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Stemness, invasion, and immunosuppression modulation in recurrent glioblastoma using nanotherapy

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Abstract

The recurrent nature of glioblastoma negatively impacts conventional treatment strategies leading to a growing need for nanomedicine. Nanotherapeutics, an approach designed to deliver drugs to specific sites, is experiencing rapid growth and gaining immense popularity. Having potential in reaching the hard-to-reach disease sites, this field has the potential to show high efficacy in combatting glioblastoma progression. The presence of glioblastoma stem cells (GSCs) is a major factor behind the poor prognosis of glioblastoma multiforme (GBM). Stemness potential, heterogeneity, and self-renewal capacity, are some of the properties that make GSCs invade across the distant regions of the brain. Despite advances in medical technology and MRI-guided maximal surgical resection, not all GSCs residing in the brain can be removed, leading to recurrent disease. The aggressiveness of GBM is often correlated with immune suppression, where the T-cells are unable to infiltrate the cancer initiating GSCs. Standard of care therapies, including surgery and chemotherapy in combination with radiation therapy, have failed to tackle all the challenges of the GSCs, making it increasingly important for researchers to develop strategies to tackle their growth and proliferation and reduce the recurrence of GBM. Here, we will focus on the advancements in the field of nanomedicine that has the potential to show positive impact in managing glioblastoma tumor microenvironment.

This article is categorized under:

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KEYWORDS

chemotherapy, drug-delivery, glioblastoma, immune suppression, nanomedicine, proliferation, recurrence, resistance

1 | INTRODUCTION

Over the last decade, the field of medicine for brain tumor management has experienced numerous advances. Some of these advancements are based on operational techniques whereas some are based on therapeutic approaches. It took years to acquire knowledge about nanomaterial-based drug delivery approaches against numerous chronic diseases that have been affecting human health continuously. Several clinical opportunities and the persuasive nature of researchers made the breakthrough of nanotechnology possible. Therapeutic strategies against some of the deadly diseases like diabetes, cancer, and neurological disorders still have a vast room for improvement. Specifically, malignancies that belong to the Central Nervous System (CNS), need to be among the top in the priority list for investigating alternative therapeutic strategies. One such cancer that has devastating outcome is glioblastoma. Glioblastoma multiforme (GBM), a dynamic and multimodal, grade IV astrocytoma, is one of the most lethal and aggressive brain cancer types (Pollard et al., 2009). Standard of care including maximal surgical resection, concomitant radiation therapy, and chemotherapy often fail to curtail the growth and proliferation of the disease (Bell et al., 2023; Stathias et al., 2018). Most common standard of care treatments for de novo GBM involves gross total surgical resection of the tumor mass, radiotherapy, and concurrent Temozolomide (TMZ) chemotherapy (Stupp et al., 2005). Despite having an improved therapeutic availability for GBM, majority of the patients experience disease recurrence in less than 6–8 months' time (Mallick et al., 2016). Currently, the best available chemotherapy for GBM has been TMZ, an alkylating agent that is known to intercalate into the cellular DNA and cause DNA damage (Ortiz et al., 2021). Despite the trimodal therapeutic strategy, patients diagnosed with GBM have a median survival of 14.6 months, making life expectancy extremely low. In addition, brain being the main coordinator of all our motor and sensory functions, it is evident that GBM patients experience a poor quality of life while they are under radiation and/or chemotherapy.

Sitting at the apex of the dynamic network of glioblastoma is a cell population known as glioblastoma stem cells (GSCs) that is resistant to almost any treatment. GSCs are phenotypically heterogeneous possessing self-renewal capacity and multilineage differentiation (Slepak et al., 2023; Thakur et al., 2022). Stemness potential of the GSCs is elevated due to the high alterations in genomic stability. The GSCs can be traced across different hemispheres of the brain which in turn makes eradicating this cell population challenging. In glioblastoma, the tumorigenic potential is closely tied to differentiation and dedifferentiation of GSCs, which may be influenced by epigenetic alterations. Another aspect is the relapse of glioblastoma. Recurrence is almost inevitable in case of patients who have already been diagnosed with GBM once and are under a treatment regimen. The residual cells that reside in the distant regions of the brain, eventually lead to formation of a recurrent tumor mass in the brain. Studies show that upon relapse, there is a dismal chance of survival (Figure 1).

Drug delivery systems based on nanotherapeutic approaches offer immense capability to address the unmet medical needs for GBM, however, these systems must overcome some specific challenges prior to reaching the target site in the brain (Figure 1). These challenges include crossing the blood–brain barrier (BBB), achieving cell-specific targeting, delivering chemotherapy drugs, and inducing apoptosis. Another challenge that nanotechnology must overcome is the infiltration of the immune cells. Glioblastoma tumor microenvironment is known for showing immune suppression which makes the GSCs to evade the immune system and exacerbates the tumor growth (Dhinakaran et al., 2022; Pinton et al., 2019). While the physicochemical properties of nanoparticles impact its circulation in the human system, proper designing of the nano-formulation with respect to the demand of the disease will help tackle this limitation (Kolishetti et al., 2010; Marrache & Dhar, 2012; Marrache, Kumar Pathak, et al., 2013).

Here we discuss the role of the cancer initiating GSCs in progression of the disease and examine how targeting this cell population can lead to significant improvements in patients diagnosed with GBM. Our focus will be on why nanomedicine is the effective method to destroy the residual GSCs which survive postsurgical resection. We will also highlight some recently published nanomedicine approaches which have the potential to cross the BBB, reach the tumor site to deliver the encapsulated payload into target cells.

2 | MODULATION OF IMMUNE SUPPRESSION IN GLIOBLASTOMA

The immune system plays a pivotal role in the failure of therapeutic approaches for GBM. While scientists across the world are developing novel targeting therapies, the tumor microenvironment of GBM is continuously adapting ways to evade such therapies. Immunotherapy is effective against multiple other cancers including hematological cancers and

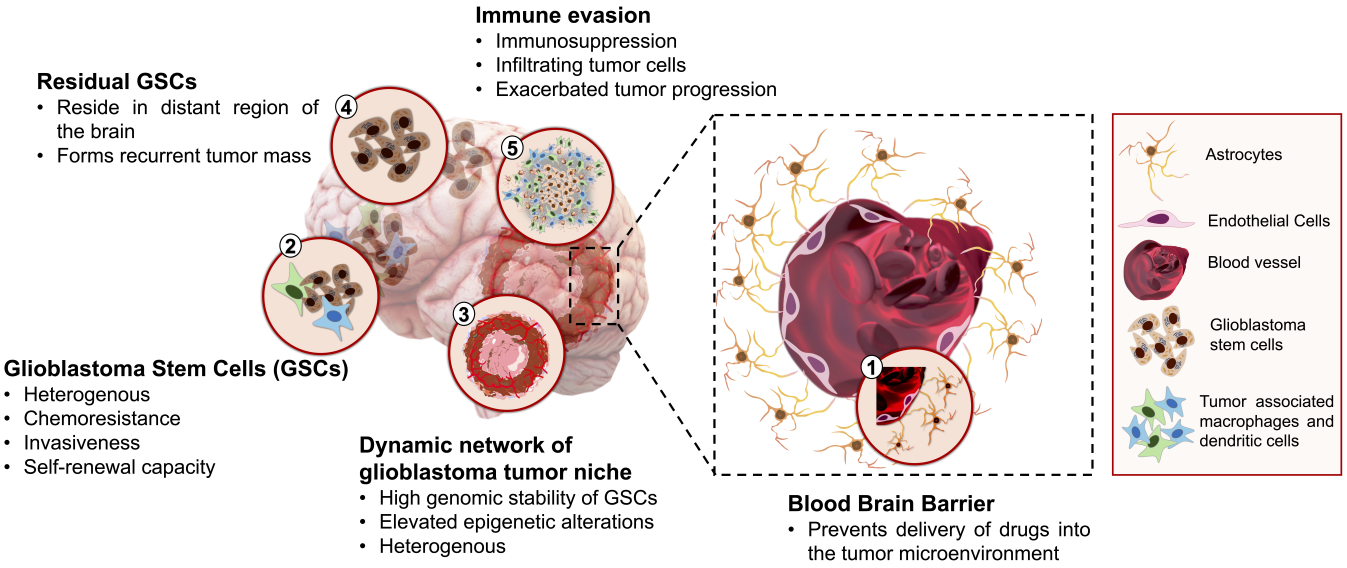

FIGURE 1 Challenges faced by glioblastoma treatment: Illustration revealing 5 major factors that hinder specific targeting of the glioblastoma. These factors often lead to the failure of the available therapeutics against glioblastoma, making tumor recurrence inevitable. 1. Blood-brain barrier (BBB), being one of the most impermeable physiological barriers, makes glioblastoma hard-to-reach for a majority of the therapeutic strategies. Further challenges are imposed by factors 2 and 3, where, presence of a highly invasive and migratory glioblastoma stem cell (GSC) population makes the glioblastoma tumor niche a dynamic network. 4. Being highly invasive and migratory, these cells travel to distant regions of the brain that leads to formation of a residual GSC population which can potentially form recurrent tumor. 5. Finally, immune suppression plays a crucial role in poor prognosis that leads to devastating outcomes in glioblastoma.

various solid cancers, but it is yet to prove successful against GBM. Failure of immunotherapy against GBM is a result of immunosuppression imposed by the GBM tumor niche, making the host's immune system vulnerable against the disease. In this context, the molecular crosstalk between the glioblastoma tumor microenvironment and immune surveillance plays a critical role in predicting the fate of the tumor progression. Whether the tumor will show poor prognosis or not depends on this molecular crosstalk as multiple factors in the tumor microenvironment lead to evasion of host immune response. (Figure 2) (Ayasoufi et al., 2020; Chongsathidkiet et al., 2018; Gustafson et al., 2010).

2.1 | Targeting the critical crosstalk between immune surveillance and glioblastoma through immunotherapy

Tumor cells in glioblastoma evade the body's immune surveillance by downregulating the expression of the major histocompatibility complex (MHC) on the cell surface. Impaired T-cell proliferation and reduced effector response while increasing hypoxia helps the tumor cells avoid antigen presentation and evade immune attack (Hao et al., 2002; Topalian et al., 2015). In addition to MHC downregulation, presence of tumor growth factors, interleukins, and prostaglandins have immunomodulatory effect on the GBM tumor niche. Macrophages and regulatory T (Treg) cells also play an important role in suppressing the immune attacks. This challenge was circumvented recently by designing a polymeric delivery vehicle to carry an immune-oncology drug to glioblastoma across the BBB (Galstyan et al., 2019). The immune-oncology drug leverages nanotechnology and immunotherapy as checkpoint inhibitors against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death-1 (PD-1). Poly(β-L-malic acid) (PMLA), a neutral polymer, was covalently conjugated to antibodies of CTLA-4 and PD-1 to deliver these impermeable antibodies across the BBB. The transferrin-receptors (TfRs) on the endothelial cells of the brain capillary mediates the entry of the PMLA-drug conjugate across the BBB (Bourassa et al., 2019). In addition to the PMLA backbone, the nanodrug comprised of mPEG5000, TfR antibody, and a trileucine moiety. Each component served a specific purpose. It was observed that, when mice were treated with this polymeric nano-formulation, there was an infiltration of immune cells with tumor-killing properties (Galstyan et al., 2019).

