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REVIEW

Advances and Challenges in Nano-Delivery Systems for Glioblastoma Treatment: A Comprehensive Review

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Abstract: Glioblastoma is the most aggressive and lethal primary brain tumor in adults, with current treatment options offering only limited improvement in patient survival. Despite the advancement of modalities such as immunotherapy, targeted therapy, gene therapy, focused ultrasound, and tumor-treating fields, therapeutic efficacy remains unsatisfactory due to challenges such as the blood-brain barrier, tumor heterogeneity, and treatment resistance. Nanotechnology has emerged as a promising platform to enhance the delivery, specificity, and combinatorial potential of these therapies. By enabling precise and multifunctional delivery of therapeutic agents, nanoscale systems hold the potential to overcome critical biological and pharmacological barriers in glioblastoma treatment. This review provides an overview of recent progress in nanomedicine-based strategies for glioblastoma, critically examines the key challenges that limit their clinical translation, and highlights innovative approaches designed to improve therapeutic outcomes. Future perspectives on how nanotechnology may reshape the landscape of brain tumor treatment are also discussed.

Keywords: glioblastoma, nanotechnology, nano-delivery systems

Introduction

Glioblastoma (GBM, World Health Organization grade IV astrocytoma) represents the most prevalent primary malignant brain tumor, characterized by a median overall survival of 13–24 months[1] and a 5-year survival rate below 10%.[2–6] The current standard of care, established in 2005 and commonly referred to as the Stupp regimen,[7,8] comprises maximal safe surgical resection followed by concurrent radiotherapy and chemotherapy, with subsequent adjuvant chemotherapy. This foundational protocol has persisted as the therapeutic mainstay for nearly two decades. Despite multimodal therapeutic strategies in recent years, tumor recurrence typically occurs within 6–9 months post-diagnosis in the majority of patients.[9] Overcoming the therapeutic limitations of GBM requires innovative strategies capable of addressing its unique biological barriers. The key challenges include the restricted permeability of the blood-brain barrier (BBB), the profound intratumoral heterogeneity that promotes treatment resistance, the immunosuppressive tumor microenvironment, and the lack of effective means to deliver combination therapies with spatial and temporal precision. These complexities collectively render monotherapies insufficient and highlight the necessity for integrated, adaptable, and targeted delivery approaches.

The emergence of nanotechnology has catalyzed a paradigm shift in neuro-oncological therapeutics. Rather than functioning as a discrete treatment modality, nanotechnology operates synergistically with conventional therapies to enhance their therapeutic effect. This interdisciplinary approach demonstrates particular promise in overcoming the

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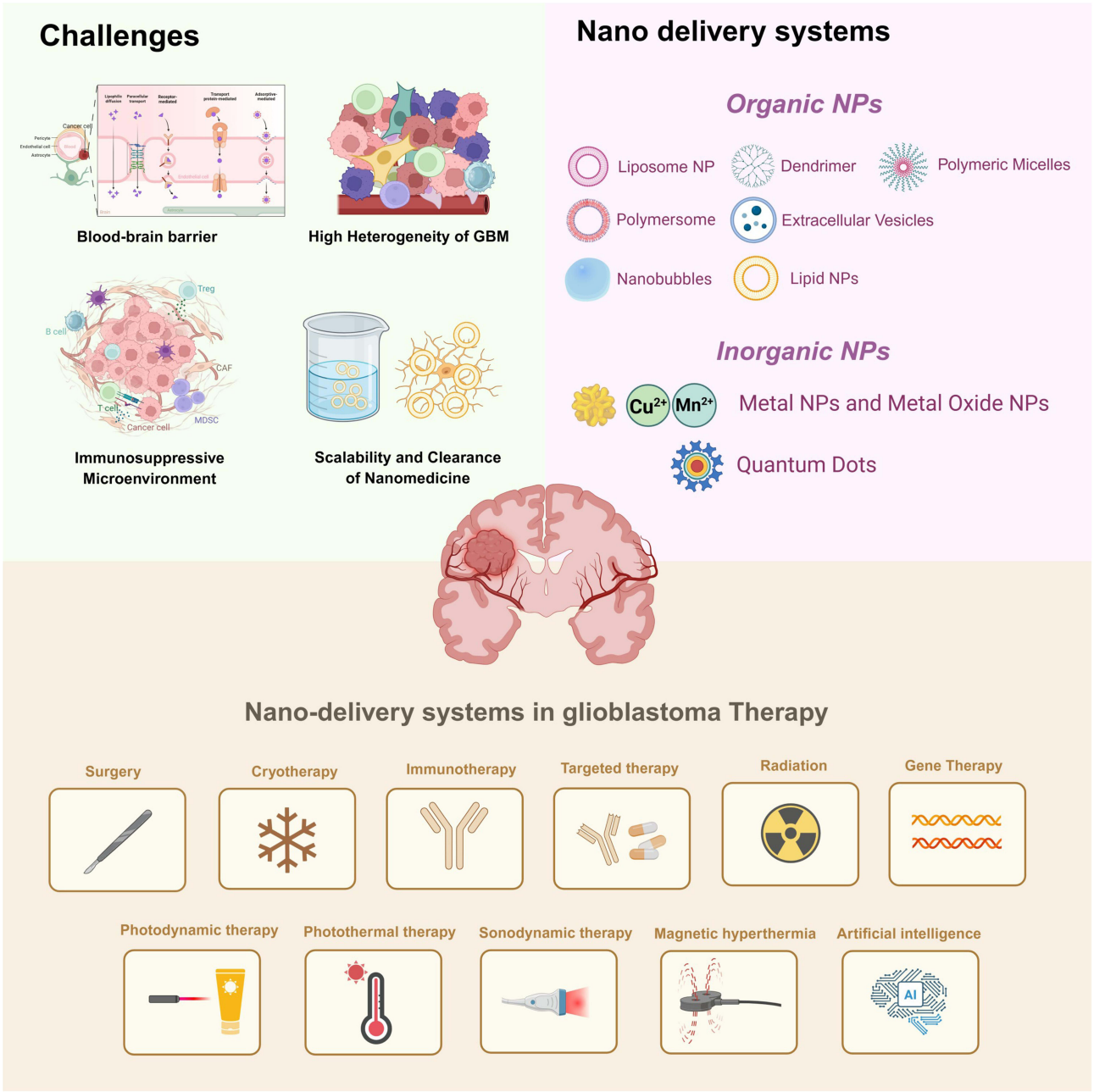
Graphical Abstract



unique challenges inherent to brain tumor treatment through its capacity to serve as a multifunctional delivery platform. Nanoscale systems enable precise co-delivery of diverse therapeutic agents, including surgical interventions, chemotherapeutics, immunomodulators, targeted molecules, radiosensitizers, and genetic material.[8]

Unlike previous reviews, this work provides a focused analysis of how rationally designed nanodelivery systems address the unique pathophysiological challenges of GBM, with special emphasis on BBB traversal. This review aims to comprehensively summarize recent advances in nanodelivery strategies for GBM treatment, analyze current limitations

and challenges in clinical treatment and translation, and highlight opportunities for future research and therapeutic development.

Challenges for Nano-Delivery Systems in GBM Treatment

As the most malignant astrocytoma, GBM has many special characteristics compared with many other tumors, such as highly heterogeneous and immunosuppressive tumor microenvironment (TME).[10] Moreover, the BBB largely contributes to the failure of effective drug permeation and concentration in the tumor region when giving systemic treatment.[10–12] In addition, we discussed the current challenges of applying nanoparticles (NPs) in GBM therapy from the perspective of nanomaterial design and function.

Blood-Brain Barrier

The BBB is a critical regulator of central nervous system (CNS) homeostasis, functioning through the neurovascular unit (NVU), a complex structure composed of endothelial cells, pericytes, and astrocytic end feet. During tumor progression, the BBB undergoes significant disruption, evolving into the blood-brain tumor barrier (BBTB). While the BBTB is more permeable than the BBB, its heterogeneous and unpredictable permeability often leads to inconsistent and suboptimal drug delivery, posing a major challenge for effective treatment. There are many excellent reviews that summarize ways to deliver drugs circumvent the BBB,[13–15] but we focused on leveraging endogenous transport mechanisms in conjunction with NPs. In the following discussion, we highlight key developments and mechanisms in this field (Figure 1a).

