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MINI REVIEW ARTICLE

Progress in Nanotechnology-Enabled Drug Delivery for Glioblastoma: Reports Since 2020

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ABSTRACT

Glioblastoma (GBM) is the highest aggressive primary brain malignancy, with a median overall survival of only ~15 months despite maximal surgical resection followed by radiotherapy and chemotherapy. A major obstacle to effective treatment is the blood–brain barrier (BBB), which significantly prevents the intracranial delivery of most therapeutics. In this review, we first outline the advantages of using nanoparticle (NPs) in GBM treatment. We then critically examine recent advances in various types of NPs designed to traverse the BBB and enhance drug accumulation in GBM. Finally, we summarize ongoing clinical trials involving NP-enabled therapies and discuss emerging design principles and future research directions necessary to translate these platforms into clinical practice. By addressing the challenges of targeted delivery and controlled release, these innovative nanoplatforms hold promise to improve therapeutic efficacy and reduce systemic toxicity, ultimately aiming to extend survival and quality of life for GBM patients.

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INTRODUCTION

Nanostructures are engineered materials possessing a minimum of one nanoscale dimension (1–100 nm), offering special physicochemical attributes, for instance, a high ratio of surface area to volume, tunable size, and surface functionality [1]. These features make them ideal candidates for biomedical applications, particularly in drug delivery, imaging, and diagnostics. Various nanostructures have been developed to encapsulate therapeutic agents, protect them from degradation, and enable controlled or targeted release [2]. Surface modification with ligands, peptides, or antibodies further enhances their ability to recognize and bind to specific cellular receptors. In the context of GBM, these capabilities are especially valuable, as nanoparticles (NPs) can be tailored to transfer the BBB and selectively concentrate in tumor tissue, thereby improving therapeutic efficacy while reducing systemic toxicity [3]. Consequently, nanostructure-based drug delivery systems are emerging as a hopeful therapeutic approach to surpass the challenges of existing GBM therapies [4].

NANOSTRUCTURES IN GBM TREATMENT

NPs enhance efficacy through several complementary pathways: (i) improved BBB transcytosis or transient BBB disruption that increases drug access to the tumor; (ii) surface functionalization with targeting ligands that promotes receptor-mediated uptake by GBM cells and tumor endothelium; (iii) controlled release profiles and endosomal-escape mechanisms that increase intracellular bioavailability of payloads and (iv) local delivery approaches that concentrate therapeutic dose while minimizing systemic exposure [5, 6]. However, translation remains challenged by tumor heterogeneity, limited deep intra-tumoral penetration, off-target accumulation,

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immunogenicity, and scale-up/regulatory hurdles; moreover, commonly used preclinical models imperfectly recapitulate human BBB and microenvironmental barriers, contributing to the translational gap [7, 8]. Importantly, patient-specific factors such as BBB integrity, tumor molecular profile, immune status, and prior treatments can critically influence NPs biodistribution, uptake, and therapeutic response, underscoring the need for personalized nanomedicine strategies in GBM [9, 10]. Building on these clinical and translational insights, the next section highlights the various types of NPs that have been developed for GBM therapy, their unique properties, and how they address specific delivery and targeting challenges [11].

Lipid-based NPs

Lipid-based NPs represent a remarkably promising class of drug delivery systems for GBM therapy due to their excellent biocompatibility, versatility in encapsulating both hydrophobic and hydrophilic compounds, and ability to penetrate the BBB. This category includes nanostructured lipid carriers, solid lipid NPs, liposomes, and micelles. Among them, liposomes have been widely explored for GBM treatment, owing to their structural similarity to biological membranes, extended circulation time, and capacity for surface functionalization to achieve targeted delivery. These carriers enhance the brain delivery of conventional chemotherapeutic agents while reducing systemic side effects. When discussing the advantages and disadvantages, one notable benefit is that lipid-based NPs allow the simultaneous delivery of multiple therapeutic compounds, enabling combination treatment strategies, and they can also be integrated with imaging molecules for theranostic applications [6].

Polymeric NPs

Polymeric NPs are considered one of the most advanced nanocarrier systems for targeted GBM treatment, owing to their customizable physicochemical characteristics, ability to provide controlled drug release, and suitability for surface modification [12]. These nanocarriers are generally synthesized from biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone, chitosan, and poly(ethylene glycol) (PEG)-based copolymers. Surface modification with targeting ligands promotes receptor-mediated transport across the BBB and improves specificity toward GBM cells. In addition, stimuli-responsive Considering the pros and cons, a key advantage of polymeric nanoparticles is that they can be engineered to release their payload in response to local physiological triggers, such as pH shifts, enzymatic activity, or redox conditions, which helps reduce off-target distribution and systemic toxicity [13].