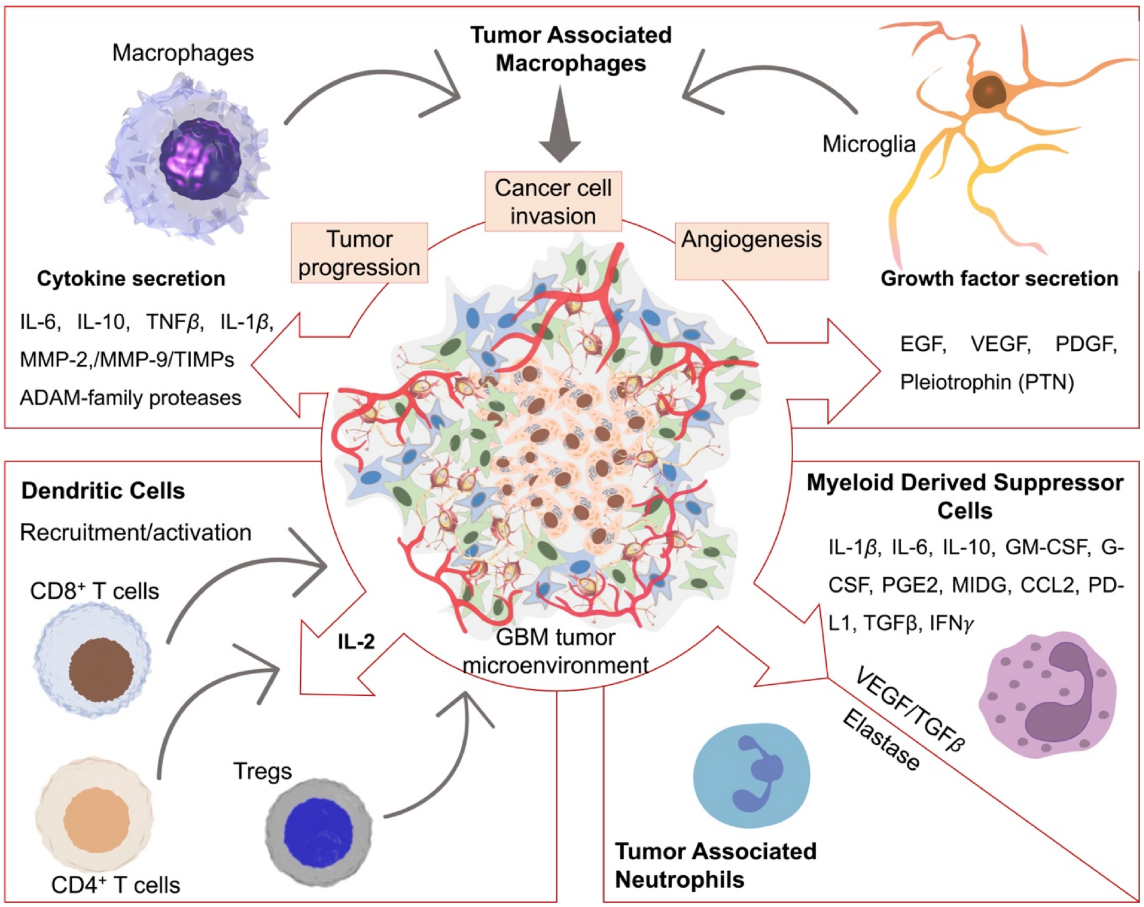

FIGURE 2 Schematic illustration showing the molecular crosstalk between the host immune system and the glioblastoma tumor niche. In the above illustration, interleukin is designated as IL; tumor necrosis factor as TNF, matric metalloprotease as MMP, epidermal growth factor as EGF, vascular epidermal growth factor as VEGF, platelet derived growth factor as PDGF.

Another aspect of immunotherapy involves the use of bacteria to treat cancers. It is evident that there are multiple ways by which bacteria can be transported across the BBB (Coureuil et al., 2017). This advantage was utilized recently to investigate whether loading bacteria with glucose polymer and photosensitizable-silicon nanoparticles can alter the immune suppression in GBM (Le Guennec et al., 2020; Sun et al., 2022). This study in an orthotopic GBM mouse model demonstrated that the bacteria-loaded silicon nanoparticle can evade the BBB and target GBM tumor tissue. The study revealed that in presence of laser irradiation at 808 nm, photothermal effect led to destruction of the bacterial cells as well as the tumor cells in the tumor microenvironment. The mice with glioblastoma also showed anti-tumor immune response against tumor-associated antigens, displaying the therapeutic potential of the nanoplatform. Rindopepimut®, an immunotherapeutic drug which is also known as CDX-110, a peptide vaccine that attacks the epidermal growth factor receptor variant III (EGFRvIII) (Elsamadicy et al., 2017) which has been used in a few clinical trials, ACTIVATE (Sampson et al., 2010), ACT II (Sampson et al., 2011), and ACT III (Schuster et al., 2015). Across these clinical trial studies, Rindopepimut® prescribed either alone or in combination with adjuvant TMZ, revealed ~15 months of progression-free survival post tumor diagnosis (Weller et al., 2017). With positive results from clinical trials utilizing the benefits of Rindopepimut® in combination with other chemotherapeutics, the potential for its use as targeted immunotherapy increased for GBM (Reardon et al., 2020).

A plethora of factors including secretion of numerous immunosuppressive factors and decreased MHC expression, GBM tumor microenvironment evades the immune response and tumor progression becomes inevitable. Dendritic cells, immune checkpoint inhibitors, and autologous cell based therapies can channel this exhaustion into activation and make the otherwise resistant cells sensitive toward the treatment modalities (Figure 3a) (Lim et al., 2018). Immunotherapy based treatments work by re-activating the immune cells, inducing immune cell infiltration, and sensitizing the cancer cells. Thereby leading to a potentially improved therapeutic outcome (Figure 3a). To date,

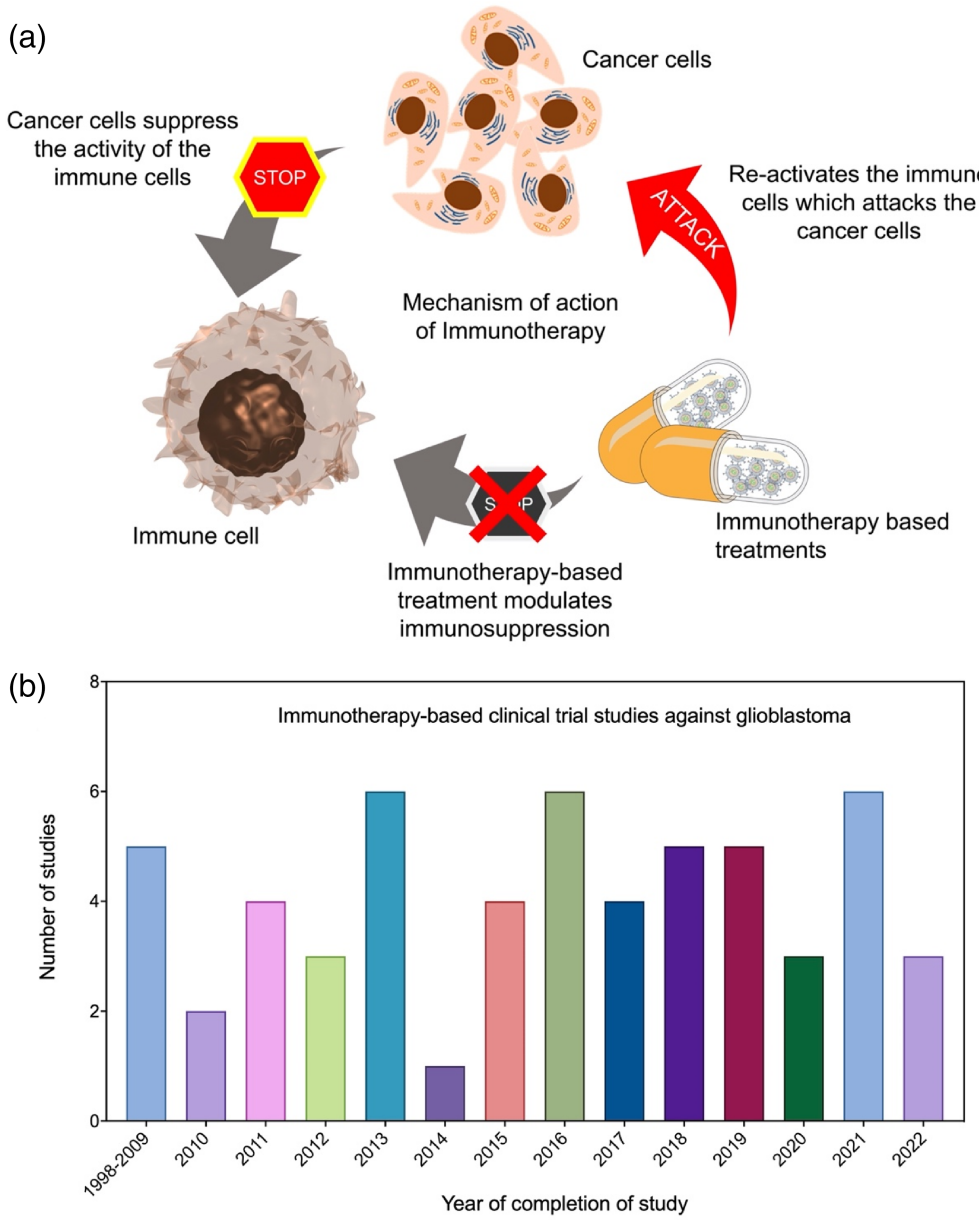

FIGURE 3 Immunotherapy against glioblastoma. (a) illustration showing the mechanism of action of immunotherapy-based treatment modalities on glioblastoma tumor cells. (b) Graph showing the number of completed studies based on immunotherapy against glioblastoma during years 1998–2022. The data were obtained using Clinicaltrials.gov.

>50 immunotherapeutic clinical trial studies have been completed against GBM (Figure 3b). Specifically, clinical studies for glioblastoma utilize autologous cell-based therapies and dendritic cell delivery platforms. In a Phase I clinical trial (NCT01588769), a cell-based immunotherapy, ALECSAT, was administered to patients suffering from GBM to investigate its efficacy in reducing tumor progression. ALECSAT, administered intravenously, took the advantage of the host's natural killer cells and cytotoxic T cells to target GBM tumor progression. Another Phase I study envisaged vaccination for 4.5 months with dendritic cell loaded in GSCs (DENDR-STEM) to assess the safety, immunosuppressive modulation, progression free survival, and quality of life of GBM patients (NCT02820584). Despite completion of these studies, there still are no results posted. ICT-107, which was investigated in a Phase 2 trial to check the improvement in overall survival of GBM patients using autologous dendritic cell based immunogenic peptides (NCT01280552), showed some promising results. The primary outcomes from the study revealed an increased median survival from 16.7 to 18.3 months in the ICT-107 treated group compared to placebo. Secondary outcomes revealed an increased time of progression free survival from 9 to 11.2 months. A total of 10% of the participants showed risk of seizures, which was 16.28% in the placebo group. Further, most recently, a Phase 1 trial (NCT00626483) revealed the efficacy of Basiliximab

in treating newly diagnosed GBM patients who are being treated with targeted immunotherapy and have a history of having TMZ-caused lymphopenia (Mitchell et al., 2011).

2.2 | Limitations of immunotherapy for glioblastoma stem cell targeting

Current immunotherapies encounter multiple challenges making them ineffective for delaying/stopping GBM tumor recurrence. The major challenge that brain accumulating immunotherapy encounters is the presence of the impermeable BBB which hinders the crossing of immunogenic interventions into the brain. Cellular heterogeneity is another significant challenge faced by immunotherapy. Heterogeneity in GSCs leads to diverse immunogenic characteristics and differential response of the cells toward interventions, deeming the therapeutics inefficient. Among other limitations, STAT3 mediated immunosuppression across the brain parenchyma, transforming growth factor-β (TGF-β) and interleukin (IL-10) secretion, enhanced expression of programmed death-ligand 1 (PD-L1) with concurrent recruitment of T_{reg} cells, and formation of myeloid derived suppressor cells (MDSCs) are at the forefront which makes failure of current immunotherapeutic approaches inevitable (Finocchiaro & Pellegatta, 2016). Despite undergoing clinical trials, translatability for these approaches remains questionable. Thus, to achieve successful targeting of GSCs to enhance the potential of immunotherapy against GBM, innovative strategies for delivering immunogenic agents at the GSCs are necessary.