Passive Transport

In GBM, abnormal angiogenesis and impaired lymphatic drainage enhance NPs accumulation at the tumor site via the enhanced permeability and retention (EPR) effect. This passive targeting strategy offers distinct advantages for traditional liposomes and other lipophilic nanocarriers, enabling targeted delivery without the need for intricate surface modifications. However, it is important to note that many lipophilic drugs still struggle to cross the BBB effectively. To enhance passive transport, the primary strategies include modifying surface ligands, reducing particle size to the 120–200 nm range, and coating particles with polyethylene glycol (PEG) to evade reticuloendothelial system (RES) clearance and prolong circulation persistence.[16]

Receptor-Mediated Transport (RMT)

The modification of ligands for receptors on the BBB and BBTB on the surface of drugs enables their penetration through the BBB via ligand-receptor interactions. Among the most extensively studied receptors are the transferrin receptor (TfR), apolipoprotein E (ApoE) and angiopep-2 (AP2). Other ligands that have been found to be able to bind to the receptors on the BBB includes bradykinin (BK),[17] Choline analog 2-methacryloyloxyethyl phosphorylcholine (MPC),[18] D-peptide vascular-associated protein (VAP).[19] To enhance BBB penetration, some researchers have simultaneously functionalized NPs surfaces with multiple ligands.[20] Glioblastoma stem cells (GSCs), identified as a $CD133^{+}$/$ALDH1^{+}$ subpopulation resistant to most chemotherapy and radiation therapy, are a target of GBM therapy. Many researchers have constructed targeted NPs with anti-CD133 monoclonal antibody (CD133mAb).[21]

Carrier-Mediated Transport (CMT)

The BBB expresses specialized carrier proteins that mediate substrate-specific transport of endogenous molecules, including glucose, amino acids, and nucleotides. NPs functionalized with these biological ligands can exploit glucose transporters 1 (GLUT1) or large neutral amino acid transporters 1 (LAT1) to achieve carrier-mediated transcytosis.[22,23] In an innovative departure from conventional strategies, Wang et al[24] designed a carboxybetaine zwitterionic nanosystem that hijacks the betaine/GABA transporter 1 (BGT-1), establishing a novel brain delivery paradigm through charge-mediated transporter interactions.

Modulating Barrier Integrity

Focused ultrasound (FUS) coupled with intravenous microbubbles has emerged as a spatially controlled modality for transient BBB modulation, achieving localized therapeutic delivery without inducing hemorrhage or edema. Preclinical

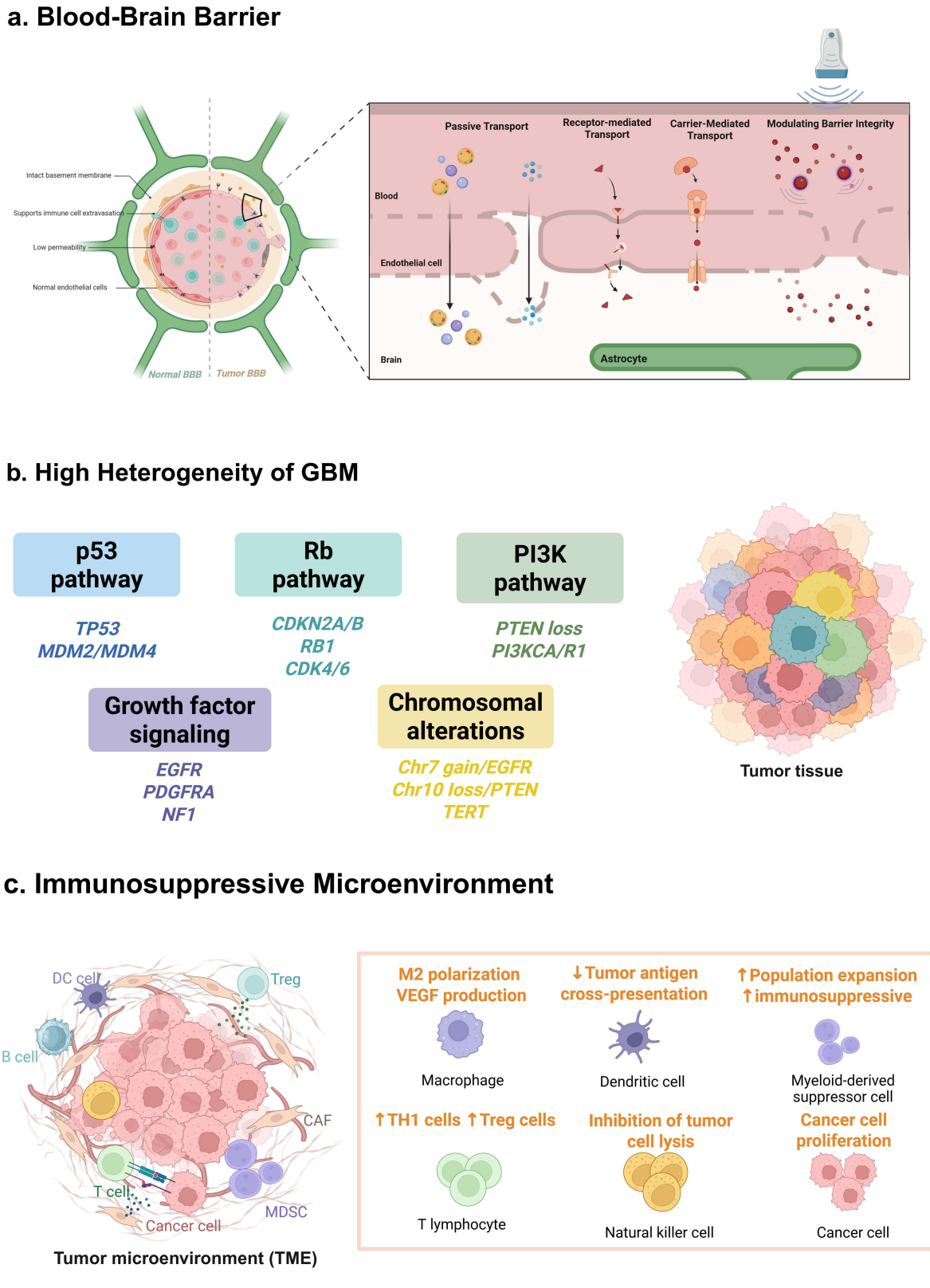


Figure 1 Challenges for nano-delivery systems in GBM treatment. (**a**) The BBB and its tumor-altered form, the BBTB, limit NP delivery to the brain. Several mechanisms are utilized to enhance NP transport, including passive targeting, RMT, CMT, and transient modulation of barrier integrity. (**b**) GBM exhibits significant intratumoral heterogeneity, driven by alterations in key signaling pathways. (**c**) The GBM TME consists of immunosuppressive cell populations, including Tregs, TAMs, MDSCs, and dysfunctional dendritic and natural killer cells. These elements inhibit anti-tumor immunity by suppressing T cell activity, promoting M2 polarization, impairing antigen presentation, and sustaining tumor proliferation.

studies confirmed this technique's precision through region-specific luciferase expression in NP-targeted cerebral areas,[25] with current translational progress reaching Phase I/II clinical trials.[26–28] Notably, Cai et al[29] pioneered a non-invasive optoBBTB platform using vascular-targeted gold NPs activated by 532 nm picosecond laser pulses to reversibly enhance BBTB permeability, improving paclitaxel delivery. However, critical concerns persist regarding the long-term safety of barrier modulation, as indiscriminate BBB disruption risks neurovascular unit damage and off-target neurotoxicity.[30]

High Heterogeneity of GBM

Tumor heterogeneity in GBM manifests as both intratumoral heterogeneity (cellular/molecular diversity within individual tumors) and intertumoral heterogeneity (variations between tumors across patients). Intertumoral heterogeneity serves as a prognostic indicator,[31,32] while intratumoral heterogeneity reflects the coexistence of molecularly distinct subclones driving therapeutic resistance. This section focuses primarily on intratumoral heterogeneity (Figure 1b).

The dynamic evolution of intratumoral heterogeneity underpins GBM's capacity to evade therapeutic interventions. Spatial and temporal genomic analyses reveal that recurrent tumors frequently develop divergent molecular profiles compared to primary lesions,[33] with rapid clonal selection enabling escape from targeted therapies. This adaptive plasticity renders monotherapeutic approaches largely ineffective, as evidenced by the transient efficacy of RTK inhibitors. Key molecular drivers of heterogeneity include p53 pathway,[34] Rb pathway,[35] Growth factor signaling,[36–38] PI3K pathway,[39] Chromosomal alterations.[40,41] Advanced analytical platforms including single-cell RNA sequencing, Cytometry by time-of-flight (CyTOF), and phosphoproteomics have revolutionized our capacity to map this heterogeneity. Importantly, such heterogeneity complicates the standardization of nanodelivery systems in GBM, as differences in target expression, endocytic activity, and tumor microenvironment across subclones may significantly alter nanoparticle uptake, distribution, and therapeutic response. To date, no optimal strategies have been developed to tailor NPs delivery systems to the dynamic evolutionary landscape of GBM.

The immunological dimensions of GBM heterogeneity will be subsequently analyzed in Immunosuppressive Microenvironment.

