]. The hypoxic niche, driven by factors such as essential fibroblast growth factor (bFGF) and VEGF, fosters tumor survival and invasiveness, thereby exacerbating resistance to therapy. It harbors a subset of stem cell-like CD133-positive cells with remarkable plasticity and self-renewal capacity, fueling tumor propagation and conferring resistance to conventional therapies. Furthermore, the hypoxic conditions modulate the expression and activity of various molecular players involved in key cellular processes, including angiogenesis, metabolism, and epithelial-mesenchymal transition (EMT), collectively contributing to the aggressive phenotype and therapeutic resistance. The invasive niche is characterized by ECM proteins such as tenascin-C (TNC) and fibronectin. Glioma cells undergo phenotypic changes that enhance migratory capabilities, thereby exacerbating disease progression and rendering treatments less effective [18]. For instance, TNC modulates cell adhesion, migration, and proliferation, exacerbating disease progression and rendering treatments less effective. Additionally, fibronectin contributes to glioma invasion and

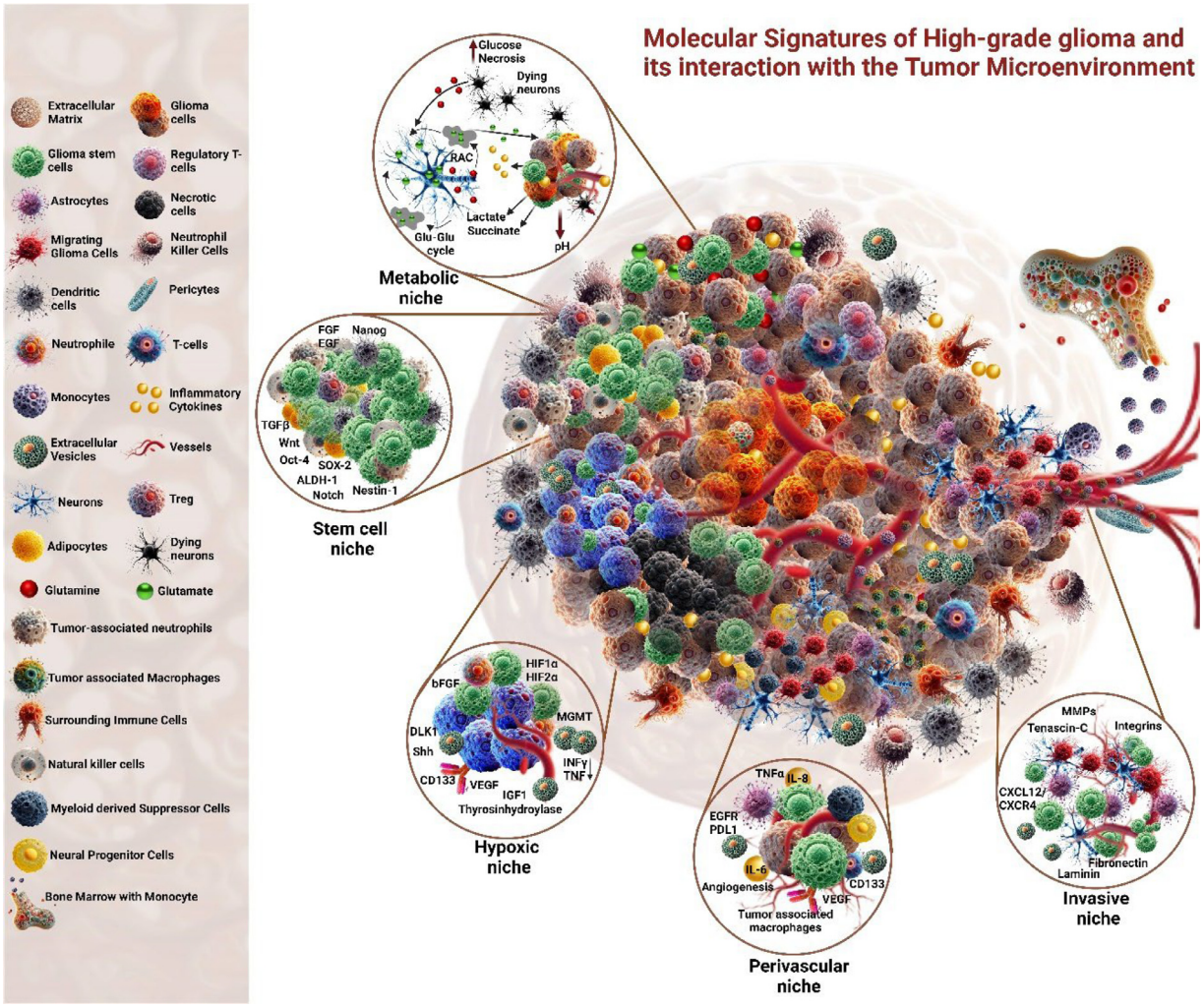

Fig. 1 – A detailed overview of the molecular signatures of HGG and their interaction with TME and highlights five distinct niche areas within GBMs. The hypoxic niche, characterized by PTEN and HIF upregulation, fosters tumor growth and resistance through VEGF and IL-8 upregulation, supporting stem cell presence marked by increased CD133. In the perivascular niche, angiogenesis and elevated VEGF levels accompany the accumulation of tumor macrophages and increased IL-6 and IL-8 cytokines, influenced by PTEN-mediated matrix proteins. The invasive niche facilitates tumor expansion into normal brain tissue, with GSCs associated with endothelial cells via CXCL12/CXCR4 signaling. The metabolic niche, driven by the Warburg effect, exhibits a metabolic shift towards aerobic glycolysis and lactate production, crucial for modulating the TME and promoting angiogenesis and immune evasion. Lastly, the stem cell niche supports GSCs' presence and maintenance, pivotal for tumor growth and resistance mechanisms.

resistance to therapy by promoting glioma cell migration and invasion [18]. Subsequently, the metabolic niche, governed by the interplay of glucose metabolism and lactate production, fosters tumor growth amidst adverse conditions and bolsters therapeutic resistance. Tumor cells exhibit a metabolic shift towards aerobic glycolysis, known as the Warburg effect, where they preferentially metabolize glucose to lactate, in the presence of oxygen, conferring a survival advantage in the hostile TME [19]. Lactate mediates cancer progression by modulating the TME, promoting angiogenesis, facilitating immune evasion, and orchestrating pathways involved in tumor cell proliferation, invasion, and metastasis. Therefore, understanding the intricate interplay of these niches is crucial for devising effective therapeutic strategies against HGG, particularly in mitigating immunosuppression and overcoming treatment resistance (Fig. 2).

Cooperatively, the immune system plays a critical role in the treatment of GBM, particularly through various immunotherapy strategies. In this regard, various tumor vaccines are under exploitation to stimulate the immune system to recognize and attack GBM cells, with some showing promising initial results in clinical trials. For instance, immune checkpoint inhibitors (ICIs), which block proteins that inhibit immune responses, aim to enhance T cell activity against tumor cells; however, their success has been mixed due to the immunosuppressive environment created by GBM. Furthermore, CAR-T cell therapy, an innovative approach involving the modification of a patient's T cells to better

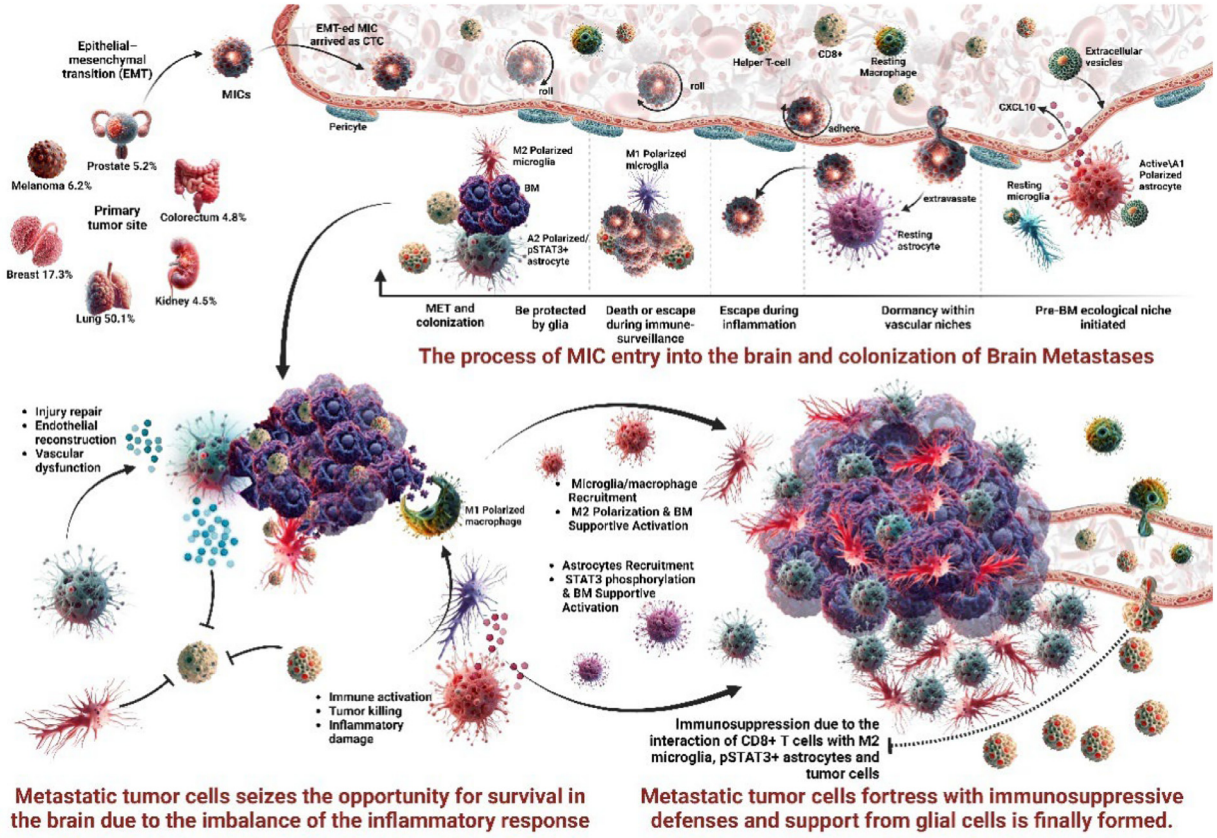

Fig. 2 – Schematic representation of the multifaceted process underlying BM. At its core, the figure delineates the journey of metastases-initiating cells (MICs) from primary tumor sites to colonization within the brain. MICs undergo crucial transitions, including EMT and mesenchymal-epithelial transition (MET), before adhering to the vascular endothelium and crossing the BBB. Subsequently, MICs interact with the brain microenvironment, navigating through a series of phases such as immune evasion, colonization, and growth, ultimately forming micro/macro metastases. Concurrently, the figure illustrates the pivotal role of polarized brain cells, notably astrocytes and microglia, in influencing BM progression. Astrocytes and microglia exhibit a dual role, contributing to both tumor promotion and inhibition, highlighting the complexity of the neuroinflammatory response. Moreover, the figure emphasizes the formation of a BM fortress characterized by immunosuppressive defenses and support from glial cells, culminating in a permissive environment for BM growth.

target GBM, is still largely experimental but represents a significant advancement in using the immune system for other cancer treatment [20]. Going forward, oncolytic viruses (OVs) genetically modified to selectively infect and kill cancer cells while stimulating an immune response also show promising potential in the treatment of GBM. Despite these advancements, challenges remain, including the tumor's ability to create an immunosuppressive microenvironment, the difficulty of delivering therapies across the BBB/ blood-tumor-barrier (BTB), and the vast genetic heterogeneity of GBM, which can lead to varied treatment responses. However, detailed investigations are essential to overcome these obstacles and harness the immune system's full potential in improving outcomes for these patients.

2.2. *Immune microenvironment of BM*

In the immune landscape of brain tumors, HGGs and BMs share similarities in their immunosuppressive microenvironments, yet subtle distinctions exist, shaping their divergent clinical behavior. Within this dynamic environment, various immune cells and stromal cells, including microglia, macrophages, cancer-associated fibroblasts (CAFs), pericytes, and astrocytes, engage in a complex interplay that modulates metastatic tumor progression. While microglia serve as resident immune sentinels in the CNS, it is important to note that neutrophils are the most abundant immune cells found in the bone marrow, with macrophages being less prevalent. Neutrophils play a crucial role in the initial immune response, while macrophages infiltrate the CNS microenvironment from the bloodstream, contributing to tumor growth and immunosuppression through cytokine secretion and IC modulation. Additionally, CAFs, pericytes, and astrocytes, among other stromal cells, mold the TME, fostering tumor progression and immunosuppression through various mechanisms, including ECM remodeling and cytokine secretion. Notably, the bone marrow is rich in neutrophils,

which play a significant role in the immune response, while macrophages are less abundant in this context [21].

Interestingly, in BM, the infiltrating immune cells from the periphery, particularly tumor-associated myeloid cells, contribute to the establishment of a pro-tumorigenic niche. Additionally, APCs and DCs act as lookouts of the immune system, shaping anti-tumor responses through antigen presentation and immune priming. However, Tregs, arising from both thymic differentiation and peripheral conversion, exert potent immunosuppressive effects within the BM microenvironment, dampening effector T cell responses and facilitating tumor immune escape. TAAs and TSAs, including neoantigens, further contribute to immune evasion by promoting tolerance or exhausting T cell response. ICs, such as PD-1 and its ligand (PD-L1), expressed on both cancer and immune cells within the BM microenvironment, inhibit T-cell activation and contribute to immune evasion [22]. The interaction between PD-1 and its ligand PD-L1 is a key mechanism of immune evasion in tumors. PD-L1, often overexpressed on cancer cells, binds to PD-1 on activated T cells, inhibiting T-cell activation and reducing cytokine production. This interaction leads to T-cell exhaustion and promotes Treg activity, fostering an immunosuppressive TME that allows cancer cells to evade immune detection. This understanding has driven the development of ICIs that block PD-1/PD-L1 interactions, reactivating T-cell responses and improving cancer treatment outcomes [23]. Furthermore, CTLA-4 and CD47 play crucial roles in immune regulation and tumor immune escape, offering potential therapeutic targets. Additionally, IDO is a key player in immune tolerance, further promoting Treg expansion and inhibiting effector T cell function, thereby fostering an immunosuppressive microenvironment conducive to metastatic tumor growth [24]. The regulation of IDO differs between BM and GBM. In BM, IDO promotes Treg expansion and inhibits effector T cell function, contributing to immune tolerance while allowing some immune response [25]. In contrast, GBM shows significantly higher IDO expression, leading to a more aggressive immunosuppressive environment. Here, IDO not only enhances Treg recruitment but also induces greater T cell dysfunction and apoptosis, facilitating tumor growth and correlating with poorer patient outcomes.

2.3. *Immune evasion by tumor cell*

The “tumor-brain-immune interplay” encompasses the complex interactions between tumor cells, brain cells, and immune cells that enable tumor cells to evade the immune system and promote tumor progression. This intricate relationship is critical for understanding how tumors thrive in the brain’s unique environment. Moreover, tumor cells interact with various types of brain cells to promote an immunosuppressive environment through up/down-regulation of unique tumor markers. For instance, tumor cells trigger mTOR-regulated STAT3 and NF-κB activity in microglia, promoting immunosuppression that inhibits T-cell infiltration, growth, and immune response [26]. mTOR is a central regulator of cell growth and metabolism, STAT3 is a transcription factor that mediates cytokine responses and promotes tumor growth, and NF-κB is a transcription factor involved in immune responses and inflammation, with persistent activation contributing to an immunosuppressive TME [27]. Additionally, astrocytes play a significant role in aiding metastatic cells by increasing the population of supportive microglial and macrophage cells near the tumor while simultaneously limiting the infiltration of $CD8^+$ *T* cells into the TME [28]. Furthermore, interactions between cancer cells and pericytes induce immunosuppressive functions that facilitate immune escape and enhance tumor growth and metastasis [29]. Additionally, the release of neurotransmitters by nearby nerves, along with the secretion of neurotrophic growth factors and miRNAs by cancer cells, further promotes these interactions, ultimately driving tumor progression [30].