Nanotherapeutic approaches, due to the ability to maximize the bioavailability of therapeutic payloads at the target site can serve as a way to modulate the immunosuppressive niche (Marrache et al., 2012; Marrache, Tundup, et al., 2013). This necessitates the development of state-of-art delivery vehicles which enhance the treatment efficacy. Nanotechnology based approaches will not only activate the immune response by delivering the immunomodulators more precisely but also minimize the requirement for multiple doses to achieve maximum therapeutic efficacy (Jackson et al., 2019; Kolb et al., 2020; Kudruk et al., 2024; Wen, Umeano, et al., 2016). Hydrogel-based nanotherapeutics proved beneficial for the sustained release of drugs at the tumor site evading the BBB, reducing off-target effects, and improving anti-tumor immunity (Kudruk et al., 2024; F. Wang et al., 2023). Hydrogel-mediated nanodrug delivery reduces the initialization time by shortening the window between maximal surgical resection and the local release of therapeutics. Recently, Artzi lab was successful in synthesizing a dendrimer with polypeptide modification for delivering a stimulator of interferon genes (STING), leading to an infiltration of cytotoxic T cells and antitumor immunity response against Melanoma. This technique if designed with optimum BBB penetrating capacities, can be helpful as immunotherapy with translational properties (Dosta et al., 2021; Kudruk et al., 2024).

3 | TREATING RECURRENT GLIOBLASTOMA

Timeline of glioblastoma tumor recurrence may vary depending on the patient; however, it is almost inevitable. Hindering recurrence of the disease is thus the major problem that sits at the apex of the pyramid of challenges faced by alternative therapeutic modalities for GBM. With a high recurrence rate, management of the disease progression continues to be an obstacle for development of alternative therapeutic approaches and treatment. Focusing on the discovery of improved therapeutic strategies and tumor cell targeting has become a necessity. When designed appropriately, nanotherapeutic strategies can be beneficial in showing enhanced permeability across the BBB, capability to diffuse across both the cerebral hemispheres along with specific cell targeting ability (Marrache et al., 2014; Surnar et al., 2018; Ashokan et al., 2024) toward cancer initiating cells. This leads to a possibility where translational research can provide a therapeutically effective treatment opportunity for recurrent GBM. The highly heterogeneous nature of GBM recurrence and its patient-to-patient variations led to a failure for most of the current therapeutic platforms. The conventional therapeutic platform revealed reduction in tumor aggressiveness observed only at the initial stages but showed no significant alteration in the fate of GBM recurrence. Surgery to remove tumors aims to reduce symptoms and increase survival rate. Radiotherapy can delay progression of the tumor and stabilize the disease. Chemotherapy used alone or in conjunction with radiotherapy delays tumor progression. Although important to the prolonged survival of patients, these treatments can affect a patient's health related quality of life (HRQoL). Surgery results in a reduction of tumor mass, but HRQoL can reduce if surrounding healthy tissue becomes damaged and neurological and cognitive issues occur (Taphoorn et al., 2005). There are also many possible negative effects of radiotherapy that can decrease the HRQoL of patients. Immediate effects include fatigue or intracranial pressure. In addition, decline in cognitive

functioning can be a long-term effect (Aaronson et al., 2011; Taphoorn et al., 2007). Adverse effects of chemotherapy include fatigue, nausea, hair loss, and anemia. Acknowledging the limitations of the conventional therapeutic approaches, our lab conceptualized and synthesized a delocalized lipophilic cation funtionalized nanoplatform to deliver hydrophobic drug molecules across the BBB at the specific target site (Marrache et al., 2014; Marrache & Dhar, 2012; Ashokan et al., 2024). This approach has immense potential in reaching the most distantly located glioblastoma cells in the brain, alter their respiratory and proliferative potential, and lead them toward undergoing apoptosis. This platform also retains immense translatable potential as it represented no toxicity in higher order animals like canines (Feldhaeusser et al., 2015). To date, search results from NIH, National Library of Medicine show that a total of 846 studies based on recurrent glioblastoma are listed under clinical trials. Out of the 846 studies, 414 (~49%) studies have a 'complete' status, and 123 (~14.5%) studies are recruiting subjects for the studies. All the completed studies are still at the "investigational" stage which means the interventions have not yet been approved by FDA. Some of these clinical trial studies use bevacizumab, which received FDA approval for recurrent glioblastoma in December 2017, in addition to other chemotherapeutic agents to verify their potential efficacy. The remaining 309 studies (~36.5%) are either withdrawn, terminated, or suspended (Figure 4). Majority (~44%) of 'completed' studies are either Phase 1 or Phase 2 studies, only ~2% of the completed studies were Phase 3 and only 3 of the studies have results which passed the quality assessment. Researchers in NCT00777153 show the efficacy of using Cediranib in combination with an FDA

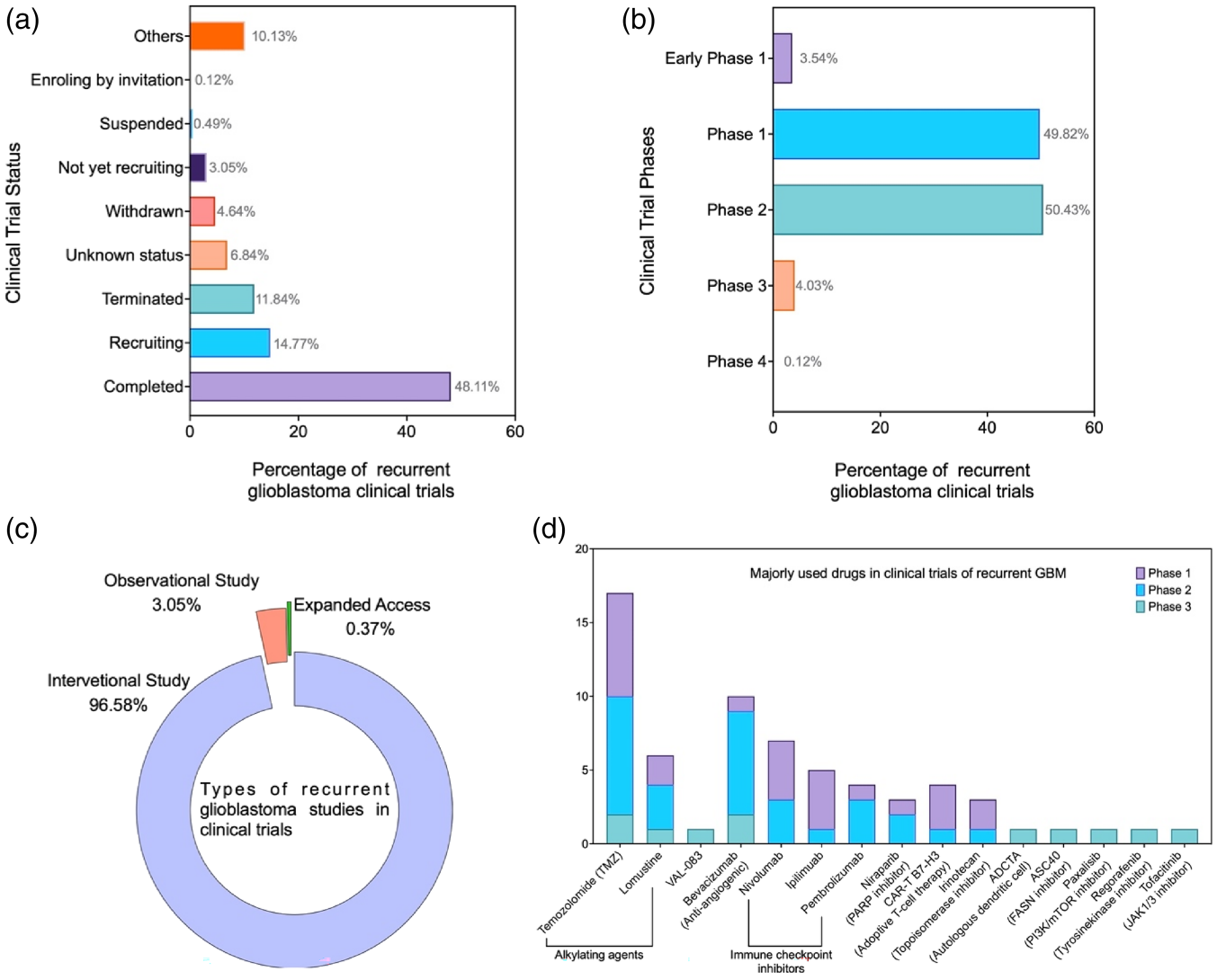

FIGURE 4 Treatments against recurrent glioblastoma multiforme in clinical trials. (a) Clinical trial status with respect to the percentage of recurrent glioblastoma clinical trials. (b) Clinical trial phases with respect to percentage of recurrent glioblastoma clinical trials (c) types of recurrent glioblastoma studies in clinical trials based on the study type (d) most represented drug groups in recurrent glioblastoma clinical trials. All data are collected from Clinicaltrials.gov.

approved drug lomustine in recurrent glioblastoma with a primary outcome that revealed improved progression free survival in the arm that received combinatorial treatment compared to the individual treatments of the respective drugs. The secondary outcomes also revealed improved overall survival and response rate. Similar efficacy and improved outcomes were observed in another Phase 3 trial study, NCT03149003, where DSP-7888 was used in combination with bevacizumab in recurrent GBM patients. It is evident from the low number of Phase 3 trials, that there is a lack of proper utilization of Phase 2 data leading to the failure of transition from Phase 2 to Phase 3 trials (Balasubramanian et al., 2021).

Aside from glioblastoma being extremely heterogeneous, which contributes greatly to this lack of progress in the field, the experimental design of these studies needs to be designed to address such tumor heterogeneity. The bulk of trials being continuously stuck in early phases despite numerous medical advances over the last few decades sheds light on the fact that there are ubiquitous flaws in experimental protocols among the neuro-oncology field. One probable cause for repeated late trial failure is the lack of routine biopsy in many early stage therapeutic-dose studies. The absence of tissue analysis leaves researchers in the dark as to why promising therapeutics are not performing as intended. Glioblastoma is unlike most other malignancies in the sense that repurposing treatment methods rarely works, understanding drug interactions in detail is vital for advancing treatment development at a faster rate. The enrolment criteria is another key factor which has been glanced over by many researchers, often patients of varying molecular subtypes are not accounted for in early phases of clinicals. These types of interactions are what lead to the eventual failure of a treatment at later phases, when patients are chosen completely at random the lack of stratification in early trials tends to materialize in the results (Singh et al., 2023). The statement above highlights the necessity of appropriate adjustments in study patterns to attain the best results for therapeutic intent against glioblastoma. Achieving breakthrough in nanotherapy-mediated targeting of glioblastoma requires a comprehensive knowledge about the tumor characteristics. Failure of multiple clinical trials in solving issues related to tumor resistance and recurrence is a consequence of challenges in tissue sampling and ambiguous preclinical models. For nanomedicines, to reach their maximum potential in translational studies, appropriate controls must be investigated alongside the tumor bearing subjects. Challenges for clinical trials to succeed include but are not limited to lower recruitment rate which corresponds to the lower number of samples, investigation of pharmacokinetic and pharmacodynamic ability corresponding to the limited dosing regimen, and timing of tissue collection outside the window of opportunity (Singh et al., 2023).