CARBON-BASED NANOSTRUCTURES

Nanodiamonds

Nanodiamonds, newly-introduced NPs from the carbon family, have become renowned for their superior optical, mechanical, and chemical properties. After examining their biocompatibility for two decades, nanodiamonds were found to be remarkably more compatible than carbon nanotubes or carbon black for biomedical applications [14]. The use of null nanodiamonds (without modification) is challenging, because of low bioavailability and biocompatibility which can be solved by surface modification [14]. The size of nanodiamonds can be under 100 nm and drugs can be adsorbed to their surface, linked or conjugated to them. In describing their benefits, it should be said that numerous studies on cellular toxicity at the in vitro level were done to confirm their low to no toxicity [15].

Graphene

Similar to nanodiamonds, graphenes possess the capacity to overcome numerous biological barriers because of their very small size [16]. They are two dimensional [16] and are highly applied for drug delivery and theranostic applications due to their small size namely molecule-like properties and reduced toxicity [17]. A change in their size, shape and surface provides graphene quantum dots optimal optical characteristics [17]. Moreover, there is a belief that they can act as chemosensitizers on U87-MG cells and other types of cancer cells [16, 18]. When weighing the pros and cons, despite the significant advantages of carbon-based structures and the promising results reported in studies, toxicity-related issues remain a concern, as these structures can induce oxidative stress, particularly affecting reproductive organs and sexual hormones [19].

DENDRIMERS

The first patent on dendrimers was certified by

Donald Tomalia in the early 1980s [20]. Dendrimers are composed of a core encompassed by branched structures named generations surrounded by a shell [20]. Dendrimers have oral bioavailability and carry multiple drugs to a targeted site, therefore they are highly effective [21]. It has been stated that the shape of dendrimers is correlated to their size and the number of generations, which is asymmetrical below 4 generations and will be globular with 5-7 generations. In addition to a change in the generation number, binding of various chemical and biological factors to the surface of dendrimers is also very effective in determining their properties [20]. A major drawback of dendrimers, despite being designed for over 40 years [20], is that they have seen limited clinical application, likely due to their expensive and complex synthesis and the many unknowns about their behavior in the body [22, 23].

METAL NPS

Gold

Gold NPs (AuNPs) have demonstrated advantageous functions in overcoming multidrug resistance and can enhance the efficacy of chemotherapeutic agents when applied in combination therapies [24]. Their surfaces can be functionalized through covalent or non-covalent methods, allowing for the attachment of proteins, polymers, nucleic acids and antibodies [21]. Depending on their size, gold NPs display a range of colors from red to blue. Key optical properties of gold nanostructures include surface-enhanced raman scattering, surface plasmon resonance and surface-enhanced fluorescence. A limitation of gold NPs, despite their unique optical properties, is that their anti-tumor activity—especially when conjugated with aptamers—has so far been demonstrated mainly in vitro, with limited evidence from in vivo or clinical studies [23].

Silver

Silver NPs (AgNPs) display multiple bioactivities, such as anti-tumor, antibacterial, and immunostimulatory effects. Their intrinsic cytotoxicity can be strategically exploited for cancer treatment, either as standalone agents or in combination with conventional chemotherapeutics [25].

Iron oxide NPs

Iron oxide NPs (IONPs), primarily composed of Fe_2O_3 and Fe_3O_4, represent the two principal forms of magnetic nanomaterials. These particles are cost-effective and can be synthesized through various methods, including hydrothermal synthesis, sol–gel processing, microemulsion techniques, and co-precipitation [21]. Owing to their magnetic properties, IONPs hold promise for applications in both identifying and treating GBM. Notably, they can induce ferroptosis, a regulated cell death mechanism initiated through iron-dependent peroxidation of lipids; leading to cancer cell apoptosis, lipid membrane damage, and autophagic activity [26]. A key advantage of iron oxide NPs is their strong magnetic properties, which enable applications in targeted drug delivery and magnetic resonance imaging, though a disadvantage is their potential for oxidative stress and accumulation in organs if not properly coated or cleared [27].

POROUS NPS

Zeolite

Zeolites were identified for the first time by Axel Fredrik, a Swedish mineralogist in the 18th century [28]. Zeolites can preserve biological cargos from enzymatic degradation. They can also adsorb drugs, molecules or therapeutic agents and release them in the targeted area, sustainably [28]. Zeolites are non-toxic structures with a high stability to acidic/basic conditions. They can absorb gas molecules, such as NO and CO_2, and desorb them at the target site [29]. These crystalline structures are SiO_4 and AlO_4 structures which are connected together, containing pores of different sizes. The properties are tunable by inserting other molecules into the structure [29]. Besides these advantages, their toxicity has not been thoroughly investigated which should be studied more [28]. One surprising property is that they can absorb O_2 molecules and release them within the tumor locale inducing hyperoxygenation and vasodilation of the GBM tumor [29]. Another surprising characteristic is that they can concentrate in brain tumors even in large particle size and can be carried to the brain through the olfactory nasal route [30].