Immunosuppressive Microenvironment

GBM maintains an immunologically inert TME that presents formidable barriers to conventional immunotherapies.[42–44] This immunosuppressive niche is orchestrated by heterogeneous cellular components, including infiltrating regulatory T cells (Tregs), tumor-associated microglia/macrophages (TAMs, constituting >30% of TME cellularity), and myeloid-derived suppressor cells (MDSCs). These populations demonstrate remarkable plasticity and functional diversity, collectively fostering a tumor-promoting and therapy-resistant niche through multiple mechanisms.[45,46]

The immunological landscape of GBM exhibits layered complexity:

- Cellular specialization: Microglial TAMs display elevated MHC II expression and lipid metabolic signatures, while monocyte-derived subsets are enriched in hypoxic regions;[47]
- Temporal evolution: tment-naïve tumors feature microglia-dominated TAM populations. In contrast, recurrent lesions show monocyte-derived TAMs;[47]
- Functional polarization: Distinct TAM subpopulations differentially regulate extracellular matrix remodeling, angiogenesis, and T cell exhaustion.[48]

This dynamic cellular ecosystem not only drives tumor aggressiveness but also establishes adaptive resistance mechanisms against targeted therapies (Figure 1c).

The Scalability and Clearance of Nanomedicine

The clinical translation of nanomedicine for GBM remains limited by scalability challenges. First, bottom-up strategies, commonly used to construct multifunctional nanoparticles with targeting ligands for BBB penetration, involve complex processes, solvent residue, and poor reproducibility.[49] Second, although carriers like liposomes and PLGA are the US Food and Drug Administration (FDA)-approved for various indications, their application in CNS diseases is still under

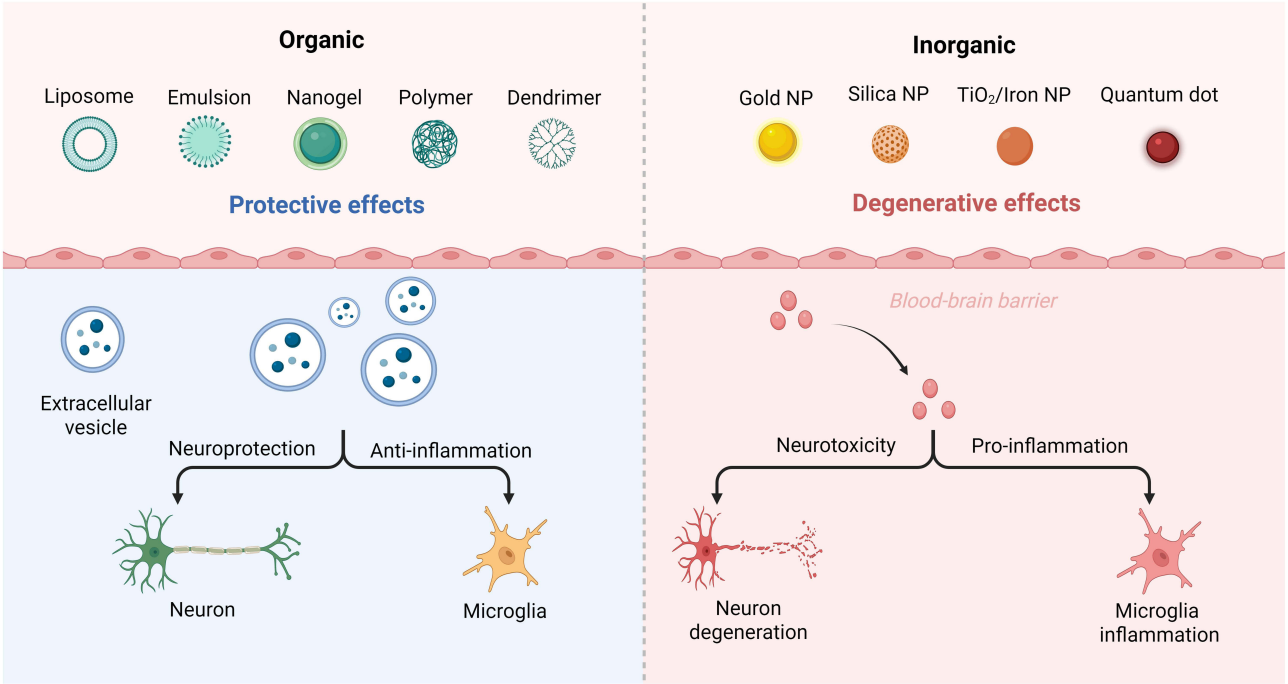


Figure 2 The Clearance of Nanomedicine. Organic NPs are partially cleared via the glymphatic system, aided by EVs derived from microglia, while inorganic NPs impair EV release and lead to intracellular accumulation.

investigation, with no approved nanoformulations for GBM to date.[50,51] Third, complex administration routes, high production costs, and limited acceptance by clinicians and patients further hinder clinical adoption. Finally, scaling up multifunctional nanocarriers risks altering particle size and composition, compromising BBB transport, stability, and batch consistency.

The accumulation of nanomaterials in the brain may trigger endoplasmic reticulum (ER) stress,[52] induce neuronal apoptosis and autophagy, and potentially increase the risk of neurodegenerative diseases.[53] While nanomaterials in peripheral organs are typically cleared via hepatic or renal pathways, their intracerebral fate remains poorly understood. After crossing the BBB, NPs may persist in the extracellular matrix or be internalized by brain-resident cells, with microglia playing a central role in phagocytosis and redistribution (Figure 2). Studies have shown that organic nanoparticles are cleared via the glymphatic system, aided by microglia-derived extracellular vesicles (EVs). In contrast, inorganic nanoparticles suppress microglial ERK1/2 signaling, impairing EV release and leading to intracellular accumulation. Reactivating ERK1/2 restores EV production and promotes clearance.[54] These findings highlight the need to modulate microglial pathways to optimize nanoparticle safety and clearance in glioblastoma therapy.

Nano Delivery Systems

It is necessary to introduce each kind of nano-delivery system before we review the detailed nano-delivery strategies in GBM. In this review, we classify nano delivery systems into two types, organic and inorganic. The former includes liposome, dendrimer, polymeric micelles (PMs), polymersome, EVs, micro/nanobubbles (NBs), and lipid NPs. And the latter incorporates metal NPs (MNPs), metal oxide NPs (MO-NPs), and quantum dots (QBs).

Organic NPs

Liposome

Liposomes are cell-like, membranous phospholipid structures, sized from nanometers to micrometers.[55,56] They are broadly classified into unmodified and engineered liposome.[57] Unmodified liposomes, highly biodegradable and biocompatible with low toxicity, are widely used as drug carriers. But they have drawbacks depending on administration routes. For example, intravenous administration of liposomes results in serum protein adsorption and subsequent

clearance by the hepatic RES in the liver, while administration via the oral route subjects the liposomes to harsh gastrointestinal conditions such as high gastric acidity, bile salts, and lipase. For GBM, targeting liposomes is challenging due to efflux transporters.[58,59] Engineered liposomes are modified to overcome limitations of traditional ones. They can be functionalized with specific ligands and often modified on the surface using substances like glucose, polysaccharides, and chitosan.[60–64]

Dendrimer

Dendrimers are synthetic, monodisperse nanostructures with hyperbranched three-dimensional (3D) architectures, composed of a core, layered branching units (generations, G), and surface functional groups. Their precisely controlled synthesis (via divergent/convergent methods) enables tailored modifications (eg, targeting ligands) and co-loading of drugs, genes, or imaging agents. Among them, PAMAM is favored due to its established synthesis, biocompatibility, functionalization ability, and drug-delivery effectiveness.[65] G6 dendrimers show great clinical promise because of enhanced tumor - targeting capabilities.[66] In GBM therapy, cationic dendrimers (eg, G5 PAMAM) exhibit enhanced BBB penetration and stimuli-responsive drug release (eg, pH/enzyme-triggered), supporting theranostic applications.

Polymeric Micelles

Self-assembled nanomicelles with a hydrophobic core and a hydrophilic shell structure are ideal hosts for the delivery of hydrophobic drugs.[67] The main physicochemical property of micelles is their small size (10–100 nm). The hydrophobic core formed by self-assembly of amphiphilic copolymers can bind poorly water-soluble drugs. While the hydrophilic shell, often made of PEG due to its hydration properties and large excluded volume effect that minimize serum protein interactions and prolong systemic circulation, protects the drug from metabolism and improves the accumulation of the delivered drug at the target tissue site.[68,69]

PMs have emerged as promising carriers for gene-based therapies in GBM treatment. Nucleic acid therapeutics, such as plasmids, antisense oligonucleotides, and small interfering RNA (siRNA), are increasingly delivered via polyion complex (PIC) NPs formed through electrostatic interactions between the negatively charged phosphate backbone of nucleic acids and cationic segments of PEG-b-PAA (poly(ethylene glycol)-block-poly(allylamine)) copolymers. This self-assembly strategy not only stabilizes nucleic acids against enzymatic degradation in vivo but also enhances cellular uptake efficiency by leveraging the "proton sponge" effect of the polyallylamine (PAA) block in endosomal compartments.[70] The HCA-A2 micelle system using redox-sensitive materials showed the ability to release 100% of the payload within 24 h in a tumor-mimicking microenvironment, compared with only 43.97% under normal conditions.[71]

Polymersome

Polymersomes are hollow polymer spheres with an aqueous core and a diblock polymer shell. The polymer membrane forms a bilayer that is very similar to the membrane of liposomes.