3.1 | Treatment options for recurrent GBM

Neuro-oncologists and neurosurgeons have very limited options which they would prescribe for the treatment of recurrent GBM. Depending on whether a patient shows prognostically favorable conditions, a second surgery may be advised. Only 50% of the recurrent tumors which undergo secondary surgery, show increase in overall survival from 5 to 11 months. After considering the radionecrotic parameters further, to amplify survival benefits, recurrent GBM can be treated with re-radiation therapy along with other systemic therapies. Despite the drug resistance executed by recurrent GBM against conventional therapeutic approaches, one field that still shows immense potential on targeting the progressive GBM tumor is immunotherapy.

3.2 | Role of immune suppression modulation in recurrent GBM treatment

Immune evasion by the GBM tumor microenvironment contribute to immune suppression and treatment challenges (Yeo & Charest, 2017). A number of pathways which become operative under tumor suppression scenario are presented in Figure 5. A major clinical trial study investigating the anti-tumor response of a multidose chimeric antigen receptor T-cell (CAR-T) therapy administered *via* intracranial route against recurrent GBM revealed reduced tumor progression to an extent where both intracranial and any spinal tumors were affected. The study successfully paved way for CAR-T therapy mediated modulation of immune suppression in high-grade glioma patients (Brown et al., 2016). Normal working of the immune system involves immune checkpoint receptor mediated activation of T cell response against any foreign environmental ques. This normalcy is affected when glioblastoma tumor shows unrestrained proliferation and exhibit an interaction between the immune checkpoints and their respective receptors. Thus, preventing this interaction using immune checkpoint blockers lead to stopping the tumor microenvironment from attaining resistance against immunosurveillance (Chakroun et al., 2018; Preusser et al., 2015). A significant amount of immunosuppressive

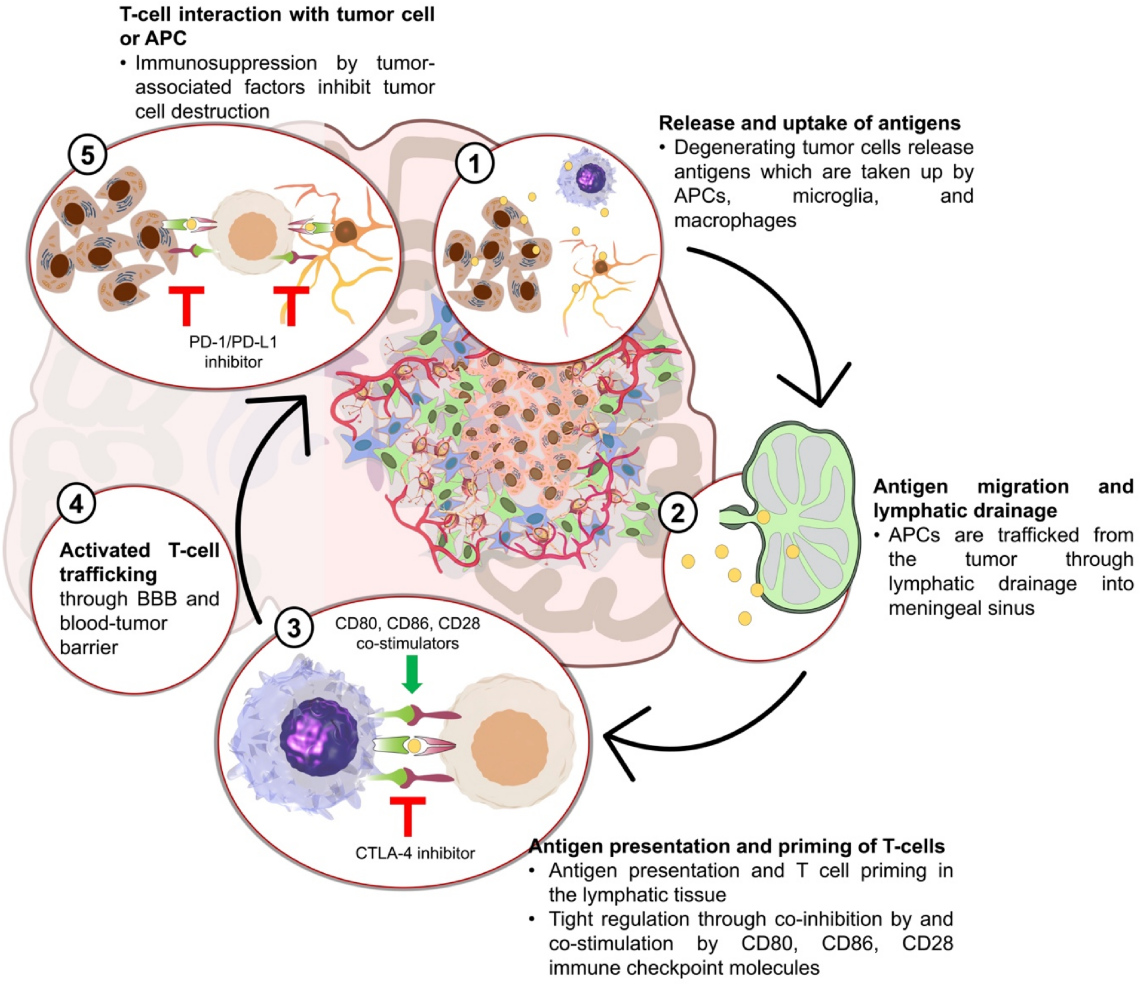

FIGURE 5 Immunosuppression and immune response in glioblastoma tumor microenvironment. Illustration revealing the overview of host's immune cell response and T cell migration in glioblastoma.

response from the glioblastoma tumor microenvironment is elicited due to the activation of PD-1, CTLA-4, T cell immunoglobulin and mucin domain (TIM-3), and lymphocyte-activation gene 3 (LAG-3) immune checkpoint signals and exhaustion of cytotoxic T-cell infiltration. Regulating the tumor microenvironment by modulating the immune checkpoint response utilizing their respective inhibitors is a promissory way to curtail the tumor progression (Kolb et al., 2020; Topalian et al., 2012). Of late, checkpoint inhibitory drugs like pembrolizumab and nivolumab have been tested for gliomas in early-stage clinical trials and multiple studies are actively working on investigating the anti-tumorigenic potential of immunotherapy against GBM. Due to the previous exposure to treatment, glioblastoma at the recurrent stage show little to no impact of immunotherapy on changing the overall survival in GBM (Lim et al., 2018). Comparing observations from multiple immune checkpoint inhibitor based interventional studies in recurrent glioblastoma suggested that reducing the recurrent tumor burden followed by administration of adjuvant and neo-adjuvant immune checkpoint inhibitors lead to improved overall survival and better therapeutic outcome (Wang et al., 2021).

4 | NANOMEDICINE TARGETING GLIOBLASTOMA

Aggressive nature, poor survival rate, and drug accumulation at the tumor site, (Tamimi & Juweid, 2017), resulted an interest in the use of advanced technology for earlier tumor diagnosis and treatment. Since only a minimal number of molecules can overcome the BBB, nano-systems offer a new approach to battle such hard-to-reach brain cancer type. Currently a major area of research, nanotechnology, improves the efficacy of chemotherapy and reduces negative effects of treatment by guiding drugs to specific target cells, locations, and/or specific organelles in the cells rendering

them vulnerable toward reaching the state of apoptosis (Marrache, Kumar Pathak, et al., 2013; Pathak et al., 2015; Wen, Banik, et al., 2016). Nanocarriers are drug carrier systems with a submicron particle size of less than 500 nm (ud Din et al., 2017). With a high surface area to volume ratio, properties of drugs as well as bioactivity can be altered by nanocarriers. The purpose of utilizing nanocarriers is to address disease whilst exhibiting minimal side effects. Depending on methods of preparation, nanocarriers can be categorized as nano-capsules, nanoparticles, or nanospheres to design combinatorial therapeutic approaches with better localization ability at the target site (Costoya et al., 2022; Zhao et al., 2020; Zhou et al., 2013). Of these classifications, nanoparticles are most used in treating GBM. Nanoparticles are nano-objects with all external dimensions in the nanoscale range. Nanoparticles have the potential to treat brain tumors using either direct delivery, direct systemic delivery, or indirect systemic delivery (Aldoghachi et al., 2022) and can be categorized as organic, carbon-based, or inorganic.

4.1 | Efficacy of organic nanomaterials in targeting glioblastoma

Organic nanoparticles include polymeric micelles, dendrimers, liposomes, and polymeric nanoparticles. The potential use of the nanostructures as efficient drug delivery vehicles is being investigated against a multitude of diseased states. When synthesized in an aqueous media, polymeric micelles form a shell that can entrap hydrophobic drugs in its core both *via* physical entrapment or covalent interaction taking the advantage of administration through the intravenous route (Cho et al., 2008). Since several anticancer drugs are poorly water soluble, polymeric micelles offer an option for increasing water solubility with hydrophobic anticancer drugs loaded in their core. The physicochemical characteristics of polymeric micelles help the particles to achieve longer circulation in the blood, reducing its chances to be recognized by the reticuloendothelial system (RES), making them efficient in targeting the hard-to-reach tumor sites (ud Din et al., 2017). Successful nanoplatforms which have already received FDA approval for their use in different cancer types and have revealed enhanced efficacy in tumor treatment include Abraxane, Doxil, Genexol-PM, and so on (Costoya et al., 2022; Shah et al., 2022). In the early years, Genexol-PM proved to have better bioavailability of the parent drug, paclitaxel, without the associated toxic side effects and leading to a better therapeutic outcome against advanced malignancies (Kim et al., 2004). In a recent study utilizing Abraxane, anti-tumorigenic potential was observed in preclinical orthotopic mouse model of glioblastoma. The study highlights ultrasound guided delivery of albumin-bound paclitaxel across the BBB leading to an increased drug concentration in the brain (Zhang et al., 2020). That being said, improvement within these systems is still needed because success of majority of the drug delivery systems relies on the interaction between drug encapsulated in the hydrophobic core and its timely release in the hydrophilic environment.

Another type of organic nanomaterial that gained immense importance recently is a dendrimer. These are symmetrical multi-branched structures which can be orchestrated with multiple functional groups at their branched ends. The highly branched structure leads to formation of multiple void spaces which can be filled with payload (Kaup et al., 2021). With the ability to carry plasmids, miRNAs, metals, and drugs across the BBB, dendrimers set a stage for being translated from preclinical to clinical studies. Recently, a preclinical study based on delivery of rapamycin across the BBB taking advantage of targeted delivery through polyamidoamine (PAMAM) based dendrimer-drug conjugation revealed promising anti-cancer therapeutic effect in orthotopic glioblastoma model. The study shows reduced glioblastoma tumor burden by inducing immune repolarization that emphasizes the potential of immunotherapy in glioblastoma (Sharma et al., 2020). Delivery of chemotherapeutic payload either across BBB or blood–brain tumor barrier has been challenging for researchers working on developing alternative therapies for glioblastoma. Such a challenge was overcome by a study where PAMAM dendrimer was PEGylated to conjugate Pep1 peptide. Pep1 has high binding affinity toward interleukin-13 receptor α2 which is overexpressed in glioma cells leading to an enhanced cellular uptake (Jiang et al., 2016) while another study utilized the anti-tumor efficacy of methotrexate by delivering it across the BBB and targeting the tumor cells using glucosamine conjugation in polyether-copolyester (PEPE) dendrimers (Dhanikula et al., 2008). Despite showing significant potential across multiple preclinical studies, dendrimer based nanoplatforms are yet to reach the clinical trial phases for glioblastoma. Our lab successfully designed a dendron-based blended polymer engineered with two different drug molecules present at a predefined stoichiometric concentration, enhancing the power of combinatorial therapeutics (Pathak & Dhar, 2015; Pathak & Dhar, 2016; Pathak et al., 2018). In addition, we observed that encapsulating such dendron-based polymeric drug combinations into actively targeting nanoformulations could elevate the effectiveness of the drugs in making cancer initiating stem cells apoptotic (Pathak et al., 2018).