In the immune system, several cells play a pivotal role in immune evasion by the tumor cells. Treg undermine immune surveillance against cancer in healthy individuals and weaken the antitumor immune response in hosts with tumors, thereby accelerating immune evasion by tumor cells, which leads to tumor growth and progression. Similarly, M2 macrophages possess various tumor-favoring abilities, including immunosuppression, angiogenesis, neovascularization, stromal activation, and remodeling. These functions adversely affect patient prognosis by promoting HGG tumor progression [31]. M2 macrophages promote tumor growth through several mechanisms, including immunosuppression, angiogenesis, and stromal remodeling. They secrete immunosuppressive cytokines like IL-10 and TGF-β, which inhibit cytotoxic T-cell activity, allowing tumors to evade immune responses [32]. Additionally, M2 macrophages produce pro-angiogenic factors such as VEGF, facilitating the formation of new blood vessels that supply the tumor with nutrients. They also activate CAFs and secrete matrix metalloproteinases, which remodel the ECM to support tumor cell migration and invasion. Collectively, these functions create a tumor-permissive microenvironment that promotes high-grade glioma progression and adversely affects patient prognosis. Regulatory B cells (Breg) include all B cells that suppress immune responses, maintain tolerance, limit ongoing immune responses, and restore immune balance [33]. In the context of tumors, Breg negatively modulate immune responses. Furthermore, DCs suppress the activation of T-cells, promote the generation of Treg, and promote immunosuppression. The reciprocal interaction between a tumor and neutrophils triggers the crucial transition from the naive form, known as the N1 type, to the more aggressive phenotype, referred to as the N2 tumor-associated neutrophils (TANs), which subsequently facilitates tumor invasion. Similarly, the mast cells influence various aspects of tumor biology, including cell growth, survival, angiogenesis, invasiveness, and metastasis [34]. Mast cells influence tumor biology through various mechanisms that promote tumor growth, survival, and metastasis. They release growth factors and cytokines such as IL-6, IL-4 and TNF-α, which enhance angiogenesis and support tumor cell proliferation. Additionally, mast cells produce proteolytic enzymes like MMP-9 that facilitate tumor invasiveness by degrading the ECM. They also interact with other immune cells, such as myeloid-derived suppressor cells (MDSCs) and Tregs, creating an immunosuppressive microenvironment that aids tumor

evasion from immune surveillance. Furthermore, mast cells can express co-inhibitory molecules like PD-L1, contributing to the suppression of anti-tumor immune responses and further promoting tumor progression through a complex interplay with the TME [35].

3. Immunotherapy

Despite the aggressive standard of care, the OS rate of HGGs and BM remained unsatisfactory, with a high relapse rate. In this regard, various immunotherapeutic drug delivery strategies pave the discovery of new areas in the management of hard-to-treat and lethal brain cancers. In following sections, we provide a comprehensive analysis of the fundamental knowledge on immunosuppressive TME modulating antitumor immune response, various resistance mechanisms to current immunotherapy, and advance strategies to prevent distinct challenges in the treatment of HGGs and BM.

3.1. *Immunoediting hypothesis*

The three E's hypothesis of immunoediting was proposed to explain these interactions by highlighting the competition between cancer and immune cells on a tumor progression from elimination to equilibrium and then escape [36]. During the elimination phase, innate and adaptive immune systems work together to recognize and eliminate the altered cells, which are harmful due to phenotypic alterations, such as excessive damage-associated molecular pattern (DAMP) molecules, the expression of tumor neoantigens, and stress ligands [37]. Some cancer-causing cells remain alive in the elimination stage and reach the equilibrium stage, where they remain latent for years or till the host's lifespan. In this stage, innate immunity is not required to regulate the tumor cell's dormancy. The main defense mechanisms involved adaptive immune components such as cytokines (IL-12, IL2, IFN-γ), cytotoxic T cells (CTLs), and type 1 T helper (Th1) cells. The escape stage is crucial in tumor development, characterized by genetic instability that promotes the rapid proliferation of tumor cells and makes them invisible to immune cells [38]. Simultaneously, they formed a proangiogenic microenvironment, facilitating the development of cells into lesions. The last step is gaining the tendency to infiltrate tissues and form metastatic cancer. In this stage, the tumor is accelerated by the infrequent necrotic lesions that cause inflammation, promoting the tumor's healing and progression. However, the inefficient immune response in the TME is inhibited by humoral and cellular components such as Treg, MDSCs and IL-10.

3.2. *Immunotherapeutic approaches in HGGs and BM*

Unlike conventional treatments, immunotherapy offers a promising approach to combating HGG and BM. It aims to produce a tumor-specific immune response to recognize and destroy cancer cells. ICs like anti-PD-1 and anti-CTLA-4 antibodies are currently under investigation to prevent the development of HGG and BM by inhibiting these iIC molecules [39]. Currently, immunotherapeutic approaches, including checkpoint inhibitors, CAR T-cell therapy, and oncolytic viral therapy, are overcoming several limitations, such as the BBB penetrance, the immunosuppressive TME, and tumor heterogeneity by targeting TSAs [40,41]. Moreover, combinatorial strategies, such as checkpoint inhibitors with other immunotherapy or with conventional treatments like radiation or chemotherapy, help to overcome tumor escape mechanisms and enhance the efficacy of treatment. Consequently, in the following sub-sections, we attempted to discuss the role of different immune candidate and their targeting approaches in the management of HGGs and BM.

3.2.1. *ICIs*

(Figs. 3 and 4) ICIs are immunotherapy that serves as inhibitory regulators of the immune system. They play a significant role in preventing autoimmunity and maintaining tolerance to self-antigens. These ICs molecules are ligand-receptor pairs that function as endogenous inhibitors to lower or eradicate inflammation after immune activation. However, tumor cells can activate these pathways by inhibiting immune surveillance. The anti-tumor immunity improves by enabling the T cells to destroy tumor cells using IC-targeted substances, such as PD-L1, PD-1 and CTLA-4. ICIs have shown increased incidences of recovery in various solid tumors; hence, their potential efficacy in HGGs is being investigated. Even though HGGs are "cold tumors" because of poor T-cell infiltration, ICIs may be a helpful strategy due to the expression of PD-1, PD-L1, CTLA-4, and their related ligands [42] (Fig. 4).

3.2.1.1. PD-1 and PD-L1 The PD-1 transmembrane receptor is primarily expressed in T cells and can be initiated by CD274 (PD-L1) or CD273 (PD-L2), which is found in APCs such as macrophages and DCs. PD-L1 is an IC molecule associated with programmed cell death. It inhibits the T lymphocyte activity and facilitates the evasion of immune cells. It has been discovered that PD-L1 expression is correlated with the grades of glioma tumors, and these results support the potential of PD-L1 as a targeted cancer therapy. A phase III clinical study (NCT02017717) [43] assessed the efficacy of nivolumab and ipilimumab in rGBM. The results demonstrated that nivolumab monotherapy was easier to tolerate and attained a good median overall survival (mOS) compared with combined treatment (10.4 vs. 9.2 months). Neoadjuvant nivolumab produces a local immunomodulatory therapeutic impact in GBM patients, and its efficacy was examined in phase II clinical trials [44]. Neoadjuvant pembrolizumab (PD-1 inhibitor) in a randomized, multicentre trial showed improved local and systemic immune responses in GBM and improved mOS to 417 d compared to 228.5 d [45]. CIs are believed to overcome immune resistance in tumors without causing the adverse effects of chemotherapy. Although, the TME prevents the efficacy of immune responses by restricting the infiltration of immune cells into the tumor, causing variable patient responses. However, combining therapies that increase immune infiltration of tumors with CIs, such as radiotherapy, has shown immunomodulatory effects and is now being used against BM [46]. For instance, a combination of pembrolizumab with bevacizumab has shown significant improvement in an objective response rate (ORR) of 20 %

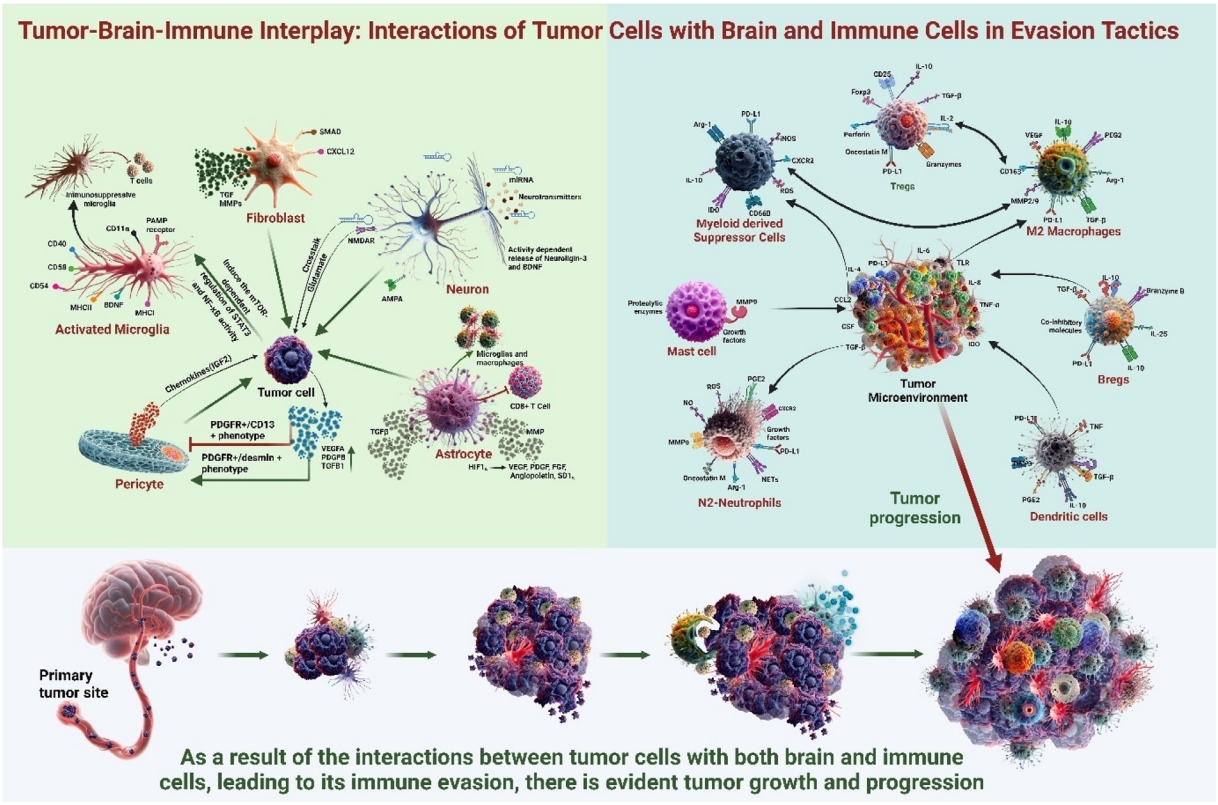

Fig. 3 – Schematic illustration of the complex interplay between tumor cells, brain cells, and immune cells. Tumor cells manipulate various brain cells (such as microglia, astrocytes, pericytes, fibroblasts, and neurons etc.) to create an immunosuppressive microenvironment, hindering effector T-cell infiltration and promoting tumor progression. For instance, tumor cells induce mTOR-dependent regulation of STAT3 and NF-$_K$B activity in microglia and interact with pericytes to evoke their immunosuppressive function. Similarly, immune cells like Tregs, M2 macrophages, Breg, DCs, N2 neutrophils, and mast cells are manipulated to inhibit antitumor immune action, remodel the ECM, promote genetic instability, and support the outgrowth of early-stage tumors. This intricate interplay enables tumor cells to escape the immune system and proliferate.

and a mOS of 8.8 months; PFS:26 %) in a small phase-II clinical study (NCT02337491) [47]. A randomized phase III clinical study, Check Mate 143 (NCT02017717), investigated the efficacy of nivolumab vs. bevacizumab in rGBM. The results were comparable between both the treatment arms (mOS of Nivolumab: 9.8 months while the mOS of bevacizumab was 10.0 months). The 1-year OS was 42 % in both the treatment groups and was not statistically significant.

3.2.1.2. *CTLA-4* CTLA-4 (CD152) is a co-inhibitory receptor that binds to B7 ligands on the surface of APCs and Treg and inhibits the immune response. The B7 ligand includes B7–1 (CD80), and B7–2 (CD86), which are also ligands of the co-stimulatory receptor CD28. Both ligands show higher affinity for CTLA-4 than CD28 as they suppress T-Cells' response by inhibiting CD28 [48]. This receptor-ligand (CTLA-4/B7) interaction suppresses the growth of T cells and the release of cytokines such as TGFβ, IL-10, and indoleamine [49]. Treatment with anti-CTLA-4 monoclonal antibody decreases the CD4, FoxP3, and Treg cell levels, eliminating glioma and enhancing long-term survival in a murine glioma model. Treatment with combined IL-12 and anti-CTLA-4 antibodies has been shown to eradicate tumors, resulting in tumor eradication [50]. Furthermore, it has been demonstrated that the combination of anti-CTLA-4 and anti-PD-1 antibodies has successfully treated 75 % of murine glioblastoma models in contrast to monotherapies by 50 % of anti-PD-1 and 15 % of anti-CTLA-4 antibodies.

A triple combination of anti-CTLA-4 antibodies, agonistic anti-4–1BB antibodies, and focal radiation therapy showed high tumor-infiltrating lymphocytes (TILs) and enhanced 50 % tumor-free survival. However, the efficacy of CTLA-4 therapy can be limited by factors like TME, mutational burden, and IC expression. Tumors can develop resistance through upregulation or antigen presentation changes. Therefore, the lack of reliable biomarkers complicates patient selection. These findings have led to the incorporation of tremelimumab (humanized anti-CTLA-4 monoclonal antibody) and durvalumab (anti-CTLA-4 IgG_2 monoclonal antibody) in phase II clinical trials (NCT02794883).

3.2.2. *DCVs*

DCVs consist of APCs that process foreign antigens and present them to T-cells, stimulating an adaptive immune response. The DCs are produced in vitro by culturing $CD14^+$ monocytes with granulocyte-macrophage colony-stimulating

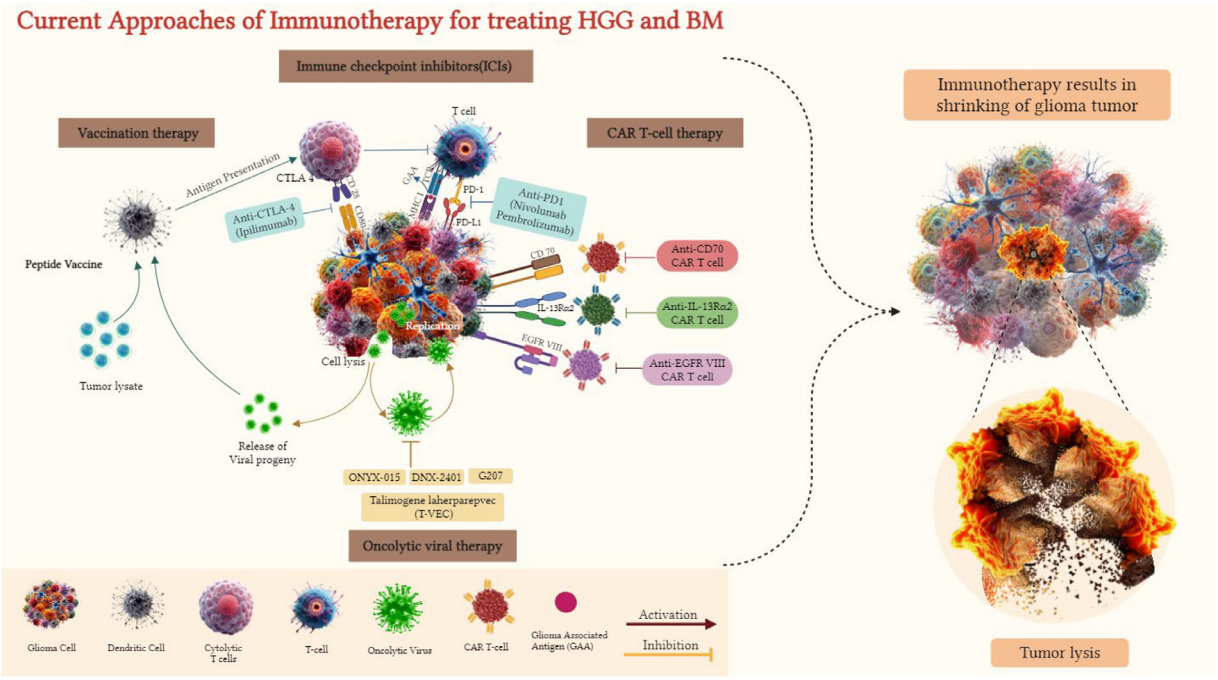

Fig. 4 – Current immunotherapy approach to treat HGGs and BM. Antibody therapy relies on DCs recognizing tumor lysates through the interaction of MHC class II T cell receptor (TCR) and CD80/86-CD28 (mainly used in the DC vaccine). DCs are effective in antigen presentation and can eliminate CTLs, which destroy glioma cells. Activation of CTL then targets and eliminates tumor cells containing glioblastoma-associated antigens (GAA) displayed on MHC class I molecules. However, tumor cells often avoid CTL destruction by activating immune ligands. For example, PD-L1 binds to PD-1 and inhibits lymphocyte activation. Blocking this interaction with monoclonal antibodies may prevent tumors from escaping. Similarly, blocking CTLA-4, an inhibitory immune molecule that blocks T cell activation by binding to CD80 and CD86, will promote dendritic growth through antibody-mediated blockade. GAAs, such as CD70, IL-13Rα2, and EGFRvIII, are present on the surface of tumor cells via MHC class I. These TAAs are genetically modified CARs-T targeting therapy. Additionally, genetic modification plays a role in the treatment of oncolytic disease by altering the virus to infect or replicate in tumor cells. Therefore, the destruction of tumor cells by these bacteria not only directly eliminates the virus but also causes immunogenic cell death. This activation may increase antigen presentation and stimulate the adaptive immune system against the tumor.

factor (GM-CSF) and IL-4, which helps to identify immature DCs. The DCs are loaded with TAA, peptides, viral antigens, RNA, or tumor lysates and then injected into the patients, resulting in the lysis of tumor cells, due to anti-tumor T cell response, thereby preventing tumor relapse [51]. Moreover, the tolerability of DCVs in HGG patients has been investigated in clinical studies, and the outcomes demonstrated the safety of DCV-loaded autologous glioma cells as the antigens. In a phase II clinical trial of 34 GBM patients in which DCVs were administered, it was found that 50% of patients showed a significant improvement in median survival of up to 642 d A recent phase I clinical trial of rindopepimut, a peptide vaccine for epidermal growth factor receptor variant III (EGFRvIII) in conjugation with keyhole limpet hemocyanin (KLH) as the antigen showed favorable results in newly diagnosed patients of GBM (mOS of 22.8 months). In the past few years, DCV has shown promising results in various clinical trials. Furthermore, another two phase-II trials have shown improved efficacy of using DCV in HGG in terms of a median survival time of 520 d and 18.8% survival over five years [52]. In the same year, another interesting phase-II study was performed where 18 newly diagnosed GBM patients received an adjuvant DCV, and 16 patients of the control group only received standard treatment. The results showed an excellent OS of 32.9 months in the DCV group compared to the control group of 15.0 months. Presently, two phase-II clinical studies are ongoing that are using DCV primed with tumor samples, stem cells, and cytotoxic lymphocytes as a first-line treatment in GBM patients (NCT01759810), and the other trial is investigating the efficacy of mRNA-transfected DCV comparing adjuvant temozolomide (TMZ) in GBM patients (NCT03548571). However, the robustness of DCV in HGG need to be established through rigorously conducted phase III clinical trials in nearby future.