The advanced properties of polymersomes make them a suitable alternative to liposomes as their thicker membranes and stronger covalent bonds in block copolymers endow them with enhanced mechanical and colloidal stability.[72,73] And their excellent chemical versatility enables precise tailoring of vesicle properties.[72,74] In GBM treatment, polymersomes show greater BBB permeability, better tumor targeting and accumulation than conventional liposomes, and their large aqueous core allows for better drug loading and tunable membranes enable controlled sustained release, suitable for long-term therapy.[75] However, their lower permeability may also lead to higher drug leakage and reduced retention efficiency, resulting in a trade-off between stability and controlled drug release.[74,76]

Extracellular Vesicles

EVs are a heterogeneous group of lipid bilayer vesicles, and are released by almost all cell types. Based on their size, EVs are typically classified into four major categories: exosomes (EXOs; 30–150 nm), microvesicles (MVs; 5–500 nm, up to 1 μm), apoptotic bodies (100–5000 7nm), and large oncosomes (LOs; 1–10 μm). GBM-derived EVs have emerged as a powerful liquid biopsy tool in GBM, offering superior stability and molecular insight compared to circulating tumor cells (CTCs) and cell-free nucleic acids (cfNAs) while efficiently crossing the BBB, even when intact; their role will be

further explored in Surgery with Nano Delivery Systems. Due to their biocompatibility, ability to cross the BBB, and inherent capacity for cargo encapsulation, EVs are increasingly being explored as nanocarriers for targeted therapies in GBM.[77] The TfR expressed on surface of blood EXOs has been shown to promote the BBB penetration without further modification.[78,79] Although EV correlation studies have increased significantly over the last decades, the main weakness is the lack of standard separation methods.

Nanobubbles

NBs are nano-sized colloidal carriers composed of a gaseous core, such as perfluorocarbon or air, encapsulated by a lipid, polymer, or protein shell.[80] Compared to microbubbles (0.1–10 μm), NBs exhibit superior deformability, allowing them to navigate capillaries more efficiently and respond dynamically to ultrasound stimulation. These advantages render NBs highly effective as nano-sized ultrasound contrast agents (UCAs) and targeted drug carriers for GBM therapy, enabling real-time molecular imaging and precise drug delivery via their ultrasound responsiveness. In particular, high-intensity focused ultrasound (HIFU) in combination with NBs enhances BBB permeability through transient cavitation at the gas-liquid interface. However, the inherent gaseous core of NBs may impose limitations on their in vivo stability and circulation time, potentially restricting their utility as standalone drug delivery vehicles.

Lipid NPs

Solid lipid NPs (SLNs) consist of lipids combined with surfactants and/or co-surfactants. The lipid matrix is pivotal in these systems, as it not only maximizes drug entrapment but also facilitates controlled release and responsiveness to various stimuli, such as temperature. This feature is particularly valuable when administering low-concentration drugs. The structural properties enable SLNs to encapsulate both lipophilic and hydrophilic drugs, as well as other therapeutic agents like oligonucleotides, peptides, and genes. However, SLNs also face challenges, such as the potential expulsion of encapsulated drugs, low encapsulation efficiency (EE)%, and a tendency to gelate during formulation.[81,82] These issues stem from the internal structure of the lipid core, which impedes the formation of voids during crystallization, ultimately affecting drug release dynamics.

To address the limitations of SLNs, Müller et al developed nanostructured lipid carriers (NLCs), which combine solid and liquid lipids to improve the lipid core structure.[81,82] There was a comparative study that evaluated the antitumor efficacy of vincristine (VCR) and temozolomide (TMZ)-loaded SLNs and NLCs. It was found that VT-NLCs had longer release time and stronger cytotoxicity in vitro, and stronger antitumor efficacy in vivo.[83] Another comparative study evaluated the anti-tumor effects of polymeric NPs, SLNs, and NLCs delivering TMZ. And the conclusion is constant with the former several studies that NLCs has higher delivering efficiency and inhibition efficacy than PNPs and SLNs.[84] While NLCs show promise in improving drug delivery and BBB penetration for GBM, challenges like safety, scalability, and efficacy remain. Future research should focus on enhancing biocompatibility and clinical translation. Ultrasmall nanostructured lipid carriers (usNLCs), a novel solid lipid nanoparticle variant, demonstrate superior drug loading, stability, and bioavailability over conventional NLCs for GBM treatment, attributed to their optimized lipid ratio and ≈50 nm size.[85,86]

Inorganic NPs

Metal NPs and Metal Oxide NPs

Composed primarily of noble metals or transition metal oxides, MNPs and MO-NPs exhibit unique physicochemical properties, including high surface-to-volume ratios, tunable surface chemistry, and multifunctionality Their intrinsic optical, catalytic, and magnetic properties enable diverse biomedical applications, ranging from drug delivery system to photodynamic therapy (PDT), photothermal therapy (PTT), radio sensitization, and ferroptosis induction. Notably, ultrasmall AuNPs have demonstrated the ability to cross the BBB.[87] However, the deposition of metallic NPs in the brain may lead to toxicity, which still limits their application in GBM.

Quantum Dots (QDs)

QDs are nanoscale semiconductor materials including semiconductor-based (CdSe, CdTe, InP) and carbon-based (graphene quantum dots [GQDs], GOQDs) variants. They have ultrasmall size (<10 nm), high surface area-to-volume

ratio. Additionally, compared to conventional NPs, QDs exhibit superior optical properties, including size-dependent emission, high photostability, and near-infrared (NIR) light responsiveness, enabling deep tissue penetration and real-time imaging.[88] QDs have demonstrated significant potential in both the diagnosis and treatment of GBM, serving as multimodal platforms for imaging, PTT and PDT. Due to their stable photoluminescence, low toxicity, and superior imaging capabilities, quantum dots—especially GQDs—offer enhanced precision and durability over conventional contrast agents in fluorescence-guided surgery and hybrid magnetic resonance imaging (MRI) imaging.[89,90]

Nano-Delivery Systems in GBM Therapy

Surgery with Nano Delivery Systems

Preoperative diagnosis of GBM relies on imaging techniques and tissue biopsy. However, for MRI the delineation of the actual tumor volume is difficult because peritumoral edema does not readily allow precise discrimination of tumor margins. Tissue biopsy, while accurate for brain tumor diagnosis, carries risks due to its invasive nature. Liquid biopsy has emerged as a promising diagnostic approach for GBM, offering a non-invasive alternative to traditional tissue biopsies and imaging techniques. However, GBM liquid biopsy faces challenges from BBB-restricted tumor material release, intratumoral heterogeneity, and the rarity of CTCs coupled with Circulating tumor DNA (ctDNA)'s undetectable levels.[91]

Nanomaterial-enhanced biosensors, leveraging unique properties such as high surface area and tunable functionality, have dramatically improved CTC detection sensitivity. Label-free GQDs-NPG impedimetric biosensors achieve a groundbreaking 1 cell/mL detection limit with robust stability and anti-interference in clinical samples.[92]

For the division of the GBM surgery range, functionalized NPs can be equipped with high-sensitivity CAs to enhance image contrast by targeting tumor-specific markers (such as EGFR or integrins) to help accurately locate tumor boundaries. Recent studies have demonstrated the significant potential of paramagnetic chemical exchange saturation transfer (PARACEST)-based nanoscale agents for improving glioma imaging. In a study, a dual-modal imaging agent was developed by conjugating a PARACEST MRI contrast agent, and a fluorescent dye, DyLight® 680, to a fifth-generation PAMAM dendrimer.[93] Similarly, Sunalee and his team conjugated Eu-DOTA-Gly4 and clinically relevant Gd-DOTA to G5 PAMAM dendrimers, demonstrating selective accumulation in glioma regions due to the disrupted blood-brain barrier, while nanoparticles remained confined to the vascular lumen in normal brain tissue.[94] These findings collectively highlight the diagnostic advantages of CEST-based nanoscale agents, particularly in enhancing tumor detection accuracy and specificity. Dendrimer-based paramagnetic nanoparticles have emerged as promising alternatives to gadolinium (Gd)-based CAs. This radical dendrimer achieved contrast enhancement comparable to that of commercial Gd-based CAs at a standard dose (0.1 mmol/kg), even when administered at a fourfold lower dose (0.025 mmol/kg).[48] Dual-modality dendrimer probes combining MRI and NIR fluorescence enable high-resolution preoperative tumor imaging, while also enhancing drug solubility and bioavailability for improved therapeutic outcomes.[95] Their results demonstrated that the ^{99m}Tc-labeled GQDs efficiently accumulated at tumor sites, highlighting the potential of this nanomaterial as a highly sensitive and specific radiotracer for glioma detection.