A substantial amount of attention was gained by liposomes for its ability to be a potential drug delivery system across physiological barriers which are otherwise impermeable to free drugs, highlighting its significance in being

used as alternative therapeutic modality for GBM. Unlike dendrimers with exotic branched structures, liposomes are given a simpler structure of a phospholipid bilayer surrounding an aqueous core. The reason behind it having exceptional pharmaceutical potential is its biodegradable and biocompatible vesicular structure which can encapsulate both hydrophilic and lipophilic agents and deliver them at hard-to-reach target sites (Torchilin, 2005; Wang et al., 2012). A phase 1 and 2 clinical trial study (NCT01044966) revealed the efficacy of intraventricular administration of liposomal cytarabine in actively delivering the cargo at the subventricular zone leading to an induction of anti-proliferative and anti-migratory effects on the precursor cells thriving across the distant regions of the brain. The study aimed at recording the therapeutic benefits of delivering cytarabine using a liposomal formulation along with oral administration of TMZ at recommended dosage in delaying or stopping the tumor recurrence. The study showed a few potentially important results, but it was terminated owing to low recruitment across the years. Clearance of liposomes by macrophages in a timely manner creates room for it to be modified using different polymers and targeting antibodies leading to an enhanced circulation time while making them available for delivery to the brain (Ashrafzadeh et al., 2020). The conjugation of liposomes with antibodies or ligands allows for the enhancement of target specificity (ud Din et al., 2017). In a study utilizing a temperature-sensitive liposomal temozolomide formulation (TMZ/Fe-TSL), nanoparticles were feasibly delivered into GBM using alternate magnetic field exposure showing production of reactive oxygen species while inducing cytotoxicity toward glioblastoma cells (Yao et al., 2022). Results showed the possibility of pyroptosis-mediated GBM cell death instead of cells being vulnerable toward apoptosis. Anti-tumoral efficacy of a dual liposomal nanoplatform for co-delivery of doxorubicin and erlotinib was developed recently to treat GBM. This nanoplatform was functionalized with transferrin, a serum glycoprotein that can improve the NP's ability to accumulate across the BBB by targeting specific receptors on the tumor cells. The efficacy of the nano drug delivery system was observed using in vivo brain tumor model and the accumulation of the nanoparticles was revealed using biodistribution studies (Lakkadwala et al., 2020). Various research groups have been working on liposomal formulations to improve transport of chemotherapeutic drugs into target sites (Anilkumar et al., 2019; Belhadj et al., 2017; Guo et al., 2019; Jhaveri et al., 2018; Papachristodoulou et al., 2019), however, most of the studies have a limited potential toward inhibiting the tumor recurrence potential.

Polymeric nanoparticles are colloidal particles composed of active pharmaceutical ingredients. Compared to other nanocarriers used in cancer therapy, polymeric nanoparticles offer advantages in the form of greater stability on storage, greater drug payload, and controlled drug release (Hu et al., 2010). Improving drug bioavailability and specific site delivery makes polymeric nanoparticles a great option for satisfying the needs of drug-delivery systems, as well as being an excellent candidate for cancer treatment (Jain, 2020). Despite holding immense potential to switch to translational platforms, polymeric nanoparticles are only undergoing clinical trials for treating GBM, but they are not yet being used in a clinic setting. In a phase 2 (NCT01663012) study on high grade gliomas showing resistance toward bevacizumab treatment, NKTR-102, a topoisomerase I inhibitor polymer conjugate, was engineered through the attachment of irinotecan molecules to a PEG polymer with the goal of eliminating side effects of irinotecan as well as enhancing the distribution throughout the body. Positive results suggest that NKTR-102 may improve clinical results in patients. Compared to normal therapy, polymeric nanoparticles effectively decrease tumor size in GBM xenograft mouse models (Madani et al., 2022; Xu et al., 2017).

An alternative therapeutic strategy can be successfully translated when it can target the major contributor of glioblastoma tumor recurrence. All other therapeutic approaches may show initial positive results, but to be considered for clinical application, it will need to specifically target the GSCs in the brain. Invasion and migration are common in GSCs, making specifically targeting this cell population at a particular site in the brain, challenging. To date, despite acknowledging the importance of GSC-specific targeting for glioblastoma disease control and mitigation, only a few studies have recently been able to show effective GSC targeting through in vitro and in vivo based investigations. One such study involved the synthesis of cationic liposomes with DSPE-PEG_{2000}-menthol conjugated surface functionalization, loaded with paclitaxel for leveraging its antitumor property, and ginsenoside Rh2 for enhanced tumor accumulation (Cai et al., 2024). Cai et al., were able to develop cationic liposomes with a size of ~100 nm, a zeta potential of ~11 mV, and a high payload encapsulation capacity. These liposomes could effectively loosen the tight junction proteins at the BBB due to the presence of menthol on its surface, increasing the permeability of BBB for liposome accumulation into the brain. Once in the brain, the cationic liposomes undergo electrostatic adsorption at the negatively charged site of the tumor cells, followed by cellular internalization, and finally lead to elevated levels of apoptotic signals along with reduced proliferative potential (Cai et al., 2024). An in vitro based study documented the potential use of chitosan-based NPs with 1,3β-glucan surface modification for active targeting toward GSCs and glioblastoma tumor cells to deliver paclitaxel as the antitumor drug (Singh et al., 2018).

4.2 | Efficacy of inorganic nanomaterials in targeting glioblastoma

Mesoporous silica nanoparticles (MSNs) are inorganic nanoparticles that have a solid framework and a porous structure, allowing for the attachment of different functional groups (Bharti et al., 2015) and to serve as host to a large amount of drugs. Demonstrating therapeutic potential in GBM treatment, a study aimed at enhancing radiosensitivity of valproic acid (VPA) in glioblastoma using a dual functional MSN acquired results suggesting that VPA-MSNs enhanced the effectiveness of radiotherapy, lowering the required doses to minimize healthy tissue damage (H. Zhang et al., 2017). This is especially important with radiotherapy being a part of the standard treatment of GBM. Vascular endothelial growth factor receptor (VEGFR) is a key component in tumor angiogenesis that is associated with gliomas. A study utilizing MSNs modified with polyethylene glycol, VEGF121, and ^{64}Cu to deliver the anti-VEGFR drug in using in vitro, in vivo, and ex vivo models confirmed the stability of the nanoconjugates, as well as a substantial improvement in tumor accumulation of targeted MSNs compared to the non-targeted group (Goel et al., 2014). Additionally, studies have demonstrated that in vitro, MSNs can induce endocytosis with different mammalian cancer cells (Živojević et al., 2021).

Metallic nanoparticles, another type of inorganic nanoparticle, are made of metals or their compounds. Important metallic NPs include gold NPs, silver NPs, iron oxide NPs, and quantum dots. The strong binding ability of gold NPs to amine, disulfide, and mercaptans, allow them to be easily modified for greater blood circulation time and targeting specificity (Mao et al., 2020; Piao et al., 2014; Tu et al., 2021; Yang et al., 2019). Gold NPs can also be used as contrast agents beneficial to bioimaging (Wang et al., 2020). Gold NPs not only play a role in the delivery of chemotherapy drugs, but also in gene delivery. This ability can be employed to silence genes for brain tumor treatment. One study used this gene delivery potential to regulate oncogene expression in GBM by producing spherical nucleic acid (SNA) nanoparticle conjugates, made of small interfering RNA (siRNA) oligonucleotides that surround a gold nanoparticle core (Jensen et al., 2013). Results demonstrated an inhibition of tumor growth and an increased survival rate in U87MG mice models. NU-0129 is a SNA gold nanoparticle that can cross the BBB and target the gene Bcl2L12 that is associated with GBM progression and tumor growth. Targeting GSCs has never been an easy task for the available therapeutics. Employing nanotechnology-based design of therapeutics can potentially lead the way to successfully targeting and killing the GSCs. Successful targeting of the GSCs was achieved by a superparamagnetic iron oxide nanoparticle (SPION) complex for delivering miR-485-5p (miR-485-5p@SPIONs) through transfection (Pan et al., 2020). Transfection of human GSCs with miR-485-5p@SPION results in reduction in Tie1 protein expression which is an important factor that drives the reduction in stemness potential worsening the tumor viability (Pan et al., 2020).

To date, efficacious targeting of glioblastoma was observed upon using biomimetic nanoparticles, embryonic stem cell derived exosomes, surface modified exosomes, liposomes, polymeric nanoparticles, and magnetic nanoparticles. These formulations take advantage of breaching the tight junction connections between the endothelial cells of the BBB and undergo absorption-mediated transcytosis to accumulate in the brain. Improved median and overall survival, decreased cell proliferation, and increased apoptosis was observed in glioblastoma-based studies upon treating with nanoparticles. Breaching the tight junction proteins at the BBB may seem beneficial for the internalization of alternative therapeutic platforms, but keeping the BBB connections loosened for a substantially long time may lead to disruption in the BBB integrity resulting failure by BBB to protect the brain from external stimuli. Thus, appropriate expertise in chemistry and nanotechnology is a prerequisite for designing brain targeted nanoparticles that affect the GSCs without affecting the normal functioning of the BBB.

Results from NCT03020017, an early phase 1/phase 0 trial demonstrated that NU-0129, a drug based on SNA platform, had no unexpected adverse effects in GBM patients and gold accumulation was seen in tumor tissue. This clinical trial evaluated the safety of intravenously injecting NU-0129. The adverse events were categorically graded from being mild to fatal as per NCI's Common Terminology Criteria in Adverse Events (CTCAE). One of the major aims of the clinical trial was to investigate the feasibility of NU-0129 as a translational drug that can be used for standard of cure for treatment of recurrent glioblastoma patients. The results show that based on the current number of participants, there was a 100% success in drug infusion followed by subsequent tumor resection. We enlist a few of the major nanoparticle based clinical trials that were studied against glioblastoma in (Table 1).

Taken together, these advancements which may lead us to an era of effective therapeutics with reduced peripheral toxicities suggest the increasing need for changing gears from conventional therapeutic modalities to alternative nanotherapeutic approaches not only against lethal malignancies but also for other hard-to-treat diseases (Marrache & Dhar, 2013, Banik et al., 2018, Surnar et al., 2019, Banik et al., 2020, Surnar et al., 2020, Surnar, Shah, Guin, et al., 2021,

TABLE 1 Summary of the major nanoparticle based clinical trials in glioblastoma.