3.2.3. *Oncolytic viral therapy*

Oncolytic viral (OV) therapy is a type of immunotherapy that uses engineered viruses to infect and eradicate tumor cells through oncolysis, wherein new infectious virus particles are released by this process, aiding in destroying the remaining tumor (Fig. 4). These therapeutic approaches have shown their potential in treating brain tumors, suggesting they could

be effective in treating BM. OV therapy has demonstrated efficacy in preclinical models and early-phase clinical trials for glioblastoma and other primary brain tumors, making it a promising approach for treating BM. Recent studies, such as those by Todo et al., have shown promising results in prolonging survival and enhancing immune responses in patients with malignant gliomas.

An oncolytic adenovirus (ADV) DNX-2401, in combination with pembrolizumab (anti-PD-1 antibody), delivered intratumorally and showed an increased OS of 52.7 % in one year with mOS of 12.5 months in a multicentric phase I/II clinical trial on GBM patients [53]. Another oncolytic herpes simplex virus (HSV), G47Δ (an alternative version of G207), has shown its potential in treating GBM in phase II clinical trials (JPRN-UMIN000002661), and its combination with IL-12 has shown enhancement in mOS, suggesting that it can be evaluated further in clinical trials [54]. The results of this study demonstrated the prolonged survival, well-tolerance, and effectiveness in rGBM (mOS of 28.8 months from initial surgery] [55]. Recently, a multicentric CAPTIVE/KEYNOTE-192 phase II clinical trial (NCT02798406) was completed. They have investigated the combination of oncolytic ADV DNX-2401 (tasadenoturev) with pembrolizumab, but the results of clinical outcomes are awaited. Earlier, in clinical trials, oncolytic reoviruses are administered intratumorally into tissues of malignant glioma patients due to the limitation of the poor BBB permeability. Moreover, a study by Desjardins and the group evaluated 61 patients of HGG administrated with oncolytic poliovirus, PVSRIPO, and showed a 21 % OS at 24 and 36 months compared to the control group, indicating that oncolytic poliovirus has the potential to treat metastatic brain tumors. Several studies have demonstrated the efficacy and reliability of OV in treating glioma. However, more research is needed to find out whether OV can be employed as a standard treatment for HGG and BM patients.

3.2.4. *CAR-T therapy*

CAR-T are genetically engineered T cells used to target cancer due to their ability to detect and target a specific antigen without the use of MHC or HLA antigens and lead to T cell activation (Fig. 4). The structure of CARs typically consists of an ectodomain, transmembrane domain, and endodomain, and each has specific functions and efficacy [56]. The ectodomain contains the antigen-recognition domain connected by a linker (short peptide) or single-chain variable fragment (scFv), and the hinge domain (HD) acts as a spacer that holds scFvs. It can recognize TAAs in cancer treatment. In contrast, the endodomain contains co-stimulatory and activation domains that trigger the T-cell activation signaling. The "first generation" CARs are those in which the antigen-recognition domain is connected to CD3ζ of TCR, but they showed poor anti-tumor activity and survival. Subsequent generations were incorporated with co-stimulatory domains, overcoming the drawbacks by improving the proliferation of T cells and survival in clinical studies. The major used co-stimulatory molecules in CARs include CD28, ICOS, 4–1BB, OX40 and CD27. Earlier, the FDA approved two CAR-T cell therapies for treating hematologic malignancies. Furthermore, the advent of CAR-T cell therapy ushered in a new phase in cancer treatment; several CARs have been modified to focus on GBM, such as IL13Rα2, EGFRVIII, HER2, and CD70. In the past years, a clinical study showed that intracranial administration of IL13Rα2 CAR-T cells has efficacy against HGG and high tolerability. Additionally, phase I clinical studies found total recovery in one patient. Going forward second-generation IL13Rα2 CAR-T cells incorporated with CD137 costimulatory domain have shown higher antitumor effects and durability than first-generation IL13Rα2 CAR-T cells in GBM mouse models. Moreover, a group of researchers found CD70 as a novel immunosuppressive ligand in GBM. They also demonstrated that CD70 expression was correlated with lower survival rates and that, in murine models, CD70 CAR T-cells could selectively reduce CD70-positive GBM, presenting a new CAR target for glioma immunotherapy. Currently, multiple clinical trials use CAR T-cells for glioma treatment, targeting GBM antigens such as EGFRVIII, IL13Ra2, and Her2 and some new targets, including GD2, EphA2, MUC1, and CD147. Due to their precision, CAR T-cells not only enhance the effectiveness but also minimize toxicity. However, to further improve the efficiency of CAR T-cells, new approaches to bypass CIs and transgenic expression of cytokines to enhance T-cell activity are currently under investigation.

4. Mechanisms of immunotherapy resistance and strategies to overcome them

Although immunotherapy has demonstrated promising outcomes in preclinical studies of HGG and BM, these outcomes have yet to be effectively replicated in clinical studies. Clinical observations of primary and recurrent tumors studied over a long period highlighted the four types of tumor resistance: type 1 (melanoma), type-2, type-3 and type IV (GBM). For instance, in melanoma, around 50 % of patients respond to a combination blockade of PD-1 and CTLA-4, and this response proves its durability in 75 % of cases. Type 2 tumors initially respond to immunotherapy but quickly escape through adaptive resistance, whereas type 3 tumors initially show reduced levels of inflammation and possess restricted mechanisms to block the immune response. Types 2 and 3, however, need to be more clearly defined clinically. On the other hand, type-IV GBM has less than 10 % of patients responding to immunotherapy, and these responses are typically short-lived due to potent adaptive and acquired resistance mechanisms [57]. Correspondingly, an illustrative study involving 17 GBM patients who initially responded to PD-1 blockade revealed that tumors developing resistance exhibited a loss of neoepitopes and slowed down the increasing response of genes associated with immunosuppression [58]. Furthermore, two major mechanisms of resistance to immunotherapy for HGG and BM along with strategies employed to overcome this resistance, are subsequently discussed

4.1. *Intrinsic mechanisms of resistance (Primary)*

GBM showed significant challenges for immunotherapy due to its extensive intra-tumoral heterogeneity, which complicates the identification of effective clonal neoantigens

across different immunotherapy approaches. The immunosuppressive microenvironment within GBM tumors also hinders the effectiveness of immunotherapy [59]. Moreover, glioma individuals showed reduced levels of circulating T cells before receiving treatment. This is because of tumor-mediated internalization of the G-protein coupled receptor sphingosine-1-phosphate receptor 1 (GPCR S1P1). However, inhibiting S1P1 internalization has shown promise in reversing T-cell sequestration in murine GBM models, suggesting a potential strategy for enhancing immunotherapy efficacy. Furthermore, in GBM, circulating T cells often lead to dysfunctional T cell characteristics such as resistance and fatigue. The fatigued characteristics are frequently observed when cancer, chronic infection, or other conditions result in prolonged activation of the body's immune system. It is now believed to be potentially irreversible due to a novel concept termed *'epigenetic scarring'*, even after antigen clearance. Subsequently, continuous proliferation results in T cell senescence, leading to a shortening of telomeric ends. Notably, GBM employs innate immune tolerance mechanisms to facilitate FasL-mediated peripheral deletion of T cells and recruit Tregs by expressing IDO1 and TIM4. MDSCs contribute to immune suppression and tumor progression by expressing arginase, inducible nitric oxide synthase (NOS), and reactive oxygen species (ROS). Similarly, GAMs play a role through the secretion of immunosuppressive cytokines IL10 and TGFβ, induced by GSCs. Although the CNS is typically considered a site of immune privilege due to inherent mechanisms like the BBB and microglia. However, when comparing the microenvironment and immunotherapeutic outcomes of GBM to those of BM, it is evident that GBM is intrinsically immunosuppressive, regardless of its location within the CNS [60]. The analysis of individual cells has unveiled that the GBM microenvironment exhibits higher levels of tissue-resident microglia, whereas the environment of metastatic tumors shows an increased presence of tissue-invading leukocytes. Simultaneously, the majority of leukocytes detected in the metastatic tumor environment are T cells, whereas around 80% of leukocytes found in the GBM microenvironment are typically immunosuppressive GAMs. These findings may elucidate why ICIs have demonstrated greater efficacy in treating BM originating from other tumors (e.g. melanoma or non-small cell lung cancer) than individuals with HGG.

4.2. *Adaptive mechanisms of resistance (Secondary)*

HGG can develop secondary resistance during recurrence. This resistance often manifests through a reduction or complete loss of neoepitopes—novel peptide sequences presented by MHC molecules on tumor cells derived from tumor-specific mutations. The initial response to immunotherapy is often predicated on the presence of these neoepitopes, which are critical for immune recognition [61]. However, recurrent individuals who initially responded to anti-PD1 immunotherapy may experience a loss of these neoepitopes and decreased expression of immunosuppressive genes. While primary tumors may initially exhibit high PD-L1 expression, inhibiting T-cell activity, recurrent tumors might downregulate PD-L1 or alter other checkpoint molecules, effectively escaping the inhibition intended by checkpoint blockade therapies. Additionally, the TME can become increasingly immunosuppressive, with elevated levels of Tregs, MDSCs, and other factors like TGF-β and IL-10 [62].

In both HGG and BM, tumor cells can adapt by altering their phenotype, including adopting a more mesenchymal phenotype, which is associated with increased invasiveness and resistance to therapies and immune responses. Some tumor cells may also express proteins that inhibit immune cell function or recruit cells that suppress immune responses [63]. These mechanisms of secondary resistance highlight the complexity of treating recurrent brain tumors and underscore the need for developing new therapeutic strategies that target these adaptive changes.

ICIs have transformed cancer treatment, but their effectiveness remains limited in HGG and BM due to several immune-resistant mechanisms. Reverse translational research is now uncovering the mechanisms by which immune systems eradicate cancer cells, as well as the immune-resistant mechanisms that may exist [64]. Advanced technologies, such as comprehensive immune cell analyses and multi-omics studies, are being utilized to compare responders and non-responders, helping to develop new management strategies for HGG and BM.

4.3. *Overcoming resistance mechanism*

The limited efficacy of immunotherapeutic agents in treating HGG likely results from a complex interplay of factors, including immunosuppression, dysfunction of local immune cells, and tumor cell heterogeneity and complexity. Therefore, most research has been directed toward exploring the adjuvant methods to prepare the TME to initiate a robust immune response [65]. Likewise, we discussed different approaches that remodel the TME to enhance immunotherapy by reducing its immunosuppressive characteristics, improving its ability to induce cell death, and its side effects. For instance, CD47 is a protein linked with signal-regulatory alpha (SIRPα) on macrophages to prevent phagocytosis [66]. Combinatorial therapy of TMZ with CD47 blockade has increased the OS and boosted the PD-1 blockade responses. It has been examined in clinical trials for various cancers including HGG. The pre-clinical investigation on mice showed high tolerance and fewer side effects, but at the same time, clinical trials faced challenges such as anemia, leukopenia, and thrombocytopenia as major side effects [67]. Studies on HGG have investigated administering lower doses of anti-CD47 antibodies to address hematological toxicity [68]. Similar to CD47, colony-stimulating factor-1 receptor (CSF-1R) is involved in differentiating myeloid cells into M2 macrophages. Inhibited CSF-1R downregulates the M2 markers in GBM xenograft models, but it does not deplete the population of cells. Despite that, inhibited CSF-1R upregulates the expression of critical chemotactic factors that encourage lymphocytes to infiltrate tumors. In GBM, immunological resistance to active vaccination can be overcome by combinatorial suppression of CSF-1R (cabiralizumab] and PD-1 (nivolumab], undergoing clinical studies [69].

Furthermore, adjuvant therapies being explored for GBM aim at M2-type macrophages, notably CD73, an ectonucleotidase associated with CD39, to generate adenosine, a molecule supporting tumor growth. The expression of CD73 on myeloid cells correlates with increased co-expression of immunosuppressive and tumor-promoting chemokine receptors [70]. While clinical trials are underway targeting these receptors, CD73 emerges as a potentially more pertinent target due to its increased co-expression and the modest efficacy of existing approaches. Anti-CCL2 (mAb) targeting CCL2 has effectively decreased MDSCs and enhanced survival in GBM xenograft models. Combining CCL2 receptor inhibition with PD-1 checkpoint blockade prolongs survival in mice with GBM. Although mild-to-moderate adverse effects have been reported in a clinical investigation. However, neutropenia is frequently experienced, possibly due to the removal of CCL2's anti-apoptotic influence [71]. IL-6 stimulates immunosuppressive activity in myeloid cells by inducing PD-L1 expression on MDSCs [72]. Although neutralizing IL-6 has been found to increase T cell infiltration into tumors, it alone does not sensitize the tumors and remains resistant to ICIs. However, when CD40 stimulation is combined with IL-6 inhibition and IC blockade targeting PD-1 and CTLA-4, significant clinical responses are observed in syngeneic murine GBM models. This combination also showed reversed macrophage-mediated immune suppression and prolonged survival [73]

Apart from myeloid-derived cells, lymphoid lineage cells (e.g. Treg) also exhibit immunosuppressive capabilities and represent potential targets for therapy. Treg are a subset of $CD4^+$ cells marked by $CD25^+$ and FOXP3+ expression, redirect immune responses away from cytotoxic Th1 reactions toward Th2 responses by upregulating CTLA-4 expression and reducing IL-2 and IFN-γ secretion. In GBM murine models, Treg depletion therapy is used to overcome immune response via combining anti-CXCR4 and anti-PD1 immunotherapy and showed enhanced survival rates by lowering Treg and MDSC levels, improving $CD4^+/CD8^+$ ratios, and boosting pro-inflammatory cytokines [74]. Recent studies focusing on GITR (immunomodulatory receptor), which is highly expressed in GBM Treg but low in systemic Treg, hold potential. This approach alters murine Treg into $CD4^+$ Th1 cells that produce IFN-γ and can attack γ cells [75]. Collectively, these findings demonstrated that combining anti-GITR with anti-PD1 therapies prolongs survival in HGG animals, with some instances achieving complete tumor elimination and establishing immune memory upon tumor re-exposure [75]

5. Biomimetic nano-delivery remodeling immune responses

Recent advancements in different types of BNPs have attracted considerable interest in the treatment sensitization of highly aggressive gliomas and brain metastasis. We emphasize our discussion on how this bioinspired nano-delivery reverses immunosuppressive TME into a responsive niche to improve highly aggressive glioma treatment efficacy (Fig. 7).