FGS has revolutionized neuro-oncology by enabling real-time intraoperative tumor visualization, enhancing resection accuracy while preserving healthy tissue. NP-based fluorescent probes offer superior tumor specificity, prolonged signal retention, and multimodal imaging capabilities compared to conventional dyes. Shi et al[96] developed DOTA-FA-ICG, a folic acid-conjugated nanoplatform integrating ICG dye and a DOTA chelator for targeted PET and fluorescence imaging of GBM. The self-assembled NIR-II-emitting nanoparticles, particularly in their radiolabeled form (^{64}Cu-DOTA-FA-ICG), demonstrated precise GBM accumulation, facilitating high-resolution intraoperative tumor delineation via PET, NIR-I, and NIR-II fluorescence. Additionally, QDs-c(RGDyk) NP, a glioma-targeting quantum dot system, enabled real-time fluorescence-guided resection, further improving tumor localization. When combined with ultrasound-targeted microbubble destruction (UTMD), QDs-c(RGDyk)NP exhibited enhanced glioma accumulation, ensuring precise visualization of tumor margins in orthotopic GBM models.[97] These nanodelivery platforms provide highly specific, multimodal imaging solutions for FGS, facilitating maximal safe resection and improving surgical outcomes in GBM treatment.

After surgery, drug-loaded nanohydrogels can be directly filled into the post-operative resection cavity, enabling localized, sustained drug release to suppress residual tumor cell proliferation while minimizing systemic toxicity. Yu et al demonstrated that upon injection, a photopolymerizable TMZ-loaded hydrogel rapidly solidifies under UV light, facilitating controlled, prolonged TMZ release, which significantly enhances in vivo antitumor efficacy.[98,99]

Chemotherapeutic Nanodelivery System

FDA has approved multiple chemotherapeutic agents for brain tumor treatment. Among these, TMZ is the first-line chemotherapeutic agent for GBM. However, dose-dependent toxicities limit its clinical utility.[100] Nanoscale drug delivery systems have emerged as a transformative strategy to enhance TMZ bioavailability, prolong circulation time, improve BBB permeability, and mitigate off-target effects. Extensive preclinical studies have validated the potential of TMZ-loaded nanocarriers to optimize tumor targeting and therapeutic efficacy.[101–103]

Emerging NP-based co-delivery systems have been strategically designed to overcome TMZ resistance through simultaneous encapsulation of chemotherapeutic agents and resistance-modulating compounds. Notably, the integration of O6-methylguanine-DNA methyltransferase (MGMT) inhibitors with TMZ has shown promise in addressing chemoresistance in MGMT promoter-unmethylated GBM subtypes.[104–106] Song et al[107] devised intranasally administered borneol-gastrodin liposomes (Bo-Gas-LP) to reverse TMZ resistance via P-glycoprotein inhibition and oxidative stress modulation. To circumvent TMZ's intrinsic limitations of low bioavailability and systemic toxicity, Duan et al[108] developed a lipophilic TMZ derivative (TMZ16e) with improved cellular internalization. Building on this, they engineered anti-EphA3-targeted thermosensitive liposomes incorporating TMZ16e and gold nanoparticles (antiEphA3-TMZ16e-GNPs-TSL) for intranasal brain delivery. This platform enables spatiotemporal control through NIR irradiation, where plasmonic heating of AuNPs triggers phase transition-mediated TMZ16e release at the tumor site. Jiang et al[109] implemented a paradigm-shifting cation-free siRNA micelle system combining TMZ with STAT3-targeted siRNA (si-STAT3), mechanistically demonstrating that STAT3 silencing sensitizes GBM cells to TMZ through MGMT expression downregulation and DNA repair pathway modulation. Complementarily, CD133 aptamer-conjugated PEGylated gold NPs (Au-PEG-CD133-CB-839) encapsulating the glutaminase inhibitor telaglenastat (CB-839) exhibited dose-dependent GSC cytotoxicity, with combinatorial efficacy surpassing individual nanodrug components.[110]

Beyond TMZ, nanodelivery systems have revolutionized the administration of diverse chemotherapeutic agents by addressing formulation challenges including poor aqueous solubility, restricted BBB permeability, and systemic toxicity. Lipid-based nanocarriers such as NLCs and SLNs have demonstrated exceptional potential for hydrophobic drugs, with documented success in delivering COX-2 inhibitor celecoxib (CXB),[111] doxorubicin,[112,113] paclitaxel (PTX),[114,115] carmustine,[116] batimastat (BB-94),[117] and kaempferol,[118] sorafenib micelles.[119,120] These systems enhance drug solubility by 3–5 orders of magnitude while improving tumor-selective cellular uptake and cytotoxicity profiles. Advanced polymer architectures are expanding therapeutic frontiers in GBM management. PAMAM dendrimers functionalized with 5-fluorouracil,[121] celecoxib-simvastatin dual therapies,[122] xanthone derivatives,[123] cabazitaxel,[124] and DOX[125] demonstrate enhanced pharmacokinetics through controlled release mechanisms. Innovatively, redox-responsive nanoparticles co-delivering TMZ and β-lapachone (β-Lapa) exhibited tumor growth inhibition via synergistic ROS amplification.[71] Dendrimer-rapamycin conjugates achieved TAM depletion in orthotopic models through mTOR pathway modulation, concurrently suppressing tumor angiogenesis.[126] Amphiphilic block copolymer micelles encapsulating panobinostat and imatinib showed increased cytotoxicity versus free drugs, maintaining viability in normal astrocytes.[127] PH-responsive xanthone-loaded micelles (XGAc-Micelles) demonstrated tumor-specific drug release with encapsulation efficiency, preserving healthy cell viability.[128]

Nanoscale formulation strategies are being used to reengineer bioactive plant-derived compounds. For example, ApoE-functionalized liposomes loaded with artesunate (ApoE-ARTPC@TMZ) reverse TMZ resistance by inhibiting the Wnt/β-catenin/MGMT axis, lowering the IC_{50} in recurrent GBM models.[129–131] Exosomal carriers co-loaded with tanshinone IIA and glycyrrhizin suppress STAT3 phosphorylation, synergizing with TMZ to extend median survival.[78] Resveratrol-conjugated gold nanoparticles enhance the bioavailability of resveratrol,[132] and dendrimer-encapsulated triptolide reduces hepatotoxicity via targeted release.[123]

Immunotherapy with Nano Delivery Systems

We have introduced the immune escape mechanism and therapeutic challenges of GBM in 2.3. It is the key for GBM treatment to remodeled the tumor microenvironment from "cold" to "hot". GBM immunotherapy targets multiple pathways within the complex TME, where immune components interact dynamically. Strategies include the blockade of immune checkpoints (ICB) and the inhibition of immunosuppressive cells, the recruitment, depletion, and polarization of macrophages, and the activation of immune cells.[133]

Nanodelivery systems are revolutionizing ICB in GBM. Yin et al[132] engineered a macrophage membrane-coated NP platform, leveraging PD-1-rich membranes to compete for PD-L1 binding, effectively disrupting immunosuppressive signaling and boosting $CD8^+$ T cell infiltration at tumor sites. Additionally, the adenosine-mediated immune checkpoint CD73, upregulated in the hypoxic GBM microenvironment, suppresses anti-tumor immunity. Au@$Cu_{2-x}Se$ nanoparticles (ACS NPs) release Cu^{2+} ions, forming the cytotoxic CuET complex, which inhibits CD73 expression, reducing adenosine-driven immunosuppression and amplifying T cell-mediated tumor attack, particularly when combined with radiotherapy.[134] Beyond checkpoint inhibition, Jiang et al[58] developed a cathepsin B-responsive nanocarrier co-delivering DOX and resiquimod (R848) to reprogram TAMs from an M2 immunosuppressive state to a pro-inflammatory M1 phenotype, further reinforcing ICB-induced anti-tumor responses. Despite the remarkable success of ICB in many cancer types, the same effects have not been observed in GBM, highlighting the importance of understanding the various factors that determine the immune response in this type of brain tumor and the specificity of the BBB. Galstyan's team designed a polymer delivery vehicle using poly (β-l-malic acid) (PMLA), a neutral polymer. This vehicle enables the delivery of immuno-oncology drugs—nanotechnology- and immunotherapy- based checkpoint inhibitors targeting CTLA-4 or PD-1—across the BBB to GBM. PMLA is covalently bound to CTLA-4 and PD-1 antibodies, making these otherwise impermeable antibodies capable of crossing the BBB.[59]