Intervention	NCT number	Study status	Disease condition	Clinical trial phase	Study purpose
Polysiloxane Gd-Chelates based nanoparticles (AGulX)	NCT04881032	Recruiting	Newly diagnosed glioblastoma	Phase I/II	*Phase I*: Determine recommended dose of AGulX in combination with radiotherapy and TMZ treatment. *Phase II*: Estimation of efficacy of the combination therapy at the recommended dose, determined using the 6-month PFS rate.
(NU-0129) nucleic acids arranged on surface of gold nanoparticles	NCT03020017	Completed	Recurrent glioblastoma multiforme or gliosarcoma	Early phase I	*Primary purpose*: Safety assessment of intravenously injected NU-0129. *Secondary purposes*: Analyze serum drug concentration at specific time points post drug administration; demonstrate intratumoral penetration; and assess the feasibility of translational capability. *Tertiary purpose*: Investigate change in target gene (Bcl2L12) expression level upon drug administration and preliminary responses like PFS, OS, and ORR.
(SGT-53) Cationic liposome encapsulating a normal human wild type p53 DNA in plasmid backbone	NCT02340156	Terminated	Recurrent glioblastoma	Phase II	Determination of the efficacy and safety of a combinatorial treatment of tumor targeting SGT-53 nanocomplex ad TMZ in recurrent glioblastoma patients.
(ABI-009) Nab-Rapamycin	NCT03463265	Active, not recruiting	Recurrent and newly diagnosed glioblastoma	Phase 2	Investigation of ORR, treatment-related adverse events, PFS, and OS. All factors will be monitored for a period of 12 months.
(NL CPT-11) Nanoliposome CPT-11	NCT00734682	Completed	Recurrent high-grade gliomas	Phase 1	Assessing the safety and pharmacokinetics and measuring the MTD of the drug in patients with high grade gliomas.

Note: Data were obtained from Clinicaltrials.gov.
Abbreviations: MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Surnar, Shah, Park, et al., 2021). Thus, nanomedicine based therapeutics are the need-of-the hour for glioblastoma due to the advantages of effectively targeting the tumor sites and efficacious loading of therapeutics (Figure 6).

5 | THERAPEUTIC INNOVATIONS AGAINST GLIOBLASTOMA

5.1 | RNA-based therapy targeting glioblastoma progression

Advancement in effective glioblastoma therapy lies in the hands of innovative technology that circumvents the critical challenges at the BBB. One such technique is RNA-based delivery of macromolecules at the target site. RNA-based GBM therapy holds promise as an effective alternative treatment for GBM on the one hand, whereas, on the other, it faces various obstacles. BBB, RNA stability, and rapid RES clearance are among the major challenges for RNA-based therapy. Studies by Zhang et al., have proved noncoding RNAs (ncRNAs) to be a crucial part of the human genome (Y. Zhang et al., 2017). In 2016, an RNA-based study approach utilized the advantages of combinatorial targeting strategy using tumor suppressor miR-137 and an agonist of oncomiR, miR-10b resulting in decreased tumor proliferation (Esposito et al., 2016). An innovative siRNA-based delivery strategy was discovered in 2020 with both in vitro and in vivo therapeutic efficacy. The study suggested the use of biomimetic nanoparticles (Ang-RBCm-CA/siRNA) to deliver siRNA through a charge conversion technique (Liu et al., 2020).

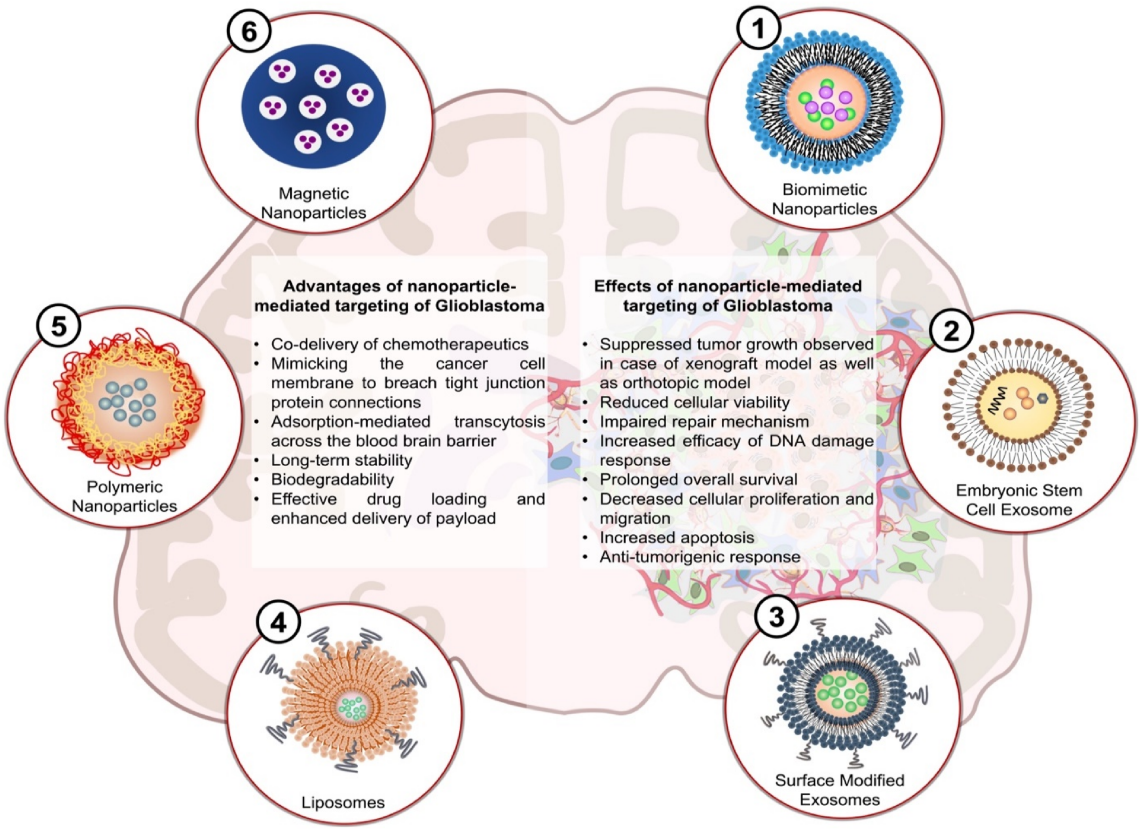

FIGURE 6 Nanomedicine showing potential in suppressing glioblastoma tumor progression and aggressiveness in preclinical studies.

The efficacy of Ang-RBCm-CA/siRNA was determined in an orthotopic glioblastoma mouse model which revealed biocompatibility, BBB crossing, tumor targeting, tumor retention, and pH triggered siRNA release at a sustained manner (Liu et al., 2020). So far, no RNA-based therapy against GBM has received FDA approval, however, multiple RNA-based strategies are being studied until clinical trials currently (Singh et al., 2024). Reduction in proliferative potential of glioblastoma and GSCs comes from the miR-10b agonist delivered using exosomes (Lozada-Delgado et al., 2017).

A few clinical trials have studied the effect of RNA interference-based technology in recurrent glioblastoma. One such study was a Phase 0 study which took advantage of the "golden opportunity" to tackle glioblastoma (Kumthekar et al., 2021). This trial followed systemic administration of NU-0129 siRNA-based SNAs which revealed effective crossing of BBB, glioblastoma tumor targeting, and no long-term toxicity association (Kumthekar et al., 2021).

An intelligent combination of innovation, expertise in therapeutic designing, and knowledge of biological spatio-temporal characteristics of glioblastoma is a promissory way to develop alternative modalities that will either serve as an adjuvant or replace conventional therapeutic approaches.

5.2 | Crossing the highly impermeable BBB

In this review, we talked about the multiple facets that, if tackled appropriately, will lead to the development of effective therapeutic strategies with translational values, however, the major limitation that causes failure of most therapeutics to reach the clinics is the presence of BBB. To date, temozolomide (TMZ) alone, owing to its small size and lipophilic nature has shown distribution across brain parenchyma, making its way to be a part of the trimodal conventional therapeutic strategy for GBM. Though TMZ revealed improved median survival in GBM patients, there are certain limitations associated with it. Starting from the development of multidrug resistance by activation of DNA damage repair genes, to inefficient targeting of GSCs, TMZ treatment remains insufficient for stopping tumor recurrence postsurgical resection. Hence, there is a need for the development of effective BBB

crossing drug delivery vehicles. Crossing of BBB can be achieved by noninvasive techniques which include transcytosis across the BBB taking advantage of the receptors–ligand interaction, carrier-mediated transport of molecules, or adsorptive transcytosis.

5.2.1 | Transcytosis across BBB

Transcytosis across the BBB may either be paracellular or intracellular depending on whether molecules enter through the tight junctions while the BBB undergoes destruction as seen in some brain related diseases, or whether the molecules traverse through the endothelial cells at the BBB by undergoing partitioning of the cell membrane. Small molecules with low molecular weight and lipophilicity can breach the tight junction proteins and accumulate across BBB through free diffusion.

5.2.2 | Receptor-ligand mediated crossing of BBB

Endothelial cells at the BBB are characterized with elevated expression of multiple receptors. Among the multiple receptors, transferrin, folate, dopamine, and insulin receptors are the ones that are being studied extensively. Successful targeting of glioma post crossing the BBB was achieved by Guo et al., where they investigated the role of conjugating anti-PD-L1 antibody with p-hydroxybenzoic acid (pHA-αPDL1) to undergo dopamine receptor mediated crossing of the BBB (Guo et al., 2020). Biodistribution studies revealed a significant amount of the antibody-benzamide analogue conjugate in healthy C57BL/6 mouse brain compared to unconjugated αPDL1. In addition, pHA-αPDL1 distribution was significantly higher at orthotopically implanted GL261 glioma tumor site compared to αPDL1, suggesting the crucial role of p-hydroxybenzoic acid in targeting the dopamine receptors on the endothelial cells lining the BBB (Guo et al., 2020). Further, receptor-mediate transcytosis has also proved successful in delivering nanoparticles with transferrin ligand conjugation. Cancer cells express ∼100-fold higher transferrin receptors compared to normal cells owing to their role in supporting tumor cell growth. Brain endothelial cells have elevated levels of transferrin receptors as well, suggesting the use of transferrin in transporting drug molecules into the brain (Choudhury et al., 2018).

5.2.3 | Biomimetic drug delivery approaches across BBB

Inspired by the advantages of biomimetic drug delivery vehicles across multiple hard-to-reach diseases (Kang et al., 2017), extensive investigation is now being performed where nanoparticles are modified with specific cell membrane structures, encapsulating activable chemotherapeutic drugs for targeting glioblastoma. Though currently at the initial stage, drug delivery across impermeable barriers like BBB will experience evolution through biomimetic drug delivery approach owing to their low immunogenicity. Studies reveal camouflaging nanoparticles with natural killer (NK) cell membrane properties can successfully lead to an interaction between the integrin proteins of the NK cell membrane and adhesion molecules at the brain microvascular endothelial cells. In this context, Deng et al., developed nanorobots which mimic the surface of NK cells (Deng et al., 2020). They utilize the aggregation induced emission (AIE) system to design the nanobots and named them NK@AIEdots. Such therapeutic strategies can take advantage of tight junction disruption at the activation stage when integrins on the NK cell surface bind to ICAM-1 or VCAM on the endothelial cells of the BBB leading to breaching of intercellular tight junctions (Deng et al., 2020). A combinatorial therapeutic strategy delivering TMZ and cisplatin using glioblastoma cell membrane mimetic nanoformulation was developed by Zou et al., which revealed specific targeting of glioblastoma post crossing BBB. Anti-tumor therapeutic potential of MNPs@TMZ + cis-diamminedichloroplatinum (II) (CDDP) was studied in two different orthotopic mouse models (i.e., U87MG and U251^{R}) (Zou et al., 2022). Another study takes advantage of exosome mediated delivery of molecules across the BBB by synthesizing nanovesicles inspired by exosome structure. In vivo efficacy studies in zebra fish and orthotopic mouse models reveal efficient reduction in tumor progression (Wu et al., 2021).