5.1. *Enhancing cytotoxic functions of immune cells*

The immune escape phenomenon of tumor cells disappointed the initial clinical trial outcome of immunotherapy in HGG. Meanwhile, the immunosuppressive cytokines (e.g. IL10, TGF-β) secreted by tumor cells reduce the cytotoxic functions of immune cells like T-cells, and NK cells due to persistent antigen stimulation. For the past few years, many research groups have investigated the causes behind this reduced infiltration of T-cells in gliomas that lead to the failure of immunotherapy. For instance, the loss/downregulation of surface receptors S1PR1 expression on the T cells due to their sequestration in bone marrow leading to T-cells deficiency in blood and lymphoid tissues (known as T-cell deficient lymphoid organs). Similarly, T-cells dysfunctions are associated with increased expression of co-inhibitory receptors (e.g. PD-1, CTLA-4, mucin-domain containing molecule-3 TIM-3). Consequently, to improve the success of glioma immunotherapy different approaches such as increasing the release of bone marrow sequestered T-cells using granulocyte-CSF, hindering internalization of the T-cell surface receptors, and preventing T-cell exhaustion, etc. were reported to be effective techniques [76,77]. Therefore, to improve the treatment sensitization in HGG strengthening of the body's cells (immune cells) opens potential avenues to recalibrate the immunosuppressive TME. Although various small molecules and antibodies were investigated to improve immunotherapy benefits in HGG however IC blocking strategy with a monotherapy (i.e. single antibody, blocking single checkpoint) has limited therapeutic efficacy mainly due to effective blood-to-brain delivery challenged by the BBB. To address this issue various BNP-based strategies have been under investigation that trigger IC molecules to augment potent and long-term antitumor immune response as a revolutionized treatment against HGG [78].

More interestingly, Wang and co-workers redesigned their previously developed ultra-small tumor cell membrane-coated biomimetic nano platform (CS-J-CM/6NP) for repurposing old drug paroxetine [PX, a GPCR-kinase 2 (GRK2) inhibitor] to stabilize S1PR1 on T-cells surface. This approach resulted in the release of sequestered T cells in the bone marrow followed by an amplified immunotherapy effect against GBM. The oral delivery of these BNPs in GBM-bearing mice freed sequestered T-cells in the bone marrow resulting in an increase in their infiltration at the tumor site. Additionally, the BNPs simultaneously target multiple receptors (PD-1, TIM-3 on T-cells and PD-L1 on glioma cells) to improve T-cell functions/activity. The biomimetic coating of the nanoparticles facilitates easy crossing of the BBB and then targets tumor cells through interaction between CD6 and endothelial cells expressing protein (i.e. activated leukocyte cell adhesion molecule) followed by homologous adhesion effect. Furthermore, ROS generated by these nanoparticles through Fenton-like reaction activate immune response on the discharge of TAAs (e.g. DAMPs like HGBM1, calreticulin) released by immunogenic tumor cell death. Together, these findings demonstrated the potential of the combination of biomimetic nano-delivery in repurposing old drugs to boost

HGG immunotherapy via improving cytotoxic functions of T-cells via multiple mechanisms [79].

Furthermore, the first line chemo-drug (TMZ), and radiotherapy induce cellular stress, and DNA damage via the ATM pathway, and upregulating expression of NKG2D pathway (potently activated NK cells receptor) whereas, the glioma cells express cognate receptor i.e. NKG2DL. Both *in vitro/in vivo* glioma sample analyses had shown increased expression of NKG2D after exposure to chemo/radiotherapy with increased cytotoxic function of NK cells thereby promoting the anti-tumor immune response against tumor cells. However, the antitumor effects of this chemo/radiotherapy in glioma were reduced upon inhibition of the NKG2D pathway due to attenuation by O6-methylguanine-DNA-methyltransferase (MGMT). This suggested the potential rationale for combining NKG2D-based immunotherapy with conventional treatment modalities in GBM [80]. Inspired by the potential of NK cells in glioma immunotherapy Zhang and co-researchers reported NK cell membrane camouflaged Trojan-Horse-Like BNPs further decorated with brain-tumor targeting ligand (e.g. cRGD), and/or co-loaded with immunomodulatory cytokines (e.g. IL15) to elicit immunostimulatory TME for glioma therapy. The synergistic activity of TMZ and IL15 promotes the proliferation and activity of NK cells in glioma tissue and subsequently leads to DC cells maturation and infiltration of cytotoxic $CD8^{+}$-T cells responses against GBM [81].

5.2. Re-*educating* GAM

Under healthy conditions, residential microglia have the self-renewal capability and are ontogenically discrete cells from peripheral macrophages (under pathological states differentiated from peripheral bone monocytes that originated in hematopoietic stem cells). Microglia helps to maintain brain homeostasis and immune defense in healthy states. However, the cold immunogenic TME of HGG i.e. predominant lymphocytes infiltration, immunosuppressive Treg, and gliomas-derived factors (e.g. CSF1, CCL2, CXCL1, GM-CSF, MCP1/3, EGF, SDF1, OPN) affect the phenotypic plasticity of these cells (i.e. classically activated M1 state with antitumor properties and alternatively activated M2 state with pro-tumorigenic potential). These phenotypic changes and their impact on glioma progression and therapy resistance have been meticulously reviewed [82,83]. GAMs constitute around 80 % of the total immune cells composition of glioma tumors and are nowadays considered to be an important promoter of immunosuppression. The immune functions analysis of GAMs isolated from GBM biopsies samples suggested that the release of co-stimulatory molecules (CD80, CD86) and activation of MHC-II were remarkably reduced thereby eliciting inhibitory functions on T-cell activation and antigen cross-presentation. Furthermore, GAMs overexpress tryptophan 2,3-dioxygenase (TDO2) and IDO1 that activate aryl hydrocarbon receptor (AHR) via metabolite (e.g. L-Kynurenine) released by their enzymatic reaction. The activated AHR in GAMs promotes the expression of various immunosuppressive chemokines (e.g. CCL2, CCL5 and CCL20) subsequently enhancing the recruitment of Treg cells which further inhibit the activity of CD4, CD8 T-cells, NK cells, and APCs through different mechanisms to suppress T-cells immune function, proliferation, and infiltration thereby leading to immune evasion of HGG. Recently, various nanotherapeutics targeting pro-tumorigenic functions of GAMs are under investigation as therapeutic targets in gliomas [84]. For instance, educating recruitment of antitumor phenotypes at the target site, depletion of GAMs, repolarization of M2 phenotypes into M1 by manipulating cytokines expression, and enhancing phagocytosis potential of these GAMs to eat up glioma cells [85]. Interestingly, cell membrane camouflaged BNPs eliciting homotypic targeting (cancer cells recognize each other and interact owing to surface membrane protein) are considered to be promising over ligand functionalization strategy against heterogenous tumors including gliomas. In this context, Sen et al. designed the dual cell membrane (isolated from human HMC3 microglia and human U87MG glioblastoma cells) coated doxorubicin loaded nanoflakes of hexagonal boron nitride (hBN, size 360 nm, −42 mV) for specific and selective targeting of GBM. The proteomic analysis of U87 cells treated with hBN showed modulation of protein markers associated with M2 polarization of microglia cells to promote anti-inflammatory and tissue repair functions whereas, the apoptosis and Ki67 analysis showed anti-glioma effects [86]. Moreover, the intrinsic characteristic of macrophages at dynamic polarization states (M1 state and M2 states) was used to infuse them with liposomes (M2/M1-MML, 100 nm size). Their study design was different from the previously reported studies where the cell membrane was coated around the nanoparticle's cores. They showed that distinct properties between M1 and M2 phenotypes of macrophages significantly affect the ability of MML to get internalized into glioma cells followed by their cytotoxic potential. The different expression of surface markers (e.g. integrins) between macrophage subtypes could be attributed to this effectiveness. Although, the M2 macrophage-infused MML showed better uptake and glioma cell killing, the M1 macrophages-infused MML are worth considering for modulating TME. However, more evidences are required to conclude the effectiveness of these phenotype combination strategies. More recently, macrophages camouflaged angiopep-2 conjugated small activating RNA-loaded mesoporous polydopamine hybrid nanoparticles were developed to promote ferroptosis through mitochondrial targeting via a newly discovered lipoxygenase marker (ALOX15). This hybrid biomimetic strategy showed long-term circulation (thanks to self-recognition function evading RES elimination and immunological surveillance) and specific interaction with glioma cells due to macrophage mimicking tumor tropism characteristic and targeting angiopep-2 peptide and with the potential to sensitize radiotherapy [87]. Moreover, Wang and co-workers designed the M1 macrophages-derived extracellular vesicles (M1EVs) for synergistic multimodal delivery of hypoxia-activated prodrug AQ4N and chemiexcited photodynamic therapy using excitation source CPPO and Ce6 photosensitizer against U87MG cell-derived and GBM patient-derived xenograft models. The inherent nature of M1 macrophages easily permeates the BBB and modulates immunosuppressive TME by polarization of M2

macrophages into the M1 state after systemic administration of the M1EVs. This M1 polarization leads to an increased level of H_2O_2 within glioma TME. Subsequently, a large amount of ROS is generated by activated photosensitizer through the chemical energy produced by CPPO and H_2O_2 [88]. Collectively, these multimodal biomimetic nanotherapeutics are poised to adjunct and advanced treatment against aggressive gliomas thus, proclaiming tremendous potential with a new edge in the war against cancers.

5.3. *Modulation of tumor metabolism*

The oxygen gradient and the nutrients in the proximity of abnormal neoangiogenic blood vessels within the HGG microenvironment with heterogenous cell population, i.e., oxidative phenotypes and glycolytic phenotypes, play an important role in gliomagenesis. Moreover, altered metabolism is an emerging hallmark of tumorigenesis as it promotes tumor invasion, metastasis, and immune escape. Several studies reported that aerobic metabolism is the preferential mechanism through which cancer cells produce their energy (converting glucose into lactate followed by ATP production) to maintain their sustained and rapid proliferation in the hypoxic TME. Subsequently, extracellular concentration of the lactate concentration was found to be significantly higher (10–30 mM) compared to intracellular concentration as the tumor progressed [89]. Subsequently, the tumor cells with glycolytic phenotypes secrete a higher amount of lactate followed by their metabolism by oxidative phenotypes that increase their tolerance to survive even under unfavorable conditions. Lactate metabolism is mainly regulated by lactate dehydrogenase (LDH) and the expression of monocarboxylate transporters (e.g. MCT1, MCT4) in the plasma membrane [90,91]. The precise mechanism underlying how lactate metabolism influences the crosstalk between glioma cells and TAM has been extensively studied by Yan et al. Their study demonstrated the elevated expression of LDHA and MCT1 in glioma-induced GAMs towards M2-phenotypes and their infiltration through GPR65 (highly expressed on GAMs) mediated release of HMGB1via cAMP/PKA/CREB signaling pathway due to lactate stimulation. Therefore, modulating this feedback loop by blocking GPR65 or inhibition of HMGB1 release showed promising mitigation of glioma progression in vivo subcutaneous and orthotopic xenograft GBM models [92]. BNP-based targeting of lactate metabolism is emerging as a therapeutic strategy to treat various cancers including HGG through inhibition, blockage, and saturation of these regulators. For instance, Lu et al. designed the U251 glioma cell membrane camouflaged nanoparticles for homotypic recognition to cross the BBB releasing combined payload targeting lactate metabolism followed by chemiexcited photodynamic therapy in a synergistic manner. These BNPs formed via self-assembly of hemoglobin (sourcing oxygen for lactate metabolism and chemiexcited photodynamic therapy), lactate oxidase [LOX, enzyme converting lactate into pyruvic acid (PA) and H_2O_2], and chemiluminescence agent bis [2,4,5-trichloro-6-(pentyloxycarbonyl) phenyl] oxalate (CPPO) with photosensitizer chlorin e6 (Ce6). Their systemic administration showed effective permeation across the BBB followed by selective accumulation at the glioma target site due to the homotypic targeting ability of the biomimetic membrane. The accumulated LOX is released from the nanoparticles metabolizing lactate into PA and H_2O_2 via O_2 consumption carried by hemoglobin. Furthermore, released PA stimulates histone downregulation promoting cell cycle arrest. Consequently, the CPPO payload reacts with H_2O_2 producing chemical energy to activate Ce6 to generate singlet cytotoxic oxygen ($^1O_2$) for tumor cells apoptosis in patient derived as well as cell derived GBM *in vivo* studies. The survival of this BNPs treated group was found to significantly higher than control (48 d vs. 26 d) [93]. Interestingly, Ke and co-workers demonstrated that glucose starvation can be used as powerful strategy to alter this energy metabolism in glioma cells. To prove this hypothesis, they designed the metal organic framework (MOF) based cRGD modified RBCs membrane camouflaged nanoparticles co-loaded with glucose oxidase (GOX) and chemotherapeutic like doxorubicin. This multifunctional bioreactor showed enhanced circulation time and target specificity inherited from the RBCs and targeted RGD peptide respectively. After accumulating at the targeted site, the GOX consumed intra-tumoral glucose and O_2 inducing robust starvation of tumor cells. Furthermore, the acidic TME induce decomposition of MOF thereby release doxorubicin to synergistic and spatiotemporal targeted starvation coupled chemotherapy in glioma [94]. Furthermore, another research group developed the GOX loaded CuO deposited BSA nanoparticles coated with the PEG_{2K}-$PEI_{1.8K}$ to prolonged circulation time for effective Fenton-like H_2O_2 generation and starvation based anti-glioma therapy [95]. Similarly, inhibition of glucose transporter (e.g. Glut-1) another starvation-based strategy to mitigate glioma progression which was explored by Jego et al. To achieve this, they conjugated the Glut1 inhibitor to CD44 targeted gold nanorods to promote energy disbalance in glioma cells (i.e. reduced ATP synthesis and heat shock proteins over-expression on tumor cells) thereby playing an important role in thermo resistance. In conclusion, the development of these biomimetic nano-therapy for starvation/metabolism targeting has paved the way for multifunctional carriers to promote spatiotemporal chemotherapy in HGG.

5.4. *Reconnoitering immunological memory for glioma vaccines*

Recent years have witnessed rapid advances in the progress of therapeutic vaccines for HGG although their successful clinical translation is yet to be defined. After vaccine administration, the adjuvants and/or pre-defined tumor antigens TAA (overexpressing on tumor cells with a low expression on normal cells e.g. SOX2, Her2), TSAs [specific only for tumor cells and completely absent on healthy cells like neoantigens, viral antigens e.g. IDH1, EGFRvIII, cytomegalovirus phosphoprotein 65 (pp65)] promote the APCs maturation (mainly DCs) to induce an anti-tumor immune response against the existing tumor. Migration

of antigen-carrying DCs to the lymph nodes prime naive T-cells via engagement of T-cell receptors and co-stimulatory molecules (e.g. CD80) with MHC complex-I. Furthermore, Nan et al. and Weller et al. meticulously reviewed the glioma-specific nano vaccines such as peptide vaccine, DCs vaccine, etc. that are under pre-clinical/clinical investigation to improve anti-glioma immunotherapy [96]. However, poor tumor eradication, variable survival benefits, and lack of selective delivery of vaccine to lymphoid organs were noticed by several researchers' post-immunization. The vaccine deposition mediated T-cells buildup and apoptosis at the delivery site, disappointed priming of T-cells in distal lymph nodes (dLNs), immune tolerance, and/or rapid diffusion of peptide vaccine to peripheral blood vessels on subcutaneous immunization, etc. were noted in previous studies. Therefore, various attempts were made to co-deliver neoantigens and adjuvant [e.g. CpG, toll-like receptor-9 (TRL9) agonist] using biomimetic nanomaterials for their effective drainage to the LNs. For instance, Scheetz and co-workers designed the synthetic high-density lipoprotein (mimic natural lipoprotein) nanodiscs loaded CpG and GL261 specific neoantigens as personalized vaccines for glioma anti-PD-L1 IC blockade therapy. Their finding demonstrated the robust immunologic memory on tumor re-challenged in the contralateral hemisphere of orthotopic GL261 mice. Moreover, their genetically engineered IDH1 mutant orthotopic GBM murine model showed tumor eradication in 30 % of animals with significantly extended survival suggesting the versatility of biomimetic nanodiscs in various HGG treatments [97]. Interestingly, Liu et al. reported that compared to traditional tumor lysate, tumor-derived exosomes served as more potent antigens to load DCs. They developed tumor-derived exosomes and α-galactosylceramide (α-GalCer, glycolipid antigen) for co-delivery of TAAs-specific DCs and invariant NK cells (a special subset of T-cells having characteristics of both NK cells and T-cells) as adjuvant for improved anti-glioma immunotherapy. The exosome treatment induces strong antigen-specific activation of CTLs thereby improving immunosuppressive glioma TME suggesting their potential to enhance DCs-based vaccination for highly aggressive GBM [98]. Similarly, the natural stimulating properties of viruses were explored further to activate TLRs to induce potent *in-situ* cancer vaccination such as virus-like particles (VLPs) containing Cowpea mosaic virus (CPMV, a non-enveloped plant virus capsid without nucleic acids) exhibited strong anticancer efficacy through selective induction of cytokines (e.g. type-I IFNs) and chemokines [99]. In this regard, Kerstetter-Fogle et al. critically assessed the nanotechnology based on CPMV-VLPs against HGG. Their findings demonstrated the effective recruitment of innate/adaptive immune cells to the brain parenchyma with a significant reduction of immunosuppressive molecular signatures after in situ administration of the CPMV immunotherapy [100]. Collectively, BNP-based vaccine offers potent and localized immunotherapy for glioma treatment. However, dose-limiting toxicity, immunological toxicities, inflammation-associated toxicity (i.e. pro-inflammatory cytokines abnormalities), and comprehensive evaluation of safety profile, etc. are the burning matter for bench-to-clinic translation of these strategies.