Nanodelivery systems offer a promising strategy for modulating immunosuppressive cells in GBM, including Tregs, TAMs, and myeloid cells, to restore anti-tumor immunity. Nano-reshaper, co-delivering lymphocyte-depleting agent, cannabidiol, and lymphocyte-recruiting cytokine, LIGHT (TNFSF14), enhances systemic T cell numbers and tumor infiltration,[135] while glutathione-responsive nanoprobes encapsulating TMZ and αCD25-Cy7 efficiently deplete Tregs.[136] rGOQD-based PD-L1-targeted nanoplatforms, combined with NIR-triggered tumor cell death and R848-mediated dendritic cell activation, amplify T cell infiltration.[137] TAM reprogramming is a key strategy in nanodelivery-based GBM immunotherapy, shifting them from an immunosuppressive to a pro-inflammatory phenotype to enhance anti-tumor immunity. It has been achieved using glycopolymer-like NPs decorated with galactose, which both polarize TAMs to an M1 phenotype and suppress lactate efflux via MCT-4 inhibition,[138] while galactose-TLR7/8 agonist dendritic nanostructures selectively target M2 TAMs after crossing the BBB.[139] CSF-1R inhibition through hydroxyl dendrimer-based BLZ945 delivery effectively repolarizes TAMs,[140] and BV2 microglia membrane-coated nanoplatforms encapsulating Mn^{2+} and aPD-1 leverage PTT to induce an immunogenic TME.[141] Myeloid cell-targeting approaches, such as D@MLL NPs hitchhiking on circulating monocytes to transport DOXHCl into intracranial GBM tumors, are effective strategies.[142] Additionally, biodegradable microneedles releasing TLR9 agonists and nano-stimulants locally shift GAMs toward a pro-inflammatory state, reducing tumor recurrence.[143] These nanoplatforms effectively suppress Tregs, reprogram TAMs, and enhance myeloid targeting, reshaping the GBM immune landscape. Mitochondria play a crucial role in immune cell function, making them a key target for nanodelivery-based GBM immunotherapy. Anjali et al[144] designed a mitochondria-targeted dendrimer (D-DPA) by conjugating with the TSPO ligand DPA, enhancing mitochondrial localization and activating stronger antitumor immune signaling than the free ligand PK11195. Additionally, two-photon-activated nanosystems disrupt mitochondrial electron transport, boosting tumor immunogenicity and further amplifying immune responses.[145]

Despite progress, GBM immunotherapy faces challenges in identifying targets, sustaining responses, and overcoming immune evasion, as seen in failed Phase 3 trials. Combining immune checkpoint blockade (eg, PD-1, CD73 inhibition) with radiotherapy or PTT enhances immune activation. Future efforts will focus on overcoming resistance, optimizing delivery, and integrating multimodal strategies.

Targeted Nanotherapeutic Strategies

Distinct from conventional chemotherapy and radiotherapy, targeted therapy focuses on key oncogenic drivers to maximize therapeutic specificity while minimizing systemic toxicity.

The C-X-C chemokine receptor type 4 (CXCR4) has emerged as a dual diagnostic and therapeutic target in GBM. Wojciech et al[146] engineered fifth-generation CXCR4-targeted polyamidoamine (G5-X4) dendrimers, demonstrating optimized pharmacokinetics and tumor-selective drug delivery. Although RAS mutations are infrequent in GBM, constitutive activation of the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways—driven by EGFR amplification and neurofibromin 1 (NF1) loss—remains a critical oncogenic mechanism. Polo-like kinase 1 (PLK1), a mitotic regulator implicated in DNA damage repair and gliomagenesis, is frequently overexpressed in GBM. A polymersome-based system encapsulating the PLK1 inhibitor volasertib exhibited enhanced colloidal stability, prolonged circulation half-life ($t_{1/2}$= 18.7 h), and reduced off-target effects, significantly prolonging survival in orthotopic models.[147]

Anti-angiogenic strategies targeting tumor neovascularization have gained prominence. Angiogenin (ANG), a copper-binding ribonuclease secreted by vascular endothelial cells, was leveraged by Irina et al[23] through AuNP conjugation, creating a theranostic platform capable of dual angiogenesis inhibition and tumor targeting.

While immunotherapeutic approaches (discussed previously) exemplify targeted strategies, their clinical translation remains constrained by tumor heterogeneity (High Heterogeneity of GBM).

Radiosensitizing Nanoplatforms

Radiotherapy remains a cornerstone of GBM management, exerting direct cytotoxic effects through DNA damage while inducing immunogenic cell death (ICD) to potentiate antitumor immunity. However, therapeutic efficacy is limited by radioresistance, inadequate radiosensitizer biodistribution, and hypoxia-driven immunosuppression. Nanodelivery systems overcome these barriers through enhanced radiosensitizer accumulation and ICD-mediated immune activation.

Metallic nanoparticles—including AuNPs, AgNPs, iron oxide (Fe_3O_4), and bismuth (BiNPs)—serve as potent radiosensitizers by augmenting radiation absorption cross-sections and tumor-selective deposition. Targeted AuNPs with BBB-penetrating modifications demonstrated higher tumor-to-normal tissue ratios compared to untargeted counterparts, synergizing with radiotherapy to delay tumor progression.[148–150]

Beyond physical dose enhancement, nanocarriers amplify ICD-mediated immune activation. NP-encapsulated chemotherapeutics combined with irradiation promote calreticulin membrane translocation, high-mobility group box 1 (HMGB1) release, and adenosine triphosphate (ATP)-driven dendritic cell maturation, culminating in enhanced cytotoxic T lymphocyte infiltration.[151] Radiation-induced chemokine (C-C motif) ligand 2 (CCL2) upregulation in gliomas enhances mesenchymal stem cell (MSC) tropism. Wang et al[152] engineered CCR2-overexpressing MSCs (CCR2-MSCs) and fabricated MSC membrane-coated mesoporous silica nanoparticles. When combined with X–irradiation, this system amplified ICD markers while achieving tumor growth inhibition.

Gene Therapy via Nanodelivery Systems

Gene therapy has emerged as a transformative strategy for GBM by targeting oncogenic drivers, drug resistance genes, and immune evasion pathways. RNA interference (RNAi) and CRISPR-based approaches have shown particular promise in overcoming TMZ resistance through MGMT silencing and apoptotic pathway modulation.

Parallel developments include NLCs co-delivering TMZ and plasmid-enhanced green fluorescent protein (pEGFP), which achieved higher transfection rates than conventional liposomal vectors while significantly suppressing tumor growth.[153] Building on these lipid-based systems, polycationic phosphorus dendrimers loaded with anti-Lyn siRNA demonstrated dual functionality—reducing GSC viability and modulating immune checkpoints (PD-L1 and CD86), suggesting a combined antitumor-immunomodulatory mechanism.[154]

Transitioning to combinatorial strategies, AP2 peptide-modified polymeric micelles (A2PEC) co-encapsulating TMZ and PLK1-targeted siRNA induced G2/M phase arrest in treated cells, synergistically enhancing apoptosis compared to TMZ monotherapy.[155] Further innovation is exemplified by folate-conjugated triblock copolymers (Fa-PEG-PEI-PCL), which attained EGFRvIII gene silencing in vivo, outperforming commercial transfection reagents.[156] Notably, Jiang et al

constructed a cationic free micelle siRNA delivery system. The siRNA molecule acts as both a structural scaffold and a therapeutic carrier. By utilizing the tumor homing property of siRNA itself, tumor suppression without targeted ligands is achieved while avoiding the toxicity of cationic carriers.[109,157] Concurrently, polyethyleneimine-functionalized quantum dots (QD-PEI) demonstrated robust siRNA protection, achieving higher cellular uptake than naked siRNA and suppressing TERT expression in preclinical models.[158]

Expanding beyond siRNA, microRNA (miRNA)-based nanotherapeutics have gained traction. Dysregulated miRNAs such as oncogenic miR-21 and tumor-suppressive miR-34a are being harnessed through advanced formulations. Nanoencapsulated miR-34a mimics combined with locked nucleic acid (LNA)-modified anti-miR-21 inhibitors selectively eradicated GSCs.[159]

Collectively, these advances highlight the capacity of nanocarrier-mediated gene therapy to enhance silencing specificity, tumor targeting, and multimodal therapeutic outcomes in GBM, establishing a new frontier in precision neuro-oncology.

Nanotechnology-Enabled Non-Invasive Therapeutic Modalities

Emerging non-invasive nanotherapeutic approaches—including phototherapy, sonodynamic therapy (SDT), and magnetic hyperthermia (MHT)—leverage external energy sources (NIR light, ultrasound, magnetic fields) to achieve spatially controlled tumor ablation with minimized systemic toxicity. While challenges such as tissue penetration depth and energy conversion efficiency persist, advancements in photosensitizer engineering, nanocarrier design, and stimuli-responsive drug release mechanisms are expanding their clinical translation potential.

PDT, PTT, and photochemical internalization (PCI) have emerged as precision adjuncts for GBM management, particularly in eradicating residual post-surgical tumor foci. NLCs encapsulating chlorin e6 (Ce6) achieved tumor selectivity through AP2 peptide-mediated transport, doubling ROS production compared to free Ce6.[160] Li et al[161] engineered neodymium-coordinated black phosphorus quantum dots (BPNd) that synergize NIR/X-ray dual-activated PDT with chemotherapy. The system exploits Nd3+ ions to convert X-ray energy into the electronic excitation of BP QDs, overcoming traditional photosensitizer energy mismatches while co-delivering doxorubicin via ROS-sensitive linkers for combinatorial efficacy. Transitioning to PTT, plasmonic gold nanorods (GNRs) demonstrate exceptional photothermal conversion efficiencies, enabling pyroptosis-mediated immunogenic cell death without exogenous drug modification.[162] Size-dependent targeting studies by Javier et al[163] revealed that larger GNRs exhibit higher cellular uptake in GBM due to enhanced surface ligand density. PCI further enhances therapeutic precision through light-controlled endosomal escape. Nanocarrier-delivered protoporphyrin IX (PpIX) achieved almost 2-fold higher cellular uptake versus free PpIX, as quantified by flow cytometry, enabling membrane disruption and targeted drug release upon illumination.[164] Shen et al[165] augmented this approach with folate-IR-780 iodide nanobubbles (FA/IR-780 NBs), leveraging quantum confinement effects to optimize NIR absorption.