5.2.4 | External stimuli response for weakening the tight junction proteins at the BBB

Tight junction proteins between the brain microvascular endothelial cells renders the BBB impermeable to almost all available therapeutic strategies. Exploring potential of external stimuli responses like radiotherapy, focused ultrasound, light, and electric field to disrupt this tight junction is increasing consistently. Near infrared radiation (NIR-II) has enabled deep tissue penetration for enhancing therapeutic efficacy (Tao & Farokhzad, 2022). NIR can result in transient local hyperthermia which enables short mechanical waves to increase the permeability of the BBB (D. Wu et al., 2023). Another way that can lead to short-term BBB disruption is by focusing ultrasound vibrations in combination with nanodrugs for efficient distribution of the drug (Aryal et al., 2014; Gorick et al., 2022). Recently, tumor-treating fields have been investigated for their utilization in opening the BBB for delivering chemotherapy, through a process termed electrochemotherapy (Davies et al., 2013). This strategy focuses on electroporation-mediated electric field pulses at low intensity (∼1–3 V/cm) and optimum frequency (∼100–300 kHz) (Neal et al., 2014). The efficacy of tumor treating fields has been investigated in phase 2 clinical trial for brain metastases (Rodrigues et al., 2012) and in patients with recurrent glioblastoma (Ansstas & Tran, 2016).

Evidence suggests that BBB crossing by nanoparticles has evolved substantially in the last decade showing the rise in innovative approaches for targeting brain related diseases. Though characterized with immense potential in increasing the bioavailability of the therapeutic intervention across the brain, certain strategies are more translatable compared to others. In our perspective, only such nanotechnology mediated therapeutics will cross the activation barrier of moving from bench-to-bedside which can take advantage of intracellular transcytosis without encountering any disruption of the BBB. For nanoparticles to accumulate across the BBB, target GSCs, and have anti-tumor efficacy, researchers are designing complex delivery systems. The degree of translational ability is directly related to how stable the nanoplatform will be when synthesized in large scale. Thus, we see a majority of nanodrug delivery systems reaching the clinical trial phases but failing to reach the clinics. Similarly, disrupting BBB may improve drug accumulation and targeting initially, but if the disruption persists beyond a threshold, it may cause severe neurocognitive impairments. In this context, our lab was successful in developing a brain accumulating nanoplatform that reveals no BBB disruption, but results in distributing across the major parts of the brain (Surnar et al., 2018). Taking advantage of lipophilicity and delocalized positive charge across the nanoparticle surface, we establish a nanoplatform with highly reproducible scalability keeping the physicochemical properties intact. Keeping in mind that GSCs are highly invasive and migratory, therapeutics once across the BBB must have the potential to accumulate across distant regions of the brain. Hence, whether a brain targeted therapeutic strategy for glioblastoma has translational potential not only lies on the pattern with which it crosses the BBB, but also on its physicochemical characteristics after crossing the BBB.

6 | IMPACT ON OVERALL SURVIVAL

GBM being the most malignant brain tumor, due to the presence of highly invasive glioblastoma stem cells, patients suffer from high risk of recurrence. To overcome the challenges posed by these stem cells, various therapeutics strategies, a wide range of nano-therapies are under investigation. The clinical benefit of reoperating on patients who have previously suffered from GBM and are experiencing tumor recurrence is limited. While the overall survival of the patients who undergo reoperation is around less than 2 years post operation, it is around < 1 year for those who chose not to reoperate (Furtak et al., 2022). Given the influence that glioblastoma has on the cognition parameters and quality of life of the patients, it is not surprising that the patients often opt not to go for reoperation in order to evade the pain from treatment itself. Studies suggest that despite extent of resection being a key factor for increasing the life expectancy postsurgery in newly diagnosed GBM patients, its role in recurrent patients remain unclear. On a positive note, if gross total resection or removal of greater than 95% of volume of the tumor mass, can be achieved for recurrent patients, their overall survival could be increased (Bloch et al., 2012). The median survival upon reoperation increased to 22.9 months compared to 14.6 months without reoperation (Sacko et al., 2021). In Table 2, we have summarized the most recent nanoparticle-based studies which have revealed significance in attaining efficacious anti-tumor effects against glioblastoma multiforme which shows the immense potential of nanotechnology in the field of targeted medicine against hard-to-reach cancer types.

TABLE 2 Table summarizing the major nanoparticle-based studies utilizing either xenograft or orthotopic glioblastoma animal model in developing potentially effective alternative therapeutic strategies over the last 2 years.

Nanotherapeutic approach	Aim of study	Tumor model	Results	Reference
TLR7/8 agonist R848 encapsulated β-cyclodextrin nanoparticles (CDNP-R848).	Efficacy of systemic administration of CDNP-R848 via intravenous route on glioma tumor regression.	Orthotopic GL261 murine glioma mouse model.	• Regression of Gl261 glioma tumor in syngeneic model. • Increased rate of survival. • Reduced immunosuppression and increased tumor clearance.	(Turco et al., 2023)
TPP conjugated lonidamine encapsulated chemotactic nanoparticles.	Utilization of high expression of ROS/iNOS in the glioblastoma TME as chemoattractant leading to an induction of chemotactic behavior of the NPs.	Orthotopic GL261 murine glioma mouse model.	• Precise targeting ability across BBB. • Regulation of immune circulation for improved immunotherapy. • Efficacy in forming immune memory to prevent tumor recurrence.	(Huan Chen et al., 2023)
Bridging lipid NPs loaded with diABZI. (B-LNP/diABZI)	Enhancement of the anti-tumor immune response triggered by radiotherapy.	Orthotopic CT-2A and PVPF8 glioma mouse model.	• Promotion of tumor associated myeloid cell phagocytic activity. • Increased T cell recruitment and improved anti-tumor response. • B-LNP/diABZI and radiotherapy in preclinical mouse models lead to brain tumor regression. • Immunological memory against glioma.	(Zhang et al., 2023)
Carmustine loaded PLGA nanoparticles. (BCNU-NP-222)	Introducing a new nanomedicine-gel-based therapeutic strategy for drug delivery in the brain.	Orthotopic rat glioma model.	• Release study of BCNU-NP gel in artificial cerebrospinal fluid showed sustained release profile. • BCNU-NP gel showed ~45% cytotoxicity toward glioma cells. • Improved tissue penetration, retention, and diffusion of the drug. • Intracranial injection of the NP-gel revealed enhanced anti-tumor efficacy.	(Das et al., 2023)
Poly(ε-caprolactone)-diselenium-poly (ethylene glycol) dual redox responsive nanocarrier to achieve site specific delivery of fingolimod. (AF-NPs)	Alteration in the BBB integrity to improve the accumulation of AF-NPs across blood brain tumor barrier.	Orthotopic GL261 murine glioma mouse model and orthotopic U87 glioma model.	• Regulation of permeability in the blood vessels and improved ability to accumulate in the brain tumor tissue. • Enhanced anti-tumor efficacy while suppressing the invasiveness of the tumor. • The AF-NPs show the potential to be used as an agent for modulation of the BBB and can be a promising therapeutic strategy for other brain related disease.	(H. Wu et al., 2023)
Transferrin coated lipid nanoparticles loaded with paclitaxel and miltefosine. (Tf-PTX-LNPs)	Anti-tumor efficacy of Tf-PTX-LNPs administered though intranasal route.	Orthotopic NOD/SCID glioblastoma multiforme mouse model.	• Administration of alternative targeted therapeutic strategy for direct transportation from nose to brain. • Enhanced anti-tumor efficacy with PTX and miltefosine. • Evasion of the drug resistance in GBM induced by O^6-methylguanine-DNA methyltransferase leading to an improved efficacy for GBM treatment.	(Sandbhor et al., 2023)

(Continues)

TABLE 2 (Continued)

Nanotherapeutic approach	Aim of study	Tumor model	Results	Reference
			• Improved bioavailability of the drug in the brain, reduced systemic toxicity in comparison to the free drug.	
Lipid nanoparticles encapsulated with ATO, a chemotherapy drug; Mn for MRI; and α-Melittin for immune activation (Mel-LNPs/MnAs).	Introducing a multimodal therapeutic strategy for achieving reduction in glioblastoma progression and recurrence.	Orthotopic GL261 murine glioma mouse model.	• BBB penetration capability, tumor targeting ability. • Real-time visualization of drug release. • Improved anti-tumor efficacy in orthotopic mouse model, increased survival, and reduced tumor recurrence by downregulating the stemness potential of the tumor cells. • Enhanced immune response mediated protection against tumor recurrence post-surgical resection.	(R. Wang et al., 2023)
Aggregation-induced emission nanoparticles modified with a genetically engineered T cell membrane coating to mimic T cells. (CM@AIE NPs)	Prevention of glioblastoma tumor recurrence.	Orthotopic U87-MG glioblastoma mouse model.	• Targeting ability for GBM cells as well as GSCs. • Penetration across BBB by mimicking immune cells. • Efficacy in enhancement of photothermal therapy. • Reduced glioblastoma tumor recurrence.	(W. Wang et al., 2023)
Synthetic dual loaded nanoconstructs. (CANDI)	Introduction of a myeloid-targeted therapeutic strategy to evade immune suppression at the glioblastoma tumor microenvironment.	Orthotopic murine CT2A, GL261, and 005 glioma mouse model.	• Enhanced accumulation in tumor tissue. • Myeloid cells can readily uptake these synthetic nanoconstructs leading to improved anti-tumor immune response.	(Lugani et al., 2023)
PLGA-based polymeric nanoparticle coated with activated- dendritic cell membrane, encapsulating rapamycin. (aDCM@PLGA/RAPA)	Improvement of the immune microenvironment in GBM.	Orthotopic C6-LUC glioma mouse model.	• Enhanced immune activation and long-lasting immune response. • Inhibition of tumor progression. • Increase survival.	(Ma et al., 2023)
Graphene oxide nanosheets for efficient delivery of bortezomib (BTZ).	Improved anti-tumor efficacy of nonstandard chemotherapeutic drug BTZ post intratumoral injection.	Orthotopic U87-MG glioblastoma mouse model.	• Improved diffusion and retention in the tumor tissue. • A significantly lower dosage of BTZ is required to observe anti-tumor efficacy.	(Sharp et al., 2023)
Endogenous exosomes co-delivering pure nanomicelles and immune adjuvants. (CpG-EXO/TGM)	Improved efficacy of exosome mediated delivery of anticancer agents and immune adjuvants for targeted delivery and prevention of tumor recurrence.	Orthotopic GL261 murine glioma mouse model.	• Prolonged blood circulation and improved BBB penetration. • Efficient cellular uptake and increased apoptosis in GBM cells. • Generation of anti-tumor immune response by maturation of DCs and polarization of TAMs. • CpG-EXO/TGM in combination with TMZ increases anti-GBM efficacy while reducing the tumor recurrent potential.	(Cui et al., 2023)
Biomimetic nanosonosensitizers in combination with ultrasound actuation. (MDNPs)	Achievement of reversal from chemotherapeutic drug resistance.	Orthotopic U87 glioblastoma mouse model.	• In the presence of ultrasound, the NPs readily cross the BBB. • Generation of ROS response leads to increase in apoptosis while decreasing the drug resistance. • Improved anti-tumor efficacy and survival rate.	(Huaqing Chen et al., 2023)

TABLE 2 (Continued)