6. NanoBioTechnology opening new avenues for immunotherapy

Past decades have witnessed the potential use of nature-inspired materials for various biomedical applications including cancer therapy. The bioinspired/ BNPs synthesized by the natural process and/or by using natural, and biocompatible components with potential anti-cancer therapy having target specificity when used with conventional nanotherapy. The ability of these bioinspired nanomaterials to mimic the natural biological features and cellular functions of the body favors their escape from the reticuloendothelial system (RES). This unique characteristic of BNPs sustainably improves the therapeutic efficacy of the payload encapsulated into/onto the nanoparticles by reducing their systemic accumulation. Consequently, their biomimetic characteristics may overcome major challenges such as poor therapeutic performance with unwanted adverse events, undesirable immune responses, and BBB penetration etc. encountered by conventional nanoparticles. Furthermore, surface modification of nanoparticles can be performed by using specific biomimetic natural resources such as cell membranes isolated from the host erythrocytes (RBC), platelets, immune cells like macrophages, NK cells, neutrophils, exosomes, cancer cells and/or their membranes, and natural proteins (e.g. albumin). Moreover, various semi-synthetic/synthetic nature-inspired biomaterials such as antibodies, proteins, peptide, and viral capsids can be used to design the BNPs. These modifications enable their biomimicking ability to resembles the biological and native cells functions in the body leading to the improve target specificity and retention in the vicinity of the target site. BNPs for cancer treatment and diagnosis has been systematically reviewed [101]. Although, the emergence of biomimetic/ bioinspired nanomaterials has further advanced the knowledge of nanotechnology for effective drug delivery. We specifically attempted to describe different immunotherapeutic strategies including BNPs used against HGGs and BM as a therapeutic paradigm in this review article (Fig. 5).

6.1. *Biomimicry using synthetic materials*

6.1.1. *Antibody-drug conjugate strategy modification for targeted biomimetic nano-delivery*

In early 20th century, Paul Ehrlich coined the concept of "*Magic Bullets*" wherein upregulated expression of tumor antigen (intra/extracellular) was targeted by specific antibody [e.g. monoclonal antibodies (mAbs)] for selective cancer cell killing. However, these antibodies alone were not sufficient to control the tumor growth/recurrence due to their sub-lethality against heterogenous and complex TME. To improve the therapeutic window a novel paradigm, known as antibody-drug conjugates (ADCs) started gaining attention in the past few years. The ADCs are specific antibody(s) linked to the molecule (e.g. cytotoxic agent) having inherent anticancer potential) for direct delivery of the payload in the vicinity of the tumor tissue. The ADCs are composed of major three components i.e. target-specific antibody, a linker, and payload like chemo-drugs, toxins, etc. The antibody conjugated

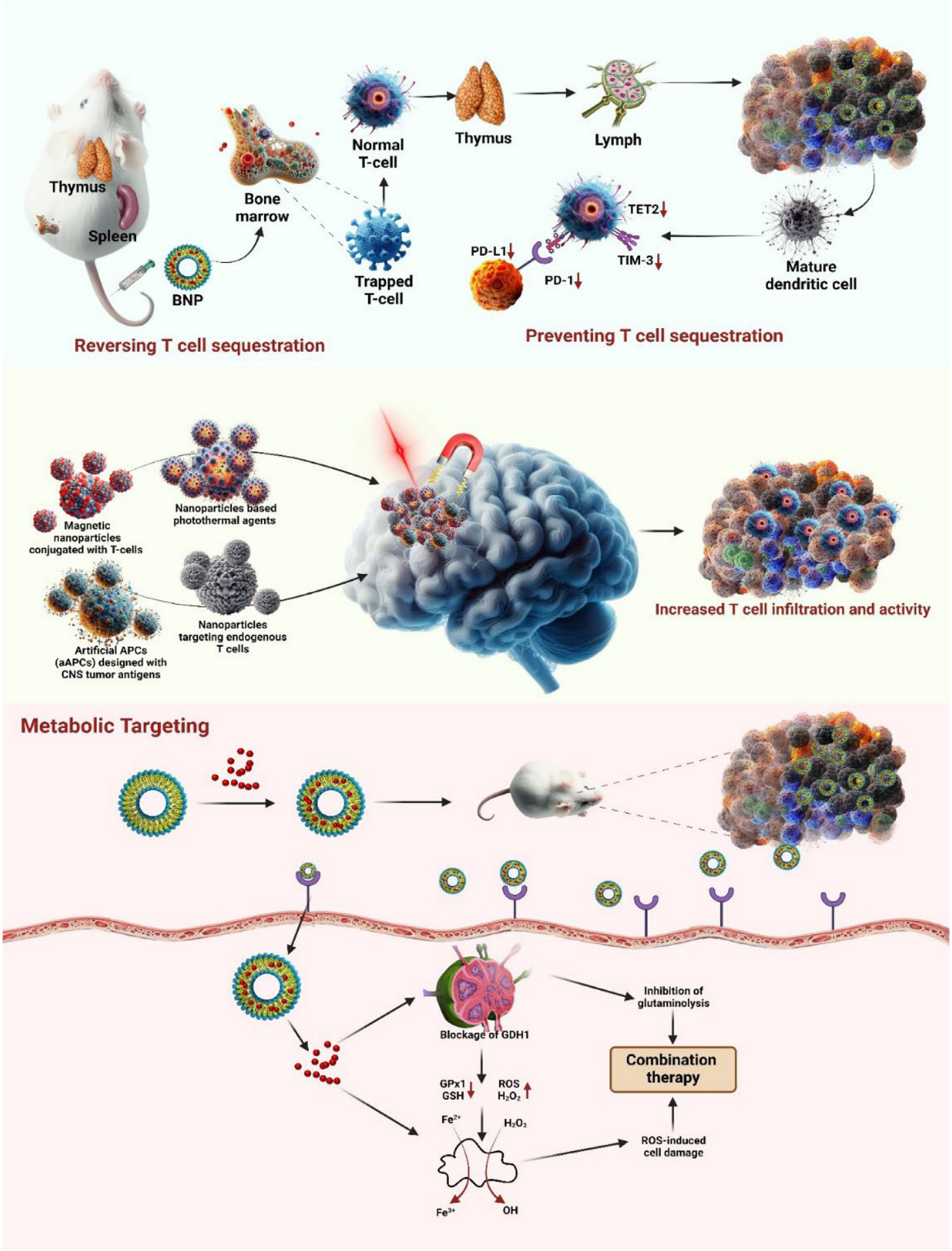

Fig. 5 – The figure illustrates a dual-pronged approach to glioma therapy using advanced biomimetic drug delivery nanoplatforms. On the left, the sequential process of antigen-presenting dendritic cells (aDCs) is depicted, showcasing the activation by glioma cell lysates. The activated DCs then encapsulate BNPs loaded with therapeutic agents, forming aDCM@BNP complexes. On the right, a parallel mechanism is shown involving natural killer (NK) cells. Here, NK cells facilitate the encapsulation of BNPs containing anti-glioma drugs within a pegylated copolymer shell. The bottom section of the figure synergistically combines these two pathways, demonstrating their collective impact on the glioma TME. This dual approach not only targets the tumor cells but also modulates the surrounding stroma, leading to an amplified therapeutic effect against glioma.

to natural toxins (e.g. *Pseudomonas aeruginosa* exotoxin A (PE), diphtheria toxin (DT) known as immunotoxins) and radioisotope as payload (e.g. iodine-125 and 131 known as radioimmuno-conjugates) to target unique HGG biomarkers such as EGFRvIII mutant (20 %−40 % overexpression in HGG), IL4 receptor, transferrin receptors, and IL13Rα2 receptors, etc. are considered the first-generation ADCs, The intracellular uptake of these ADCs-based immunotoxins occurs through receptor-mediated endocytosis followed by trafficking and subsequent degradation of toxin payload within the lysosomes, thereby eliciting inhibition of translation of the protein of interest. Likewise, radioimmunoconjugates targeting cell surface receptors (e.g. EGFR) or extracellular proteins (e.g. TNC) cause damage to cellular structures like DNA, mitochondria, etc. For instance, phase-I and II studies of human transferrin antibody conjugated to the DT (Tf-CRM107) were reported to inhibit the transferrin receptors overexpressed on the glioma cells in newly diagnosed GBM and anaplastic astrocytoma patients. The localized delivery of the ADCs using convection-enhanced delivery (CED) showed early signs of efficacy and significant tumor reductions. However, subsequent phase III studies failed to confirm its therapeutic efficacy (NCT00083447, NCT00088400). Similarly, microtubule disturbing agents i.e. ABT-414 (anti-EGFR ADCs) containing tumor specific antibody ABT-806 conjugated to monomethyl auristatin-F (MMAF) had shown significant outcomes in preclinical and clinical (phase-I and II with TMZ) studies. However, ocular toxicities were noticeable. Currently, randomized phase-II trials of ABT-414 with/without TMZ/lomustine is ongoing in recurrent EGFCR-amplified GBM patients (NCT02343406). Various studies have reported fundamental parameters influencing the delivery of ADCs for glioma patients. For instance, efficacy and BBB permeabilization properties of ADCs, the influence of drug-to-antibody ratio (DAR) on payload concentration and their diffusion with target tissue/cell selectivity, linker design, and potential of payload smartly bypassing multidrug efflux transporters (e.g. ABC transporters) to improve brain bioavailability, etc. are important to be considered in optimal design of the ADCs for HGG and BM [102,103]. Various studies have provided a brief overview of clinical trials on ADCs in patients with BM. For instance, transtuzumab conjugated to emtansine (TDMA1), transtuzumab conjugated to deruxtecan (T-DXd), sacituzumab govitecan (mAb targeting tumor-associated calcium signal transducer-2 against HER2 positive breast cancer brain metastasis), TDXd (HER2 low breast cancer brain metastasis), T-DXd (HER2 mutant non-small cell lung cancer for lungs to brain metastasis) [104]. However, the clinical success of these ADCs was not promising due to lack of biomarkers to address tumor heterogeneity (i.e. variable target antigen expression), high immunogenicity, unstable linker, limited data availability on an antibody to drug ratio required for optimal therapeutic effect, poor delivery of payload via CED, inadequate BBB penetration through systemic delivery, and acquired resistance to chemo/radiotherapy etc.

Therefore, advance strategies have been investigated to improve the ADCs-based payload delivery to HGGs and BM from other solid tumors. Nanosized carrier acting as an envelope to encapsulate therapeutic payloads are being developed having potential to improve payload solubility, decrease its degradation/rapid clearance from physiological environment, reduce off-target events, and enable their permeability across the BBB with tunable release kinetics etc. for HGGs. Furthermore, surface engineering of the nanoparticles with targeting ligands to enhance accumulation in the glioma cells/tissue has allowed for augmenting HGG management. Incidentally, several research groups have investigated the specific targeting of unique receptors (biomarkers) overexpress on glioma cells such as folate receptor, transferrin receptor, HER2, and EGFR (are structural analogue of tyrosine kinase receptors associated with epithelial, mesenchymal, and neuronal cell lineage) etc. One of the ways to smartly and precisely target these receptor(s) is by modification/functionalization of antibodies (e.g. mAb, recombinant Ab) to the surface of the nanoparticles to promote exclusive and selective uptake of payload by glioma cells instead of normal/healthy brain cells. For instance, Chou et al. reported PMLA nanoconjugates (poly-β-L-malic acid-based nanoparticles 15 nm size, −3.7 nm zeta potential) to cross the BBB for treatment of HGG (U87MG and LN229 orthotopic mouse models). The PMLA is covalently conjugated to anti-transferrin receptor mAb to target glioma vasculature and transcytosis through the BBB. Subsequently, a second antibody (cetuximab) was conjugated to facilitate the targeting of a second bio-barrier i.e. EGFR overexpressing glioma cell membrane to deliver the payload to cytoplasm using pH-sensitive endosomal disruption glutathione modification. Additionally, a morpholino antisense oligonucleotide (ANO) for catalytic α subunit of serine–threonine protein kinase (CK2α, 30 %−34 % overexpressed on glioma cells) was co-delivered to improve survival benefits (increased 2-fold compared to vehicle control) in tumor-induced animals. The dual targeting nanobioconjugates markedly suppress the expression of GSC markers (c-Myc, nestin and CD133 through inhibition of STAT3), and cross-talk and silencing of both EGFR and CK2α mediated downstream pathways (e.g. angiogenic signaling, PD-L1) together contributing to improving the efficacy of the treatment. Although, effect of this nanobioconjugates on tumor size reduction was not revealed. However, simultaneous inhibition of more than one tumor biomarker with this nanotherapy has shown significant survival improvement which could be translated in the clinic where glioma genotypes are heterogenous and hard to treat. Similarly, Guo and co-workers reported the doxorubicin encapsulated PEGylated liposomes (DOPC, DSPE, PEG-COOH) modified with novel ligand integrin-α2 (ITGA2 significantly overexpressed on glioma cells vs. normal brain cells) for selective targeting against GBM. Their findings reported that ITGA2 targeted liposomes effectively cross leaky but not the healthy BBB (IC_{50}: 0.28 μg/ml for ITGA2-liposomes vs 0.16 μg/ml free doxorubicin) through GBM induced angiogenic effects and anti-migration effects in vitro studies. Their findings revealed the potential of the novel molecular ligand ITGA2 as a therapeutic target for gliomas and encouraged advanced research to be carried out in the future [105]. Surprisingly, anti-HER2 mAb (e.g. Trastuzumab) have shown significant therapeutic potential against primary breast tumors in controlling tumor size and survival improvement however, their effectiveness

against BM from breast cancer is still controversial. Poor BBB permeability of the anti-HER2 mAb and the absence of HER2 positive BM genotype after migration from the primary breast tumor site could be responsible for its ineffectiveness. Thus, poor BBB penetration seems to be a common cause of the sub-therapeutic effect of many mAb. Therefore, different methods have been investigated to improve brain therapeutic concentration of mAb through increased BBB penetration via receptor-mediated transcytosis [e.g. insulin, transferrin, low-density lipoprotein like receptor-1 (LRP-1)] in the brain capillary endothelial cells (BCECs). For instance, Regina et al. demonstrated that a new chemical entity termed ANG1005 developed by conjugation between targeting peptide angiopep-2 (19-amino acid peptide obtained from Kunitz domain of LRP1 ligands having affinity to LRP1 and efficiently bypasses the BBB through LRP-1 mediated transcytosis) to high molecular weight anti-HER2 mAb to amplify their uptake through BBB (i.e. higher rate of brain penetration (Kin) of 1.6×10^{-3} ml/g/s after systemic administration). Subsequently, several research groups studied these new brain-penetrant peptide-mAb conjugates (e.g. ANG1005, GRN1005) to treat primary/secondary brain tumors with promising clinical activity.

Furthermore, the ADC-modified nanotherapy was extended to induce local anti-tumor immune responses such as targeting ICs for HGG treatment. For instance, Galstyan and co-workers investigated the BBB permeable nano-immunoconjugates composed of natural biopolymeric scaffold poly (β-L-malic acid) covalently modified with PD-1 and CTLA4 for IC blockade-based brain tumor therapy. The activation of local anti-tumor immune response (i.e. increased in $CD8^+$ T cells, macrophages, and NK cells with reduced Treg infiltration within the GL261 tumor area) showed significantly longer survival of tumor-induced mice compared to mice treated with ICIs monotherapy or free CTLA-4/PD-1 [106]. Thus, as evidenced by the findings presented by several other research groups, surface functionalization/modification of nanoparticles with specific antibody(s) and/or ADC targeting endogenous receptors overexpressed on the tumor cells and/or BCECs are crucial for selective HGGs and BM therapy. However, the complexity of the biological systems impacting the success of these BNPs, advanced techniques for their detailed characterizations, optimal target specificity, and their cost-effective scaling-up for mass production, etc. are still in their infancy to meet the comprehensive hit.