SDT capitalizes on ultrasound-triggered sonosensitizer activation for deep-seated tumor treatment (penetration depth >30 cm). Sun et al[166] combined UTMD with iRGD-modified DVDMS liposomes (iRGD-Lipo-DVDMS), demonstrating tumor regression through BBB opening and peptide-directed sonosensitizer delivery.

MHT exploits alternating magnetic fields (AMFs) to activate magnetic nanoparticles (MNPs), generating localized hyperthermia that sensitizes tumors to chemo/radiotherapy while sparing healthy tissue. Lilia et al[167] optimized AMF waveforms, revealing that trapezoidal (TP) signals enhance specific loss power (SLP) versus sinusoidal fields, correlating with increased glioma cell death. Makoto et al[168] pioneered organic Fe(Salen) NPs that synergize intrinsic antitumor activity with AMF-induced thermal effects, achieving high tumor suppression in orthotopic models with undetectable systemic toxicity.

AI Combined with Nanotechnology in Drug and Biomarker Discovery for GBM

Artificial intelligence (AI), encompassing machine learning (ML) and deep learning (DL), has transformed drug and biomarker discovery for GBM. For drug discovery, AI methodologies like AtomNet and convolutional neural networks (CNNs) have identified small-molecule inhibitors (eg, PTPmu antagonists, LXRβ agonists) and optimized drug-NP interactions. Notably, Munteanu et al[169] used ML to predict anti-glioma drug-decorated nanoparticle (DDNP) delivery

systems, highlighting AI's potential in designing NP-based therapies. In biomarker discovery, AI identified immune-related markers (eg, PDCD1, CTLA4) and genetic signatures (eg, KIF20A, MGMT), which could guide NP targeting strategies. These findings underscore AI's ability to streamline the development of NP delivery systems by predicting efficacy and specificity.

AI enhances NP delivery systems by modeling complex interactions and optimizing design parameters. Habeeb et al[170] employed an artificial neural network (ANN) with the Levenberg-Marquardt (LM) algorithm to predict the density and hardness of CCONP/PDLG nanocomposites, achieving high correlation coefficients (R = 0.8834–0.9737). This predictive modeling approach could be adapted to optimize NP properties for glioma, such as size, charge, and drug release kinetics, ensuring efficient BBB penetration and tumor targeting. Similarly, Conte et al[171] reported AI techniques like molecular docking and virtual screening, which prioritize compounds for NP encapsulation and assess their anti-glioma activity. For example, ML models predicted the efficacy of thioredoxin reductase inhibitors delivered via NPs, demonstrating reduced tumor growth in vivo. These studies illustrate AI's capacity to refine NP systems beyond traditional trial-and-error methods.

While Chang et al[172] focused on breast cancer and mindfulness-based stress reduction (MBSR), their use of generative AI (eg, ChatGPT) to analyze patient responses offers a parallel for glioma research. Generative AI could process clinical data to identify patient-specific glioma profiles, informing personalized NP delivery strategies. Integrating this with the drug discovery insights from Conte et al[171] and the NP optimization from Habeeb et al,[170] AI could create a cohesive pipeline: identifying targets, designing NPs, and tailoring therapies to individual patients. For instance, AI-driven DDNPs could deliver TMZ with enhanced precision, overcoming resistance mechanisms identified via biomarkers like MGMT.

Despite advances, major challenges remain for AI applications in GBM therapy, including inconsistent data quality, the gap between computational predictions and clinical validation, and the limited interpretability of deep learning models, which hinders clinical trust and regulatory approval. Future research should focus on prospective trials, integrating multi-omics data, and developing explainable AI frameworks. Expanding NP studies like CCONP/PDLG to glioma-specific contexts could further validate their therapeutic potential.

Conclusion

Over the past decade, nanotechnology has emerged as a transformative tool, offering new therapeutic avenues through targeted delivery, immune modulation, and multifunctional integration. Nano-delivery systems applied in GBM therapy are summarized in Table 1. As discussed throughout this review, nanomedicine has demonstrated remarkable potential to circumvent many of the biological and pharmacological limitations that have hindered traditional therapies in GBM

Table 1 Nanoparticle-Based Therapeutic Platforms for GBM

Nano Delivery Platform	Targeting Mechanism	Gene Silencing Agent	Chemotherapeutic Agent	External Stimuli	Ref.
Ag@AuNPs	Tf	si-ANXA1	–	X-ray	[150]
Au Nanosheets	RGD	si-PLK1	–	NIR laser	[173]
Au@$Cu_{2-x}Se$ NPs	CD73 inhibition	–	–	X-ray	[134]
AuNPs	JAM-A ligand	–	–	Free DOX (Systemic Administration)	[29]
	Tf	–	TMZ, MGMT inhibitors	–	[105]
BV2 microglia membrane-coated NPs	anti-PD-1 mAb	–	Mn^{2+} porphyrin macrocycle	NIR laser	[141]
CdSSe/ZnS QDs	–	si-TERT	–	–	[158]

(*Continued*)

Table 1 (Continued).

Nano Delivery Platform	Targeting Mechanism	Gene Silencing Agent	Chemotherapeutic Agent	External Stimuli	Ref.
Carbon QDs	Tf	–	DOX, TMZ	–	[174]
Dendrimer	galactose imidazoquinoline	–	–	–	[139]
		–	rapamycin	–	[126]
	DPA	–	–	–	[144]
	CSF-1R inhibitor BLZ945	–	–	–	[140]
	miR-34a and miR-21 synthetic inhibitor	–	–	–	[159]
	–	anti-Lyn siRNA	–	–	[154]
dimethylformamide-GQDs	–	–	DOX	–	[112,113]
Engineered macrophage-membrane-Coated NPs	PD-1	–	–	–	[132]
Exo	CpG oligonucleotides	–	TanIIA GL	–	[78]
Fe_3O_4 NPs	Magnetic targeting AP2, LAMP2B	siGPX4	–	–	[175]
Fruit-derived EVs	cRGD	–	DOX	–	[176]
G4 and G6 PAMAM dendrimers	–	–	5FU	–	[121]
G5 PAMAM dendrimer	–	–	–	Eu-DOTA-Gly4 Gd-DOTA (Surgery)	[94]
	–	–	Combrestatin A4, Curcumin	–	[177]
Genetically modified MSC membrane-coated MSNs	CCR2 αPD-L1	–	–	X-ray	[152]
Gycopolymer-like condensed NPs	galactose	–	–	–	[178]
Au nanorods	–	–	–	NIR laser	[162]
GQDs	pH-responsive	–	–	–	[89]
GQDs-nanoporous gold	AP2	–	–	–	[92]
Hydrogel-Liposome	cRGD	–	TMZ ERA	–	[179]
Lipid Nano capsules	–	–	SFN	–	[119]
Liposome	BTP-7	–	pHA-TMZ TCPP	NIR laser	[180]
	Magnetic field-responsive	–	TMZ LTF	AMF	[181]
	ApoE	–	TMZ ART	–	[129]
	Intranasal Nose-to-Brain	–	Gas Bo	–	[107]
	MMP-2 responsive LTA	–	DOX·HCl	X-ray (low-dose)	[182]
	iRGD	–	DVDMS	–	[166]
Micelle	RVG-29	si-STAT3	TMZ	–	[109]
		–	DOX	–	[125]
		–	Panobinostat imatinib	–	[127]
Microneedle	Siglec 10 Ab	si-OSM	–	–	[143]

(*Continued*)

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Table 1 (Continued).