Nanotherapeutic approach	Aim of study	Tumor model	Results	Reference
Gold nanoparticles labeled ^{177}Lu. (^{177}Lu-AuNPs)	Prevention of recurrence and improving the long-term outcome of the nanotherapeutic treatment.	Orthotopic U251-Luc human glioblastoma NRG mouse model.	• Improved retention in the tumor tissue. • Significant reduction in the tumor growth rate. • No toxicity toward the surrounding normal tissues.	(Georgiou et al., 2023)
Bacterial cells loaded with silicon nanoparticles and glucose polymer. (GP-ICG-SiNPs)	Attaining therapeutic efficacy by bypassing the BBB using bacteria-mediated delivery of photothermal immunotherapy.	Orthotopic G422-Luc glioblastoma mouse model.	• Specific targeting of GBM tumor microenvironment by evading the BBB. • Laser irradiation improves the photothermal efficacy of ICG while inducing bacterial cell and tumor cell killing. • Enhancement of anti-tumor immune response leading to improved survival time.	(Sun et al., 2022)
Biomimetic nanogel loaded with TMZ and ICG activated by NIR. (NGs@TMZ/ICG)	Efficient crossing of BBB and penetration of drugs at hard-to-reach sites.	Orthotopic U87 glioblastoma mouse model.	• Extended blood circulation. • Site specific tumor targeting. • Tumor growth suppression and improved survival rate.	(Zhang et al., 2022)
Nanoparticles targeting CXCR4 with nitric oxide donors to deliver siRNA against PD-L1. (LCP-NO NPs)	Enhancement of immunotherapy in glioblastoma.	Orthotopic mouse glioblastoma multiforme model.	• Presence of nitric oxide donors reveal BBB permeability and enhanced delivery of gene across the BBB. • Efficient silencing of PD-L1, T cell infiltration at the tumor microenvironment. • GBM tumor suppression.	(Hsieh et al., 2022)
Platelet mimicking nanoparticles with chlorine e6 (BNPD-Ce6@Plt)	Enhanced efficacy of photodynamic therapy as an alternative approach for GBM.	GL261 murine xenograft and orthotopic mouse model.	• Efficient distribution at the tumor site while inducing tumor necrosis. • Inhibition of GBM proliferation and increased survival.	(Xu et al., 2022)
CRISPR/Cas9 based brain targeted nanotherapy. (Ang-NP@RNP)	Enhancement in the efficacy of CRISPR/Cas9 based gene editing for treating GBM.	Orthotopic U87 glioblastoma mouse model.	• Improved stability while in circulation. • Efficient gene knockout and reduction in protein formation. • Suppression of tumor growth while improving median survival. • Negligible side effects related to the treatment.	(Ruan et al., 2022)
NIR activable upconversion nanoparticle. (HDX@YSN@CCM@cRGD)	Overcoming the limitations of therapeutic delivery across BBB.	Orthotopic U87 glioblastoma mouse model.	• Biomimetic nanotherapy mediated bypassing BBB. • Site specific targeting of GBM cells. • NIR activable photodynamic and chemotherapeutic anti-tumor response.	(Mo et al., 2022)
Biomimetic nanoparticles encapsulating a copper chelator and regadenoson for transient opening of the BBB. (Ang-MNPs@(Dp44mT/Reg))	Utilization of ROS generation upon targeting elevated copper levels in the brain cancer cells using copper chelators as a promissory alternative approach for GBM treatment.	Orthotopic U87 glioblastoma mouse model.	• Prevention of orthotopic GBM tumor growth and proliferation. • Increased median survival and reduced systemic toxicity. • Improved selectivity and cytotoxicity of the nanoformulation was achieved by elevating the levels of copper at the tumor site. • Suppression of anti-apoptotic genes and upregulation of the pro-apoptotic genes.	(Ismail, Yang, Li, Wang, et al., 2022)

(Continues)

TABLE 2 (Continued)

Nanotherapeutic approach	Aim of study	Tumor model	Results	Reference
Hydroxyl-PAMAM dendrimer-siRNA conjugates with GSH sensitive linker.	Advancement in the field of site-specific siRNA delivery against GBM.	Orthotopic GL261 murine glioma mouse model.	• Improvement in overcoming the limitations of RNAi based targeted therapy. • Intratumoral administration revealed improved localization at the target site.	(Liyanage et al., 2022)
Hydrogel system encapsulating BCNU and TMZ.	Achievement of tumor recurrence inhibition post-surgical resection.	Orthotopic C6-Luc glioblastoma rat model.	• Inhibition of the recurrence of glioblastoma. • Elevated therapeutic efficacy of the drugs post-maximum surgical resection.	(Chen et al., 2022)
Melittin-$RADA_{32}$ coated *C novyi* spores encapsulating metformin. (MRM-coated spores)	Reprogramming the immune suppressive tumor microenvironment using an alternative therapeutic approach.	GL261 murine glioblastoma xenograft and orthotopic mouse model.	• Sustained release profile of the MRM-coated spores leading to enhanced cytotoxicity. • Induction of anti-tumor immune response. • Improved therapeutic effect in addition to having an excellent safety profile.	(Zhu et al., 2022)
Liposome based nanotherapeutic platform co-delivering artesunate phosphatidylcholine and TMZ. (ApoE-ARTPC@TMZ)	Overcoming the limitations of single agent based therapeutic modalities and challenges imposed by BBB in glioblastoma.	Orthotopic U251-TR glioma model.	• Improved accumulation across the BBB leading to site specific targeting of the glioma tumor microenvironment while elevating the retention time in the tissue. • Sustained release and longer circulation in the blood. • Improved sensitivity toward TMZ treatment, even at lower dosage, showing effective anti-tumor efficacy.	(Ismail, Yang, Li, Chai, et al., 2022)
X-ray triggered sulfur dioxide (SO_2) releasing nanoplatform. ($NaYF_4$:Ce@$NaLuF_4$:Nd@ATD@DSPE-PEG_{5000}, ScNPs)	Reversal of chemoresistance and radio-resistance to improve the therapeutic efficacy of alternative targeted therapy.	Orthotopic TMZ-resistant glioblastoma mouse model.	• Mitochondrial destruction leading to reduction in ATP synthesis. • Downregulation of P-glycoprotein leading to a reduction in the intracellular drug efflux. • Re-sensitization of the tumor cells toward chemotherapy and radiation therapy.	(Yun et al., 2022)
Magnetic nanoparticles	Determining how tuning the nanoparticle characteristics can lead to potential efficacy in biomedical applications.	Subcutaneous U87MG glioblastoma mouse xenograft model.	• Induction of hypothermic response depending on the tuned parameters of the nanoparticles. • Doxorubicin loaded nanocubes elicit effective magneto-chemotherapy against glioblastoma. • Effective therapeutic strategy leading to activation of apoptotic pathway, cell cycle arrest, and reduction in tumor growth.	(Gupta et al., 2022)
Biomimetic magnetic nanoparticles co-delivering cisplatin and TMZ.	Efficacy of combinatorial therapeutics on glioblastoma progression.	Orthotopic TMZ resistant U251 glioblastoma mouse model.	• Longer blood circulation. • Improved retention of the nanoparticles in the tumor tissue. • Improved BBB penetration. • Effective anti-tumor efficacy utilizing the sustained release of the encapsulated payload.	(Zou et al., 2022)

7 | CONCLUSION

It is evident that the efficacy of the current trimodal treatment regimen for GBM has reached its upper limits. There has been significant improvement in overall survival over the past decades, these numbers have begun to plateau, and

the progression free survival remains unchanged due to the evasive nature of GSCs. In the development of new therapeutics for glioblastoma, there are two major goals: stopping/delaying reoccurrence of the tumor and providing a significant increase in overall survival with minimal drawbacks to quality of life. The immunosuppressive nature of the tumor microenvironment coupled with the self-renewing and highly differentiable nature of GSCs impose serious concerns for reaching these goals. The upregulation of pro-inflammatory cytokines, immune checkpoint proteins, and downregulation of the major histocompatibility complex in the glioblastoma microenvironment leads to the rapid death of healthy tissue. To date, the FDA has approved immunotherapeutic treatments for many cancers, though immunotherapy remains especially underutilized in glioblastoma treatment despite its immunosuppressive nature. The BBB also remains a major obstacle for standard drug delivery systems and the shortcomings of current chemotherapeutics in effectively permeating the barrier often result in decreases to a patient's quality of life. Nanomedicine is capable of aiding in the implementation of immunotherapy to future treatment regimens, of alleviating the struggles current therapeutics face in reliably crossing the BBB, and of targeting residual GSCs which have hindered progression in overall survival. Brain penetrating nanoparticles are earning more recognition every day for their potential to navigate through brain spaces which are otherwise inaccessible, and for offering a viable solution to consistently deliver therapeutics beyond the BBB. With both hydrophilic and hydrophobic components, modifiable surfaces, and a size ideal for crossing endothelial gap junctions, the ceiling for these nanoparticles continues to rise. Studies and clinical trials have showcased some of the auspicious incorporations of nanomedicine into GBM treatments and as researchers continue to develop nanotherapeutics, we would like to highlight our closing thoughts on parameters one can consider as we integrate nanomedicine for glioblastoma to change the current landscape of treatment options.

1. Moving forward the greatest concern for the implementation of nanomedicine in the treatment of glioblastoma is the progression through the clinical phases. While there are ~850 recurrent glioblastoma studies that have made it to clinical trials, nearly one third of these studies are canceled or suspended and only a small fraction made it to phase 3. There have been no complete studies to make it past the investigational stage and only 3 (<0.5%) have passed the quality assessment. Nanomedicine for glioblastoma will face multiple hurdles to experience potential translation at the clinics, but we as the community promoting this extraordinary science need to be well prepared so that the complete potential for nanomedicine can be realized to stop or delay GBM. It is increasingly important that early phase clinical trials based on nanotherapeutic platforms against glioblastoma utilize tissue samples collected both pre and post treatment. Ability to detect the nanoparticles in the brain tissue samples is an important parameter to confirm whether the drug delivery was successful in targeting the tumor site. These can be achieved by working alongside clinical partners and incorporating tracking components in the nanoplatforms.
2. Another aspect that needs to be discussed is the ability of the nanomedicine to distribute throughout the brain. The migratory nature of GSCs make it difficult for most therapeutic approaches to reach every single cell across the brain leading to inefficient anti-tumor efficacy while increasing the demand for more complex nanoplatforms which can reach the highly invasive GSCs. Thus, as well-informed readers and researchers, we need to embrace nanoparticle distribution throughout the brain along with the tumor rather than distribution of the particles only at the implanted tumor in mice.
3. The complex nanoplatforms may show significant efficacy in the laboratory setting, but the transition from bench to bedside would experience additional challenges. We understand, failure of many clinical trials to proceed to the clinics lies in sample size in which the therapeutic was evaluated. Considering the heterogeneity of GBM and evaluation of therapeutic efficacy of a drug candidate in a small sample size, there remains a high probability of including false positive results or outliers. Evaluating a drug candidate in a larger sample size comprising a variety of different glioblastoma patient background will help us investigate the potential efficacy of the therapy if translated to the clinical setting. Larger sample size requires large-scale synthesis of the nanoformulation and high batch-to-batch reproducibility. Scaling up nanoparticle synthesis is challenging since in most cases of complex nanoplatforms it is difficult to maintain the physicochemical parameters. Though complex nanostructures may seem necessary, a simple yet efficient nanoparticle composition would be feasible to tackle the large-scale production with reduced variability and improved batch-to-batch similarity for glioblastoma.

For the fields of neuro-oncology and nanomedicine alike, the community needs a change in experimental habits, to allow for an accelerated expansion in the understanding of glioblastoma. We realize that combatting these barriers will make nanoplatform based interventional studies against glioblastoma successful drug candidates to reach the clinics.

AUTHOR CONTRIBUTIONS

Shrita Sarkar: Writing – original draft (equal). **Jessica Greer:** Writing – original draft (supporting). **Nathaniel J. Marlowe:** Writing – original draft (supporting). **Angeline Medvid:** Writing – original draft (supporting). **Michael E. Ivan:** Writing – review and editing (supporting). **Nagesh Kolishetti:** Writing – original draft (supporting). **Shanta Dhar:** Conceptualization (equal); funding acquisition (equal); project administration (equal); resources (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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