6.1.2. *Exploring aptamer as biomimetic targeting ligands for nano-delivery*

The size-based BBB permeability limitation of the conventional antibody targeting specific ligand (protein) on the surface of the glioma cells/BCECs/GSCs reduces their therapeutic benefits. To overcome this issue, cell-specific short-stranded oligonucleotides like RNA, and DNA were investigated by the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) technique for HGGs and BM as an alternative to antibodies. The aptamers are reported to have low immunogenicity, good temperature and pH stability, and low production/batch variability, and their desirable smaller size certainly bypasses the BBB with better penetration through tumor tissue [107]. Furthermore, Tan et al. reported the promising mechanisms of aptamers internalization into the cells to deliver therapeutic payloads [108]. Hays et al. have systematically reviewed a comprehensive list of glioma-specific aptamers and their role as a theranostic application. For instance, platelet-derived growth factor receptor β (PDGFRβ) targeting 2′-F-pyrimidine containing RNA aptamer (Gint4.T) was used by several research groups to inhibit gliomagenesis and tumor progression for GBM patients to improve survival rates and disease prognosis. Moreover, various nanoplatforms were investigated to extend the BBB targeting efficacy of aptamers for the treatment of HGGs as detailed reviewed by Hegde et al. [109]. For instance, Monaco et al. biodegradable polymeric nanoparticles [PNPs composed of poly (lactic-co-glycolic)-block-poly ethylene glycol (PLGA-b-PEG)] nano-vector-based Gint4.T aptamer targeting PDGFRβ receptors used to specifically, safely and effectively deliver the PI3K-mTOR inhibitor (Dactolisib, NVP-BEZ235 potent chemotherapeutic) loaded nanocarrier to an U87MG orthotopic glioma bearing mice model. Their findings suggested the translational potential of this aptamer-based nano-vector brain delivery for GBM therapy [110]. Attractively, Shi and co-researchers in 2019 developed the self-assembled biocompatible, biodegradable, and non-immunogenic DNA nanoparticles synthesized from four single stranded DNAs. This 3D-tetrahedral framework nucleic acid (tFNA) based DNA nanotherapy was used to deliver two PDGFRβ targeting aptamers i.e. GMT8 and Gint4.T with paclitaxel to effectively penetrate the BBB and blood-brain-tumor-barrier (BBTB) of in vitro glioma (U87MG)- and BCECs (bEnd.3 cells) co-culture model. The tFNA reported to inhibit migration, invasion, and induced apoptosis of glioma cells. Their findings revealed that dual aptamers functionalized chemo-drug loaded DNA nanoparticles to have great potential for drug delivery against GBM [111]. Similarly, EGFRvIII targeting aptamers (e.g. U2, and 2′-F-pyrimidine containing siRNA aptamer E07, etc.) have shown a high affinity for glioma cells expressing this cell membrane receptors further verifying their use in clinical settings for HGGs management. Additionally, in 2017 Tang and co-workers reported the PEGylated quantum nanodots (QDs) functionalized with EGFRvIII targeted aptamer 32 (A32) for selective accumulation within the glioma tissue (41.82 %) compared to normal brain tissue (0). Furthermore, the strong fluorescence of the A32-QDs facilitates the image-guided diagnosis, surgical debulking, and postoperative examination of GBM patients [112]. However, further mechanistic studies are required to understand the BBB penetration ability and glioma vs. non-glioma cells specificity within the brain.

6.2. *Biomimicry based on natural cell membrane*

6.2.1. *T-cell mimicking nano-delivery*

Cytotoxic immune cells (e.g. CTLs) play an important role in cancer immunotherapies. They act by releasing various cytotoxic molecules such as granzyme, and Fas ligand signal (FasL) via T-cell receptor-mediated recognition of tumor antigen on MHC complex molecules. Recently, several research groups have explored this strategy using adoptively transfer T-cells with or without IC blockade

therapy (such as anti-PD-1/PD-L1 therapy) for various cancers. However, labor-intensive expansion of T-cells, selection of appropriate tumor antigens and/or their variable expression promoted by heterogenous tumor immunoediting, and immunosuppressive molecules like TGF-β1 and/or immunosuppressive TME, etc. trigger the exhaustion of T cells. Alternatively, T-cell exhaustion could be overcome by ICIs however, immune-related side effects due to over-activated immune responses, and enormous variation in therapeutic response when tested in large sets of affected populations, etc. constraint the treatment success. Therefore, to overcome the bottlenecks of cancer immunotherapy, T-cell membrane-modified nanoparticles were developed to exhibit multifunctional activity i.e. mimicking CTLs-based biomimetic anti-tumoral activity to kill cancer cells and reversing/reducing the pro-tumoral cold TME via scavenging immunosuppressive molecules. Consequently, T-cell mimetic nano-delivery assist in escaping T-cells exhaustion and hindered the ICs interaction (i.e. interactions between cancer cells and T-cells) thereby preserving the cytotoxic potential of CTLs to control tumor progression [113]. In this regard, Kang et al.. developed the T-cell (derived from the EL4 cell line stably expressing various plasma membrane proteins similar to primary T cells) coated PLGA nanoparticles loaded with dacarbazine as an anticancer payload. The biomimetic nature of these T-cell-modified nano platforms facilitates higher accumulation at the tumor site with improved circulation time and escape of RES clearance. The adhesion-related proteins such as lymphocytes function associated adhesion molecules-1 (LAF1), PSGL-1, Mac-1 facilitate the binding of the T-cells coated nanoparticles to ICAM-1, and selectins (markers expressed on the inflamed endothelium of tumor cells) thereby inducing FasL-dependent apoptosis with ICI (i.e. PD1/PD-L1 signaling blocked) [114]. More recently, T-cell receptor-based CAR-T therapy coupled with various biomimetic nanoplatforms has been widely tested in various cancers like melanoma, lymphoma, etc. However, studies in HGGs or BM are still lagging [115,116]. Furthermore, various research groups provide insight into an image-guided strategy (e.g. magnetic, photothermal) to motivate adopted T-cell infiltration into the brain tumors for instance, magnetic nanoparticles (magnetosomes, magnetic nanoclusters) conjugated to T-cells were used in the brain tumors treatment. The magnetic field could attract brain tumor-specific T-cells modified nanoparticles thereby mitigating the limitation of poor penetration of T-cells across the BBB and/or tumor [117,118]. However, variability of endogenous tumor T-cells and anatomical barriers need to be critically evaluated to improve anti-glioma treatment efficacy. Recently, Kim et al. developed the T-celled clicked biodegradable, and biocompatible photobleaching resistant fluorescent polymer-polylactide copolymeric nanoparticles loaded with doxorubicin (BPLP-PLA with the size 155 nm, −11 mV surface charge) for orthotopic U87MG glioma mouse model through azide-alkyne cycloaddition based click chemistry conjugation. The pH-sensitive hydrazine cleavage of clickable nanoparticles with the T-cells showed on-demand release of the payload in an acidic glioma microenvironment. Furthermore, to minimize potential off-target events, mutant variant of IL13 [i.e. targeted quadruple mutant-13 (TQM-13)] CAR-T cells combined with BPLP-PLA-NP were designed to achieve controlled, targeted, and trigger-responsive monotherapy. The TQM-13 CAR-T targeting approach improves the binding affinity of T-cell clicked nanoparticles to the IL-13Rα2 receptor (α2 subtype of IL13 receptor, 75 % upregulated in GBM) compared to its α1 subtype (expressed on testis also) and shared IL13/IL4 receptor (broader body distribution) in glioblastoma induced mice with low off-organs toxicity. Their findings revealed the potential of a clickable T-cells mediated nanoparticles system to overcome the challenges treating HGGs with re-educated T-cells therapy [119].

6.2.2. *GAMs mimicking monotherapy*

Bone MDMs and yolk sac-derived microglia residing within the glioma microenvironment are collectively called GAMs and they account for ∼50 % of the total tumor mass. GAMs impair the anti-tumor immune responses by various mechanisms such as by induction and/or recruitment of Treg, decreasing the nutrient supply of lymphocytes [120]. Moreover, the unique surface biomarkers expressed on GAMs respond to TSAs resulting in increased recruitment of tumor-supporting GAMs phenotypes to the TME. For instance, C–C chemokine receptor-2, vascular cell adhesion molecule-2, and scavenger receptors-A, increase the expression level of PD-L1 that activates PD-1 IC receptor (this restricts the activity of cytotoxic T-cells and further strength the cold tumor environment of GBM) and secretory protein rich in cysteine (SPARC), etc. HGG is reported to be a cold tumor, i.e., immunosuppressive. Within glioma TME, the GAMs represent M2 phenotypes that support the tumor progression, recurrence, and/or acquired resistance to conventional modalities. In this regard, various nanoparticles were strategically designed to activate the antitumor functions of GAMs through re-education/re-polarization and/or inhibition or elimination of M2 phenotypes of GAMs into pro-inflammatory phenotypes (i.e. M1) [121,122]. For instance, Wang and co-workers developed GL261 cell membraned coated BNPs (β-cyclodextrin modified ultra-small Cu_{2-x}-Se nanoparticles of 38 nm size, and 7–8.5 mV zeta potential) to remodel immunosuppressive TME with immuno checkpoint blockade therapy (decrease PD-L1 expression) as ultrasound mediated (US) GBM treatment strategy. The developed BNPs had shown increase in M1 phenotypes by re-polarizing M2 phenotypes via US mediated Fenton-like reaction between H_2O_2 within glioma microenvironment and nanoparticles. Furthermore, encapsulation of indoximod (potent inhibitor of indolamine catalyzing conversion of tryptophan into kynurenine to promote T-cells infiltration and activation of T_{reg}) and JQ1 (tumor PD-L1 inhibitor) into BNPs contributed to remodeling of immunosuppressive microenvironment with notable immunogenic cell death effect. Furthermore, wrapping nanoparticles with tumor cell membrane improved their accumulation and retention at the target site with better targeting capability due to homologues adhesion effect. With this multifunctionality, biomimetic nanoplatform showed remarkable increments in cytotoxic T-cells and memory T-cells in the spleen representing immunological memory to prevent tumor recurrence post glioma TME remodeling. This work demonstrated the biomimetic nanotherapy

strategy of reprogramming GAMs combined with other approaches such as ICs targeting to improve the immune response for hard-to-treat cold tumors like glioblastoma [123]. Interestingly, Yin et al. developed dual membrane of macrophages (extracted from mouse Raw264.7 culture) and neutrophils (extracted from mouse bone marrow) coated rapamycin-loaded PLGA BNPs as an excellent drug carrier to treat GBM. This bioinspired strategy combines inherent inflammatory chemotaxis of neutrophils with the stimuli-homing responsiveness of macrophages to eliminate tumor cells with superior tumor targeting ability [124].

6.2.3. Other immunocytes modified biomimetic nanotherapy

NK, DCs, neutrophils, etc., are the most abundant leukocytes in the peripheral blood cells, and they play an important role in HGG immunosuppressive TME. Several research groups showed that neutrophils membrane-modified nanoparticles efficiently permeate the BBB due to their native ability to transverse anatomical barriers and deliver their therapeutic payload at the target site, i.e., inflamed glioma brain due to effective penetration through the glioma tissue [125]. Xue et al. showed that inflammatory factors (e.g. IL-8, TNF-α) were release after resection of glioma tumor mass could guide the movement of neutrophils coated cationic liposomes [100 nm size made up of soy phosphatidylcholine, cholesterol and 1,5-dioctadecyl-N-histidyl-L-glutamate ($HG2C_{18}$)] into the inflamed region of the brain and enhance brain-tumor targeting ability of these nanoparticles. The priming of these intravenously delivered biomimetic liposomes occurred by chemoattractant and subsequently, they migrate towards infiltrating tumor cells via the chemotactic gradient. Additionally, the amplification of inflammatory signals (i.e. concentrated cytokines) further release neutrophil extracellular traps (NETs) within the resected tissue which consequently activated the concomitant release of paclitaxel (anticancer payload) from liposomes and provoke cytotoxicity to inhibit glioma recurrence. Thus, the neutrophils membrane coated biomimetic nanoplatforms have shown promising results in preclinical studies however, their utility in clinic is yet to be established [126] .

DCs are the main APCs that activate T-lymphocytes by presenting TSAs on peptide-bound MHC-complex on their surface. Recently, Ma et al. developed the tumor antigen-activated DCs membrane-coated biomimetic rapamycin-loaded PLGA (aDCM-PLGA/RAPA) nanoparticles for GBM treatment. These nanoparticles increase tumor-infiltrating immune stimulating $CD8^+$ T cells with a release of cytokines such as IL6, TNF-α, IL-2 and IFN-γ, etc. (2.2 times higher than saline-treated glioma induced mice), showing enhanced antitumor efficacy. Furthermore, their tumor re-challenged study demonstrated the complete elimination of tumors, suggesting a robust memory effect elicited by this DCs-modified biomimetic delivery system [127].

NK cells are another important immune cell that can invade various tumor cells. Deng and co-workers explored the potential of NK cell membranes coated aggregation-induced emission nanodots (NK-AIEdots) for NIR guided theranostic against GBM. Nanodots could bind to highly expressed proteins on cell adhesion molecules of the BCECs, such as very late antigen-4 (VLA-4), lymphocyte functions associated with antigen-1 (LFA-1), and triggered intracellular signaling cascade. This binding further resulted in the disruption of tight junctions and recognized actin cytoskeletons to pass through intracellular BBB gaps. Moreover, the NE-AIEdots effectively cross the BBB through the paracellular pathway. After reaching the tumor site within the brain, nanodots selectively recognized U87 glioma cells through NK cells membrane receptors like DNAM-1 and NKG2D. Additionally, the high quantum yield and hyperthermia induced by nanodots showed improved skull-tumor NIR-II fluorescence (808 nm laser) guided tumor growth inhibition in the U87MG bearing orthotopic GBM mice model [128].

6.2.4. Glioma cell membrane modified biomimetic nanotherapy

Application of camouflage tumor cell membrane nanoparticles for anti-glioma drug delivery has gain tremendous attention since past few years. Homotypic targeting makes the tumor cell membrane more feasible to recognize and interact to similar cells. Biomimetic cell-membrane camouflage nanotherapeutics possess characteristics features such as antigenic diversity of source of cells of interest and their functions like improve immune response to tumor antigens after being circulated in the body. The longer circulating ability of these biomimetic cell membrane coated nanoparticles evades other immune cells like macrophages, NK cells, T-lymphocytes etc. due to their natural antagonistic interactions or act as cellular backpack [129,130]. For instance, De Pasquale and co-workers developed the homotypic membrane-membrane recognition strategy for effective nanotherapeutic delivery in GBM. The developed biomimetic nanoplatform composed of doxorubicin loaded boron nitride nanotubes (made up of mPEG-DSPE lipids, 300 nm size). These nanotubes were further coated with cell membrane extracted from U87MG cells for homotypic recognition of around 15 tumor marker proteins. These proteins were absent in normal astrocytes membranes in vitro complex systems such as multicellular fluidic models, and BBB models. Interestingly, among these 15 protein markers cadherin-2 (CDw325), neuroplastin/stromal cell derived receptor-1 (associated with the cell adhesion molecules CAMs), cadherins (Ca^{2+} dependent cell adhesion protein) were found to be major mediators of homotypic targeting of nanotubes towards tumor cells. However, the mutual cooperation of these proteins identified by proteomics analysis involved in cell-cell interaction and endocytosis were found to promote selective tumor targeting with higher uptake efficiency compared to normal astrocytes. Moreover, their work demonstrated the application of cell membrane camouflage biomimetic nanotherapeutics as a promising candidate for homotypic anti-cancer targeting [131]. Another study reported the glioma cell membrane coated lanthanide-doped BNPs for intraoperative visualization of the complete extent of glioma by NIR-IIb (1,500–1,700 nm) luminescence-based imaging for precise diagnosis and accurate surgical resection of glioma tumor mass (size $<$3 mm and depth of $>$3 mm) [132]. Furthermore, several nanoplatforms such as graphene quantum dots, stimuli-responsive nanoparticles (e.g. pH, magnetic field, US, photosensitive) were camouflaged with biomimetic cancer cell membrane as a multifunction

strategy to transverse BBB to achieve selective tumor targeting within the glioma vicinity of HGGs and BM [133,134]

6.2.5. *Platelet membrane modified biomimetic nanotherapy*

The platelets (produced by mature megakaryocytes in bone marrow) are the anucleate blood cells that play an important role in maintaining homeostasis and vascular wall development during the formation of the blood vessels. However, abnormal platelet count (>450 K/ml), known as thrombocytosis, is the hallmark of cancers. Tumor endothelium releases angiogenic molecules during the process of neoangiogenesis, leading to the recruitment of more platelets at the tumor site. Their recruitment promotes tumor progression via vascular remodeling with inflammation and supporting leaky/abnormal tumor vasculature. Also, due to their strong binding affinity with collagen-IV and blood clots, they can target damaged blood vessels at tumor sites [135]. Furthermore, circulating tumor cells in the bloodstream interact with platelets and other leukocytes, forming aggregates that bind to the tumor endothelium and subsequently enhance the distant metastasis. However, the presence of unique biomarkers like CD47 receptors on the platelets makes them a suitable candidate for coating biomaterial for drug delivery to gliomas due to their immune evasion and tumor-targeting characteristics [136]. Wu et al. designed the dual (platelet and C6 glioma cell) membranes camouflaged β-mangostin-encapsulated PLGA nanoparticles to improve the cytotoxicity, and active targeting compared to the non-modified nanoparticles. The longer blood circulation time and higher anti-proliferative effect of developed nano-delivery system in glioma bearing mice confirm their enhanced immune escape and tumor targeting effect [137]. More recently, to target the vasculogenic mimicry (induced by hypoxia and rapidly invading tumor cells) by platelet mimetic pH/redox sensitive nanogels co-loaded with doxorubicin (120 nm size, −16 mV zeta potential) were developed by Li and co-workers. The stability and extended circulation time of systemically administered nanogels were attributed to the biomimetic nature of platelets camouflaged drug delivery system in improving survival (34.5 d vs. 23 d of saline treated group) of C6 glioma bearing animals. Furthermore, improved anti-glioma effect was mediated by CD62p (P-selectin)-CD47 proteins expressed on the platelets surface that interact selectively with tumor cells and SIRPα on the macrophages protecting nanogels from immune attack [138].