Nano Delivery Platform	Targeting Mechanism	Gene Silencing Agent	Chemotherapeutic Agent	External Stimuli	Ref.
Nano capsules	ApoE mAb	–	–	Exosomes derived from primary glioma cells	[183]
NBs	Folic acid AS1411	– –	IR-780 TMZ	NIR laser Ultrasound PLNs	[165] [184]
Neodymium^{3+}-Coordinated Black Phosphorus QDs	RGD	–	DOX	X-ray NIR laser	[161]
NIR-II imaging nanoprobe	Folic acid	–	–	ICG DOTA	[96]
NLC	– RGD, Tf – AP2 – – EGF, TfR	pEGFP plasmid transfection – – – – – –	TMZ TMZ, VCR kaempferol – Paclitaxel Pitavastatin batimastat	– – – Ce6 – – –	[153] [185] [118] [186] [114] [115] [117]
NLP	–	Lymphocyte recruiting cytokine LIGHT(TNFSF14)	cannabidiol		[135]
PAMAM G3 dendrimers	Biotin R-glycidylated Biotin Biotin	– – –	celecoxib simvastatin celecoxib Xanthone, αM	– – –	[122] [111] [123]
PAMAM G5 dendrimers	– cyclo(D-Tyr-Orn-Arg-2-Nal-Gly)	– –	eetoposide protoporphyrin IX –	– –	[164] [146]
PEGylation PAMAM dendrimers	AP2	–	TMZ	–	[187]
Polymeric micelle	CD133 antigen AP2 folate SRs mannopyranoside AP2 ApoE	– si-PLK1 siBCL-2 siPLK1 – –	TMZ idasanutlin TMZ TMZ TMZ DOX resiquimod SFN	– – – – – –	[188] [155] [156] [109] [58] [120]
Polymersome	– AP2 ApoE ApoE c(RGDyk) pH-sensitive AP2	– – – – – –	xanthone volasertib DOX SAP QDs Au DOX	– – – – – –	[128] [147] [189] [190] [97] [149,151]
rGOQD	anti-PD-L1	–	Resiquimod (R848)	–	[137]
SLN	β-hydroxybutyric acid	–	Carmustine, TMZ	–	[116]
SLN and NLC	–	–	VCR, TMZ	–	[83]
SPIONs	AP2	–	TMZ, DiR	NIR laser	[168]
Sterol nanoprobe	Glutathione activation αCD25-Cy7 IDO inhibitor	–	TMZ	–	[136]
SPIONs	–	–	–	AMF	[167]

(*Continued*)

Table 1 (Continued).

Nano Delivery Platform	Targeting Mechanism	Gene Silencing Agent	Chemotherapeutic Agent	External Stimuli	Ref.
TA-Fe^{3+}	TME-Responsive CXCL11	–	OA	–	[191]
Trojan-inspired nanovector	–	si-OGG1	–	Photosensitizer IrPS	[192]
Ultrasmall AuNPs	–	–	DOX Alexa Fluor 647 (AF647)	NIR laser	[193,194]

Abbreviations: NPs, Nanoparticles; Tf, Transferrin; si-ANXA1, small interference-Annexin A1; RGD, Arginine-glycine-aspartic acid; si-PLK1, small interference-polo-like kinase 1; NIR, Near-infrared; DOX, Doxorubicin; JAM-A, Junctional adhesion molecule A; TMZ, Temozolomide; MGMT, O^6-methylguanine-DNA methyltransferase; PD-1, Programmed cell death protein 1; mAb, Monoclonal antibody; si-TERT, telomerase reverse transcriptase; DPA, 5,7-dimethylpyrazolo[1,5-^{d}]pyrimidin-3-ylacetamide; GQDs, Graphene quantum dots; CpG, CpG oligodeoxynucleotide; TanIIA, Tanshinone IIA; GL, Glycyrrhizin; AP2, Angiopep-2; LAMP2B, Lysosome-associated membrane protein 2B; PAMAM, Poly(amidoamine); 5FU, 5-fluorouracil; MSC, Mesenchymal stem cell; CCR2, C–C chemokine receptor type 2; MSNs, Mesoporous silica nanoparticles; ERA, Erastin; SFN, Sorafenib; BTP-7, dg-Bcan targeting peptide (BTP-7); TCPP, Tetracarboxyphenylporphyrin; LTF, Lactoferrin; AMF, Alternating magnetic fields; ApoE, Apolipoprotein E; ART, Artesunate; Gas, Gastrodin; Bo, Borneol; MMP-2, Matrix metalloproteinase-2; LTA, Ligand targeting agent; DVDMS, Sinoporphyrin sodium; RVG-29, Rabies virus glycoprotein-29; STAT3, Signal transducer and activator of transcription 3; OSM, Oncostatin M; PLNs, Persistent luminescent nanoparticles; ICG, Indocyanine green; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; EGFP, Enhanced Green Fluorescent Protein; VCR, Vincristine; Ce6, Chlorin e6; BCL-2, B-cell lymphoma 2; SRs, Scavenger receptors; DiR, DiIC18(7), 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide; IDO, Indoleamine 2,3-dioxygenase; TME, Tumor microenvironment; CXCL11, C-X-C motif chemokine 11; OA, Oncolytic adenovirus; OGG1, 8-oxoguanine DNA glycosylase 1; IrPS, Iridium-based photosensitizer.

treatment. Yet, the journey from bench to bedside remains fraught with challenges. The dynamic and patient-specific nature of glioblastoma requires nanotherapeutic strategies that can adapt to evolving molecular profiles. At the same time, concerns surrounding the long-term biosafety, immunogenicity, and manufacturability of nanosystems continue to limit widespread clinical application. Moreover, the current disconnect between preclinical promise and clinical success underscores the need for more predictive models and translational frameworks. To move the field forward, future research must bridge these gaps through more intelligent nanosystem designs, informed by multi-omics data and responsive to tumor evolution. Equally important is the acceleration of clinical investigations that not only validate efficacy but also address practical considerations in delivery, safety, and regulatory approval. With continued interdisciplinary collaboration, nanomedicine has the potential to redefine therapeutic strategies for glioblastoma and ultimately improve patient outcomes.

Abbreviations

CCL2, (C-C motif) ligand 2; ATP, Adenosine triphosphate; AMFs, Alternating magnetic fields; ANG, Angiogenin; AP2, Angiopep-2; CD133mAb, Anti-CD133 monoclonal antibody; ApoE, Apolipoprotein E; RGD, Arginine-glycine-aspartic acid; ART, Artesunate; AI, Artificial intelligence; BGT-1, Betaine/GABA transporter 1; BBB, Blood-brain barrier; BBTB, Blood-brain tumor barrier; BK, Bradykinin; CXCR4, C-X-C chemokine receptor type 4; CMT, Carrier-mediated transport; CXB, Celecoxib; cfNAs, Cell-free nucleic acids; CNS, Central nervous system; CAs, Contrast agents; CyTOF, Cytometry by time-of-flight; CTLA-4, Cytotoxic T lymphocyte-associated antigen 4; DL, Deep learning; DOX, Doxorubicin; EE, Encapsulation efficiency; EPR, Enhanced permeability and retention; EGFR, Epidermal growth factor receptor; EXOs, Exosomes; EVs, Extracellular vesicles; FGS, Fluorescence-guided surgery; FUS, Focused ultrasound; FDA, Food and Drug Administration; GSCs, Glioblastoma stem cells; GLUT1, Glucose transporter 1; GL, Glycyrrhizin; GNPs, Gold nanoparticles; GQDs, Graphene quantum dots; HIFU, High-intensity focused ultrasound; HMGB1, High-mobility group box 1; ICB, Immune checkpoint blockade; LAT1, Large neutral amino acid transporter 1; Los, Large oncosomes; MHT, Magnetic hyperthermia therapy; MNPs, Magnetic nanoparticles; MRI, Magnetic resonance imaging; mTOR, Mechanistic target of rapamycin; MO-NPs, Metal oxide nanoparticles; miRNA, MicroRNA; MV, Microvesicles; MDSCs, Myeloid-derived suppressor cells; NPs, Nanoparticles; NLCs, Nanostructured lipid carriers; NF1, Neurofibromin 1; NVU, Neurovascular unit; MGMT, O6-methylguanine-DNA methyltransferase; PTX, Paclitaxel; PARACEST, Paramagnetic chemical exchange saturation transfer; PI3K, Phosphoinositide 3-kinase; PDT, Photodynamic therapy; PTV, Pitavastatin; PDGFR, Platelet-derived growth factor receptor; PAMAM, Poly(amidoamine); PLGA, Poly (lactic-co-glycolic acid); PMLA, Poly(β-l-malic acid); PLL, Poly-L-lysine; PEG, Polyethylene glycol; PMs, Polymeric

micelles; PPI, Polypropylene imine; PpIX, Protoporphyrin IX; QDs, Quantum dots; RNAi, RNA interference; ROS, Reactive oxygen species; RTK, Receptor tyrosine kinase; RMT, Receptor-mediated transport; Tregs, Regulatory T cells; R848, Resiquimod; RGS, Rigosertib; siRNA, Small interfering RNA; SLNs, Solid lipid nanoparticles; SDT, Sonodynamic therapy; SLP, Specific loss power; SPR, Surface plasmon resonance; TanIIA, Tanshinone IIA; TMZ, Temozolomide; 3D, Three-dimensional; TLRs, Toll-like receptors; TfR, Transferrin receptor; TP, Trapezoidal profile; TME, Tumor microenvironment; TAMs, Tumor-associated macrophages; TTFields, Tumor-treating fields; UCAs, Ultrasound contrast agents; US, Ultrasound; UTMD, Ultrasound-targeted microbubble destruction; VEGF, Vascular endothelial growth factor; VCR, Vincristine; β-Lapa, β-lapachone.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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