6.2.6. *Erythrocytes membrane modified biomimetic nanotherapy*

The application of erythrocytes i.e. RBCs membrane as drug delivery system was first introduced in 1994. Thereafter several research groups investigated the RBCs-membrane coated nanoplatforms such as PLGA nanoparticles for delivery of anticancer drugs (e.g. doxorubicin), gene therapy (DNA, RNA), and contrast agent (e.g. indocyanine green) against various cancers including HGG [139]. For instance, Liu and co-workers demonstrated excellent biocompatibility and prolonged circulation of RBCs membrane-based nanoparticles (RNP) in U87MG GBM bearing mice model. Furthermore, to improve the c-Met (highly expressed on glioma cells and its expression is corelated with poor prognosis and treatment resistance) targeting efficiency, the RNP were decorated with SL1 aptamer connected with DSPE-PEG lipids and inserted in RBC membranes. The dual strategy (targeting and biomimetic) together showed 3 folds increased localized accumulation and selective retention of RNP nanoparticles in vitro studies and the best anti-glioma effect in vivo mice studies (significantly higher survival, i.e., 23 d vs. 15 d control) [140]. Another research group developed the RGD peptide conjugated RBCs-membrane camouflaged mesoporous silica nanoparticles for bimodal image-guided gene therapy (e.g., co-loaded ICG and miR137) [141]. Conclusively, RBCs membrane-modified nanotherapy coupled with an active targeting strategy has great potential to target HGGs. However, more detailed investigation is required to extend their application in immunoengineering.

6.3. *Biomimicry based on natural proteins*

Natural proteins such as serum albumin, transporters [e.g. low-density lipoprotein (LDL), high-density lipoprotein (HDL)], ferritin and VLPs etc. have been exclusively investigated for biomimetic/bioinspired targeted drug delivery systems due to their remarkable versatility, biocompatibility, on-demand/trigger responsive drug release capability, target specificity, synergistic effects, and improve payload stability and solubility effects etc. For instance, low molecular weight protamine-coated bovine serum albumin (BSA) nanoparticles co-loaded with hydrophobic payloads (paclitaxel and fenretinide) and functionalized with cell-penetrating peptide were designed to enhance the BBB penetration via albumin binding protein pathway targeting (e.g., SPARC, gp60) and intratumoral infiltration in an orthotopic brain GBM model. The possible therapeutic mechanisms such as apoptosis, inhibition of angiogenesis, and regulation of TME could be responsible for a significant increase in the survival rate of biomimetic BSA-NPs treated animals vs saline control group [142]. Similarly, natural transporters like HDL and LDL are widely used biomimetic components for drug delivery due to their longer circulation lives and target specificity, i.e., they possess inbuild ligands like apolipoprotein-A1 for scavenger receptor-A express on the BBB and on tumor cells. Furthermore, synthetic HDL nanodiscs coloaded with docetaxel and cytosine-phosphate guanine (CpG, an agonist for TRL9) were investigated for GBM treatment. Their small size and TRL9 targeting enable them to diffuse through dense glioma tumors and accumulate solely within the tumor area. Furthermore, the combined effect of cytotoxic docetaxel and immunogenic cell death induced by CpG promoted the phagocytosis of tumor antigen by APCs in TME. Thus, HDL biomimetic nanotherapy was found to promote anti-tumoral $CD8^+$ T cells mediated long-term immunological memory along with the cytotoxic potential to cease GBM recurrence [143,144]. Extending the application of natural transporters, another research group also investigated the synthetic LDL-nanodiscs (structural analog of HDL) for targeting low-density lipoprotein receptors (LDLRs) on glioma cells to increase specificity and accumulation of glioma cells.

More recently, exosomes (a group of extracellular lipid bilayers vesicles of 20–200 nm size and with similar structure

to standard liposomes), are naturally occurring transporters containing different proteins, nucleic acid, and lipids, etc., and are found in body fluid and/or release by response to various physiological changes/activation of cells) have been widely investigated in cancer diagnosis and prognosis applications. Like other natural transporters/proteins, engineered exosomes are being used for the treatment of HGGs and BM because of their CD47 surface marker expression promoting longer stay in the circulation and inherent BBB passing potential [145,146]. However, their primary liver and spleen accumulation limit the brain's bioavailability. Therefore, to improve the brain distribution they are coupled with different nanoplatforms. In this regard, Li et al. in 2022 developed the small interfering RNA of glutathione peroxidase-4 (siGPX4) encapsulated angiopep-2 (ANG2) peptide-modified exosomes conjugated magnetic nanoparticles for targeted delivery through LRP1 receptor-mediated transcytosis in GBM. The system is composed of a ferric oxide core and a brequinar [FDA-approved dihydroorotate dehydrogenase (DHODH a newly discovered target for ferroptosis) inhibitor] of co-loaded shell of mesoporous silica modified with CD63 antibody that further binds to the CD63 antigen on the exosome (derived from human mesenchymal stem cells) surface previously engineered with ANG2 peptide for brain targeting. The composite nanotherapy has shown triple actions, i.e., ferroptosis through the disintegration of DHODH-GPX4 ferroptosis defense axis and release of Fe^{2+} mediated through localized magnetization against GBM [147]. Another study uses the exosomes packed with miRNA21 sponge construct to downregulate oncomiR-21expression and, consequently, upregulate PDCD4, and RECK (miR21 target genes) in vitro studies (U87 and C6 glioma cells). Interestingly, the orthotopic C6 GBM-induced rat model showed significant tumor reduction efficiency compared to untreated control [148]. Collectively, these studies suggested the potential of exosomes in designing novel biomimetic composite nanotherapeutics to treat HGG and their ability to transfer the payload in the vicinity of the glioma. However, detailed studies and investigation are required from a translation perspective to understand the role and brain trafficking mechanisms of these engineered exosomes when coupled with different nanoplatforms.

Another class of natural transporters that have been investigated for HGGs are different viruses such as ADV, retrovirus (RV), adeno-associated virus (AADV) and HSV. The viral vectors have capability to carry variety of genetic material, maintain their gene expression for longer period (thanks to reverse transcriptase converting ssRNA into dsDNA for host genome integration) [149]. However, various clinical trial based on these viral vector-based targeting in GBM did not show significant improvement on survival outcomes compared to control. The limited therapeutic efficacy could be attributed to the failure of the viral vector delivering/releasing payload to the target site in the brain [150]. To overcome this issue, viral mimetic nanoparticles have been studied in the past few years [151]. For instance, spherical nucleic acid (SNA used to dysregulate miRNA, i.e., miR92b target of RNA interference) encapsulated liposomal nanoparticles conjugated with brain targeting peptides, i.e., rabies virus glycoprotein (RVG, is a neurotropic viral peptide targeting nicotinic acetylcholine receptors expressed on the BCECs, neurons, and glioma cells) and apolipoprotein-E. Their systemic administration was found to improve brain accumulation and retention of RNA interference in the syngeneic GBM mice model compared to control and liposomes without RVG-treated animals [152]. Collectively, these findings show that natural proteins and transporters' mimetic delivery strategies can work synergistically to improve the brain drug delivery to HGG; however, critical evaluation of uptake/distribution of these BNPs in healthy brain parenchyma/tissue and their neurotoxicity studies are imperative to establish the treatment specificity.

7. Dynamics of biomimetic nano-targeting for treatment sensation

The complexity of the multifunctional therapeutic approaches increased the assessment parameters like effect on absorption, distribution, metabolism, elimination and transportation (ADMETs) pathways and pharmacokinetics, plasma half-life, in vitro biocompatibility, and immune-related side effects, etc. However, given the inherited immunogenicity of the aforementioned biomimetic nano-biomaterials are of great choice for improving anti-glioma therapy. The dynamics of bioinspired strategies are clarified, and their impact on glioma treatment sensitization is highlighted in a subsequent discussion (Fig. 6).

7.1. *Nanoparticle bio-surface and biological interactions*

The biological interactions between nanoparticles and circulatory proteins lead to the formation of *"protein corona"* [153]. This effect influences the nanoparticles uptake (via selective receptor-mediated targeting), lysosomal/endosome escape, transcytosis across the BBB/penetration across the BBTB, intracellular trafficking, and exocytosis from BCECs etc. Certain studies reported that targeted synthetic nanoparticles, although they enter the tumor cells, however, they lose brain tumor targeting specificity due to alterations in their protein structure, orientation, and/or functions. The binding of nanoparticles to opsonin, such as immunoglobulins, fibrinogen, complement components (C3/C4), etc., showed rapid clearance from RES and subsequently triggered immune responses. For instance, folic-acid receptor-targeted liposomes lose their specificity by macrophage-mediated phagocytosis in non-target tissue due to enhanced endogenous IgM corona on the surface of the liposomes [154]. Similarly, Xiao et al. in their findings, reported that transferrin-targeted nanoparticles reduced their ability to target transferrin receptors in vitro studies. Furthermore, they decided to investigate the impact of this protein corona against brain drug delivery. They found that the composition of protein corona was significantly altered after BBB transcytosis (that recapitulated the in vivo brain targeting) in theirBTB model. This in vitro and in vivo discrepancy in targeting specificity was probably due to the absorption of another protein like apolipoproteins (e.g., apolipoprotein A-I) on the surface of the transferrin-targeted nanoparticles, improving their permeability across the BBB.

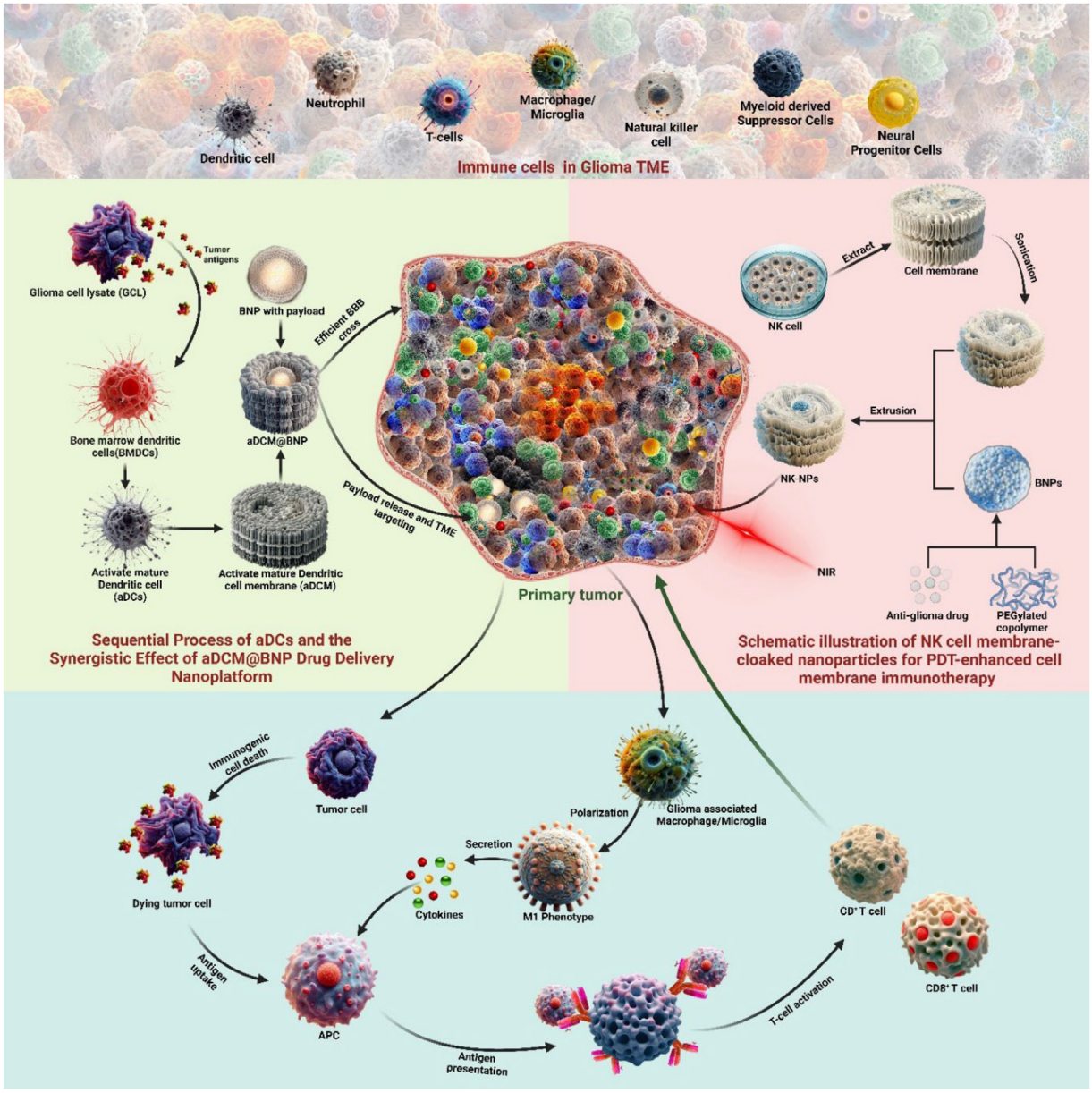

Fig. 6 – In this illustrative depiction, we observe the meticulous isolation of immunocytes, specifically neutrophils, from murine models. These cells are then ingeniously modified to encapsulate BNPs, a cutting-edge approach in targeted drug delivery. The figure highlights the strategic bio-surface modifications that enable these nanoparticles to traverse the formidable blood-brain and blood-brain-tumor barriers with remarkable specificity and selectivity. This innovative technique not only ensures the precise delivery of therapeutic agents to the glioma site but also significantly amplifies the suppression of glioma recurrence, marking a pivotal advancement in neuro-oncological therapeutics.

Collectively, these findings suggested the potential of protein corona in improving the targeting across the BBB and guiding the in vivo fate of the nanoparticle [155].

More interestingly, chimeric protein modification adopted by biomimetic/bioinspired drug delivery systems was reported to decrease the influence of biomolecular corona due to their surface occupancy. Thus, facilitating the ligand-target specificity of diseased cells' target sites with retention of their natural stealth characteristics for precision brain drug delivery [156]. In this regard, Wu and co-workers developed the angiopep-2 co-loaded exosomal membrane protein (derived from U87 cells) incorporated surface-modified biomimetic liposomes (composed of DSPE-PEG) for GBM treatment. The multifunctional exosome biomaterial was reported to manipulate protein corona effects, i.e., exosomes escape macrophage phagocytosis by protecting the targeting angiopep-2 ligand to transverse the BBB [157]. Similarly, another research group designed protein corona mediated paclitaxel loaded nano-micelles (PEG-PLA) through the surface decoration of amyloid-β protein-CN-peptide

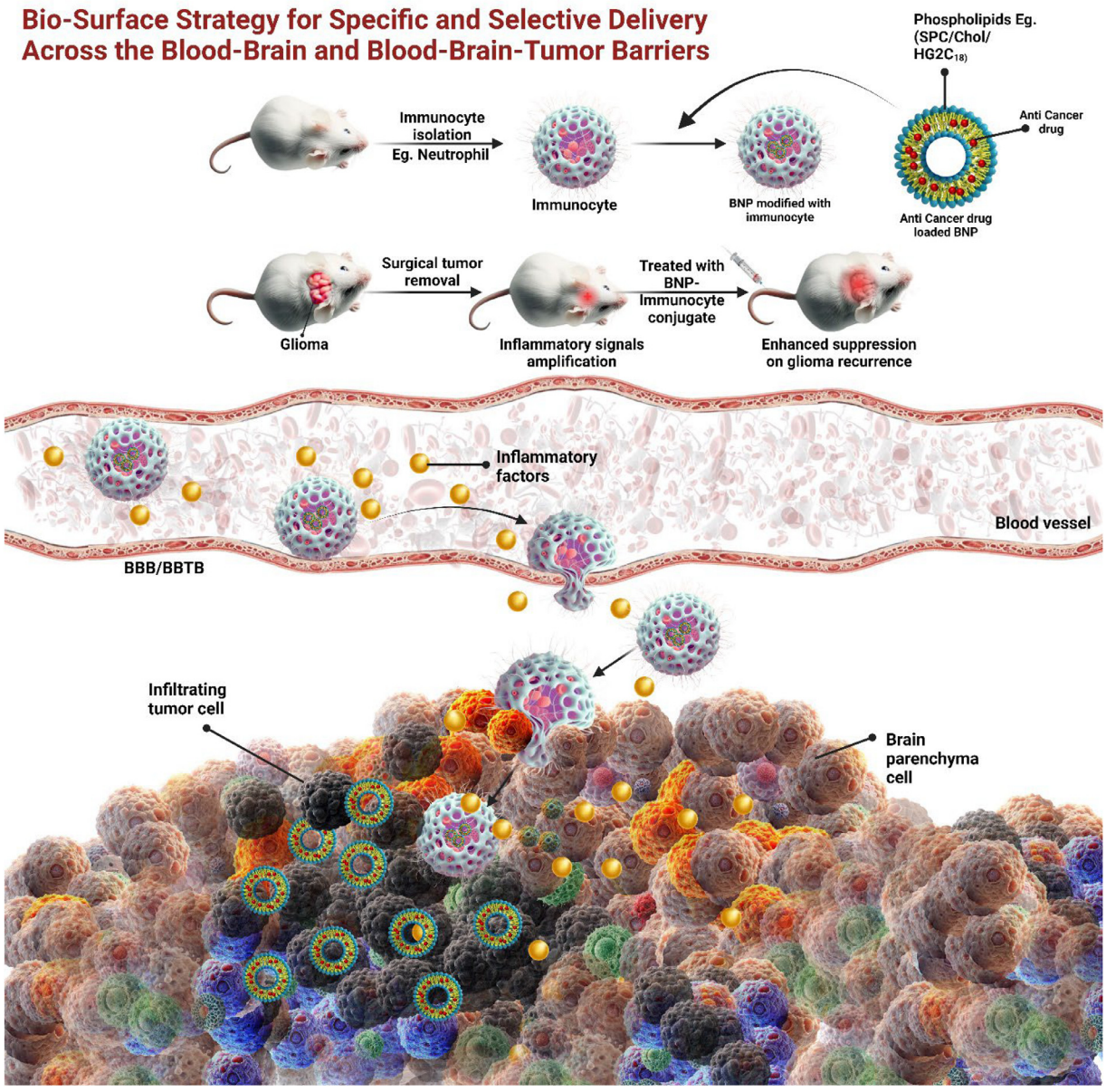

Fig. 7 – The figure presents a comprehensive overview of the therapeutic potential of BNPs in HGG immunotherapy. In the top section, it illustrates the mechanism by which these nanoparticles facilitate the release of T cells from the bone marrow, effectively modulating the TMEto prevent T cell sequestration. The middle section delves into various immunotherapeutic nanoparticles designed to target the glioma TME, resulting in enhanced T cell infiltration, and heightened immune response. Finally, the bottom section depicts the strategic metabolic targeting by the BNPs, which disrupts the tumors metabolic pathways, thereby impeding its growth and survival.

(toxic properties of $A\beta_{25-35}$ were changed by conversion of amide from the C-terminal carboxylate). The surface functionalization strategy targets the endogenous BBB and glioma cells protein, i.e., apolipoprotein-E via LDRr-LRP1r mediated endocytosis. Cooperatively, these studies showed that biomimetic materials could provide an insight into fine modulation of surface-adsorbed protein corona as a targeted nano-delivery against HGG instead of contemplating them as a complication [158].

7.2. Overcoming treatment resistance and anatomical barriers

HGGs are among the most treatment-resistant solid tumors with an elevated rate of recurrence after surgery. Different biomarkers, such as overexpression of anti-apoptotic proteins like Bcl-2, Mcl-1, Bcl-xl (Bcl-2 family protein), and phosphor-BAD, support tumor cells to acquire resistance to chemo/radiotherapy [159]. In this context, small molecule

inhibitors like ABT-263 were investigated to induce apoptosis of glioma cells. However, the therapeutic efficacy of these small molecules was hampered by the presence of BBB and BTB, drug resistance induced by Mcl-1, and treatment-related side effects like thrombocytopenia. To overcome these challenges several research groups adopted the biomimetic drug delivery strategy [160]. For instance, He et al. designed the pH-sensitive RBC-membrane decorated apolipoprotein-E peptide-modified dextran nanoparticles for co-delivery of ABT-263 and Mcl-1 inhibitor (A-1,210,477) to act synergistically to induce potent apoptosis in drug-resistant glioma cells (U87, U251, patient-derived GBM stem cells). More interestingly, their findings revealed that the RBC membrane-coated nanomedicine possesses good biocompatibility, and efficiently permeates the BBB/BTB. Furthermore, synergistic drugs co-delivery significantly suppresses tumor proliferation and improves the survival of orthotopic GBM-bearing mice without inducing noticeable adverse effects [161].

Furthermore, to improve the BBB permeability and glioma targeting specificity the hybrid membrane-based biomimetic nanotherapy is under continuous investigation. The hybrid membrane coating strategy comprised different proteins from various cell membranes (RBCs, platelets, immunocytes, GAMs, BM tumor cell membranes, etc.) to simultaneously perform complex functions such as biocompatibility, penetration across the BBB and tumor, immune evasion, prolong circulation time, improve target specificity, and improve chemotaxis, etc. as meticulously reviewed by different researchers [162]. For example, Yin et al. designed a hybrid membrane (neutrophils and macrophages) coated with rapamycin-loaded PLGA nanoparticles for the treatment of gliomas as discussed earlier. The chemotactic migration studies were done by using a neutrophil chemotactic peptide formylmethionyl-leucyl-phenylalanine (fMPL), and a potent-GAM elicitor (POSTN) expressed on GSC to evaluate the advantages of hybrid membrane coating versus individual GBM inflammatory markers. Their findings confirmed the superiority of the hybrid membrane modification strategy in the treatment of glioma due to the inherent tumor-homing ability of macrophages, and analogous inflammatory chemotaxis to neutrophils in the vicinity of inflamed TME [163]. Thus, developed biomimetic nano-delivery has multiple functions like tumor targetability and desirable BBB penetration from multiple cell types mimicking a single nanoparticle.

8. Merits of BNPs with other treatments

Nanoparticles designed with biomimetic strategies have been shown to increase therapeutic concentration of payload at the target brain site due to their ability to bypass the BBB/BTB and with high specificity to reach the brain via different mechanisms and their biomimetic complementation. Although, conventional nanoparticles like liposomes are suitable carrier for both hydrophilic and hydrophobic payloads however, their scale up and stability are the major challenges for bench to bed transition. Analogously, polymeric nanoparticles face limitations of low drug loading capacity due to high molecular weight, and safety profile of monomers release after polymer degradation is not yet well established except polymers like PLGA [164]. Similarly, inorganic and metal-based nanoparticles such as gold nanoparticles, magnetic nanoparticles use external trigger to navigate them to reach target site. However, safety profile of these nanoparticles is continuing a subject of debate and concern. On the contrary, BNPs are reported to be less immunogenic, less toxic, and confer improve targetability due to nature inspired biomimicry approach that complement with physiological conditions. Recently, evidences from clinical studies such as NCT01811992 adenoviral vector-based combination (cytotoxic and immunotherapy) therapy for HGG showed no treatment release deaths indicating the safety of viral vectors for therapeutic applications [165]. More recently, insufficient anti-tumor immune response due to dense ECM, immunosuppressive Treg infiltration and expression of IC molecules that restrict trafficking and expansion of CAR-T cells in solid tumors like GBM [166]. However, these issues could be potentially overcome by combining biomimetic nanoplatforms with CAR-T cells therapy to exploit the benefits such as high payload capacity to achieve greater homing potential of CAR-T cell membrane to tumor antigens to treat HGG. Additionally, in the subsequent section, we have explored the transition of selected biomimetic nanoplatforms from bench to bedside for treatment of HGG/BM.

8.1. *Clinical translation and future opportunities: clinical trials on BNPs*

It is undeniable that biomimetic NPs represent an outstanding strategy for overcoming numerous challenges in delivering drugs to gliomas. However, transitioning biomimetic NPs to the clinical stage is a challenging task. Currently, some of the biomimetic NPs intended for HGG and BM treatment still remain in the preclinical phase. The ongoing clinical trials on biomimetic NPs showed seven clinical trial studies on the NIH website: Five have been “completed,” one was “withdrawn,” and one was “terminated” (Table 1). Among those that have progressed to clinical trials for glioma treatment, the primary emphasis is on viral vectors. Recently, viral vector-based gene delivery has been approved for treating various diseases, including HGG and brain mets. Vectors derived from RV, alphaviruses, and ADV have also been utilized to combat human diseases. For instance, a clinical trial (NCT00589875) aimed to evaluate the safety and efficacy of aglatimagene besadenovec (AdV-tk) plus valacyclovir to newly diagnosed malignant glioma participants. Preliminary data from the Phase II study showed an improved survival rate with reduced residual disease after gross total resection [167]. Another Phase I trial (NCT01811992) was a non-randomized, dose-finding, first-in-human trial of two adenoviral vectors expressing HSV1-TK and Flt3L that was combined to target human gliomas. Administration of HSV1-TK and Flt3L with Valacyclovir appears to be both safe and feasible, suggesting that this approach merits further investigation in a phase 1b/2 clinical trial. Several phase I-III clinical trials of advanced treatments with biomimetic NPs such as adenoviral vector, glutathione, retroviral replicating vector, siBcl2L12-SNAs, Anti-EGFR mAb, Anti-TfR mAb are currently ongoing. However, the phase II/III clinical trial included

Table 1 – BNPs that have undergone clinical trials for HGG and BM.

Clinical trial number/sponsors	Biological Name	Nanoparticles (NPs)	Biomimetic System	Interventions	Phase	Recruitment Status	Targets	Outcome	Ref.
NCT00589875 Candel Therapeutics, Inc.	CAN-2409 (Adv-tk)	Viral vectors	Adenoviral vector	AdV-tk Valacyclovir Temozolomide Radiation therapy	II a	Completed	HGG	OS: 17.1 months Survival: 1 year (67 %), 2 years (35 %), 3 years (19 %)	[167]
NCT01386580 BBB-Therapeutics B.V.	2B3–101	PEGylated liposomes	Glutathione	2B3–101 (60 mg/m^2 every 4 weeks) (50 mg/m^2 every 3 weeks) Trastuzumab	I/II a	Completed	BBM from melanoma Breast cancer Recurrent HGG	HGG: 52 % stable disease (SD) and PFS 40 % for 3 months BM: 9 % PR, 48 % SD, 48 % for 3 months	[169]
NCT04105374 NRG Oncology	Toca 511 Toca FC	Viral Vectors	Retroviral replicating vector	Extended release flucytosine (Toca FC) NovoTTF-100A (optune) device Temozolomide Radiation therapy	II/III	Withdrawn	Glioblastoma Multiforme (HGG)	mOS: 12 months	[150]
NCT03020017 Northwestern University	NU-0129	Gold NPs	siBcl2L12-SNAs	NU-0129 I.V. Targeted molecular therapy	Early phase I	Completed	Recurrent HGG Gliosarcoma (GS)	NU-0129 can cross the BBB and accumulate in glioma cells	[170]
NCT03603379 University Hospital, Basel, Switzerland	C225-ILs-Dox	DSPE-PEGylated liposomes	Anti-EGFR mAb (Cetuximab)	C225-ILs- dox I.V. (anti-EGFR ILs-dox)	I	Completed	EGFR-positive GBM Relapsed or Refractory HGG	median PFS (Mpfs): 15 months mOS: 8 months	[171]
NCT01811992 University of Michigan Rogel Cancer Center	Ad-hCMV-TK and Ad-hCMV-Flt3L	Viral vectors	Adenoviral vectors	Administered with valacyclovir	I	Completed	HGG	mOS: 21.3 months mPFS: 9.9 months	[172]
NCT02340156 SynerGene Therapeutics, Inc.	SGT-53	Cationic liposomes (DOTAP/DOPE)	Anti-TfR mAb	Temozolomide Targeted P53 gene therapy (SGT-53)	II	Terminated	Recurrent HGG	NA	[168]

patients receiving tumor resection followed by vocimagene amiretrorepvec (Toca 511) with flucytosine (Toca FC) vs. standard of care (SOC) is withdrawn because it did not improve the OS and efficacy. Unfortunately, another clinical trial of phase II was terminated due to the ligand failure of SGT-53 with Anti-TfR mAb [168].

BNPs are facing challenges in reaching FDA approval despite their potential to treat brain tumors. One of the main reasons is their complex nature, which can lead to issues with reproducibility, stability, and safety. Till now, only a few BNPs have progressed through clinical trials, with many still in the preclinical phase or they are facing trial termination or withdrawal. The biomimetic NPs used for HGG and BM clinical trials are summarized in Table 1.

9. Challenges of biomimetic/bioinspired nano-delivery

The excellent biocompatibility, immune evasion, prolonged circulation, better/homologous targeting ability, and minimal adverse effects enable biomimetic modification strategies against HGGs and BM. Moreover, presence of selectively permeable BBB is one of the greatest challenges in the management of HGG and BM. Unlike other tumors which often caused leaky barrier due to rerouting of abnormally growing vasculature, the highly diffuse infiltrating nature of HGG into surrounding healthy brain parenchyma caused heterogeneously disrupted BBB. Although clinical studies on gliomas displayed heterogeneous drug permeability due to BTB leakiness, advanced imaging by positron emission tomography (PET) and contrast-enhanced MRI showed areas with vasogenic edema and intact BBB. Furthermore, when BBB integrity disruption was assessed by dynamic contrast, enhanced MRI revealed BBB heterogeneity in patients with BM [173]. Thus, the structural and functional heterogeneity of BBB and BTB may allow better delivery of active across this barrier to treat HGG/BM. Interestingly, traditional nanoparticles showed only 0.7% administered drug dose delivered to the brain due to increasing heterogeneity of the BBB/BTB. Additionally, the multidrug resistance efflux transporters express on BBB further promote removal of therapeutic molecules in the brain thereby leading to sub-therapeutic brain bioavailability of targeted agent. Despite promising advancements in preclinical models of HGG, few technologies have progressed to clinical evaluation [174]. This gap highlights an urgent need to translate these innovative approaches into clinical practice to meet the pressing clinical demand. In this regard, the nature inspired biomimetic drug delivery strategies integrated with nanotechnology and immunotherapy has been shown to improve brain uptake through natural ligand-receptor interactions, absorptive transcytosis across the BBB through electrostatic interactions, and micropinocytosis. Although, further research and enhancement are necessary to optimize clinical utility of these biomimetic nanoplatforms that could improve brain bioavailability and radicalize the treatment of HGG and BM. The biological complexity, large-scale production of cell membranes that are free from contaminants/denaturation of desired membrane proteins, and batch-to-batch variation, etc., are the challenges for clinical translation of these different cell membrane camouflaged biomimetic delivery systems [175]. Isolation of the most potent proteins from these bioinspired membranes to avoid unwanted immune responses is imperative for improving the immune system recalibration of these BNPs. More advanced bio-molecular techniques, such as proteomics, RNA/DNA sequencing, etc., are required to understand the mechanisms and influencing factors for effective glioma targeting. Additionally, biosafety assessment, quality control for the mass production process, storage, and transport stability alteration due to changes in size, shape, physical/chemical interactions between different components in clinically relevant time frames, etc. need to be taken into consideration for designing biomimetic monotherapy. However, relevant research on these concerns/challenges is still in its infancy. Nevertheless, biological effectiveness and toxicological safety evaluation are important to be considered to improve the performance of these biomimetic/bioinspired technologies to lay a solid foundation for translation success.

9.1. *Conclusion and opportunities*

Nanoparticles based on bioinspired mimicry have tremendous potential in the field of immunotherapy against hard-to-treat cancers like HGGs and BM. The membrane camouflaging with immunocytes, cancer cells, RBCs, platelets, and/ or hybrid membrane modifications boost the anti-tumor immune response by activating the body's natural defense system or immune system reprogramming. Additionally, they may benefit from homotypic recognition, ease of permeation across the BBB, longer plasma half-life, escape of RES clearance, enhanced brain retention with specific/selective biomarker targeting, and generating immunological memory to produce bio-nano immunotherapeutic for future nano-vaccines development. However, as discussed in the challenges for biomimetic nanotherapy section, advanced methods should be devised for their GMP manufacturing and scaling up without affecting their therapeutic effectiveness. The novel biomarkers like aptamer, protein, peptide, ADCs, etc., could be integrated with a biomimetic strategy to achieve multifunctional targeted nanomedicine in the treatment of deadly HGGs and BM. More importantly, with the advances of proteomics, RNA/DNA sequencing, and nanotechnology, the research should be emphasized on bench-to-clinic translation of BNPs with safety and efficacy.

Conflicts of interest

All the authors declared that the investigation was conducted in the absence of any financial/commercial interest that could be constructed as a potential conflict.

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