Silica

Mesoporous silica NPs have pores from 2-50 nm in their structure and are biocompatible at low doses (less than 50 μg/ml) [31]. They have some considerable characteristics such as: expanded surface areas of more than 700 m^2/g, tunable porosity (1.6-10 nm), internal or external

modification, as well as a variety of pore shapes and structures. Sol-gel is a commonly applied protocol for the synthesis of porous NPs based on two steps of hydrolysis and condensation of alkoxide or salts of metals [32].

A key advantage of mesoporous silica NPs is their high surface area and tunable pore size, which allow efficient drug loading and controlled release; however, a disadvantage is their potential to cause inflammation or cytotoxicity depending on particle size, dose, and surface chemistry [33].

NANOBUBBLES

Microbubbles and nanobubbles are versatile structures that hold potential for both diagnostic imaging and therapeutic applications [34]. Microbubbles typically range in size from 500 nm to 10 μm, while nanobubbles have smaller diameters, generally between 200 and 400 nm [26]. Due to their smaller size, nanobubbles can more effectively penetrate poorly permeable vasculature, making them particularly suitable for tumor-targeted delivery [34, 35]. These bubbles can encapsulate gases such as oxygen within their cores, facilitating oxygen delivery to hypoxic tumor regions. Their sizes are often optimized to circulate within the bloodstream, including within red blood cells. Based on shell composition, they are categorized into soft and hard types. Soft-shelled nanobubbles, which are sensitive to low-intensity ultrasound, are typically composed of phospholipids (e.g., phosphatidylcholine derivatives) or surfactants such as Tween or Span. In contrast, hard-shelled variants offering greater stability and they are constructed from proteins, silica, or polymers such as PLGA and polyvinyl alcohol [36]. Furthermore, they can be engineered to carry therapeutic agents, positioning them as promising theranostic platforms for brain complications such as GBM [35].

IMPLANTS

GBM recurrence typically occurs in close proximity to the original tumor site, with approximately 90% of cases presenting as tumor spheroids within 2–3 cm of the initial lesion [37]. Localized delivery strategies, such as implantable systems, offer promising adjunctive treatment options by enabling more precise administration of chemotherapeutics directly to the tumor site, Consequently minimizing systemic side effects while improving treatment effectiveness [38]. One innovative approach involves combining NPs with nanofibers to form composite delivery systems These nanofiber-based implants, loaded with anticancer agents, can be strategically placed into the surgical cavity following tumor resection to achieve sustained local drug release [39]. Table 1 summarizes recent Investigations into NP-based approaches for treating GBM.

CLINICAL STUDIES

A large number of trials have been started via nanotechnology for the treatment of GBM but only a few of them are completed. Figure 1 is a schematic view of some drug delivery formulations clinically studied for the treatment of GBM. Liposomes are the only nanostructures approved as carriers to deliver chemotherapeutics for GBM. The first formulation that received acceptance in clinical trials for GBM was NCT00734682, which was constructed from liposomal irinotecan. The second one was NCT00944801, again a liposomal structure containing doxorubicin, along with prolonged TMZ administration and radiotherapy. The effect of surface modification was applied in this study, and PEG was used to cover the liposomes. The third structure had a totally different composition: iron oxide NPs Feraheme® to control the oxygen level and hypoxia in GBM tumors. The latest nanomaterial is NCT036003379 which is an immunoliposomal structure to deliver doxorubicin. The liposome is decorated with an anti-EGFR substance and was assessed in phase one clinical trials. As it is obvious, the trend of clinical trials for GBM has centered on liposomes (an ancient type of nanoplatform for drug delivery) and progressed from a simple delivery platform to liposome surface modification via PEG and targeting agents. According to these results, the clinical trials of a newly-designed nanoplatform will occur some decades later. Based on recent findings, it is evident that further modifications and strategic advancements, outlined in Figure 2 are essential to enhance therapeutic efficacy and achieve more effective clinical outcomes in GBM management.

CONCLUSION

Nanotechnology offers significant promise in overcoming the limitations of conventional GBM therapies, primarily by improving drug delivery across the blood–brain barrier, enhancing tumor targeting, and reducing systemic toxicity. NPs

Table 1. Recent studies on NP and GBM treatment

Carrier	Delivery agent	Cells and GBM models	Key findings	Reference
Albumin	Paclitaxel	U87-EGFP cells in GBM-on-a-chip model	Suppressed tumor growth and spheroid formation	[40]
T7-cholesterol NPs micelles	Temozolomide		Efficient transport of NPs in vitro	[41]
Liposomes decorated with ApoE[1]	Temozolomide	U251-TR in mice	Prolonged survival	[42]
Lipid-small molecule hybrid NPs	Pheophorbide a–quinolinium conjugate	GL261 in C57BL/6 mice	Extended survival	[43]
Poloxamer 188 surface-modified PLGA NPs	Paclitaxel, methotrexate	C6 in wistar rats	Reduced tumor size and tumor metabolic activity	[10]
Ultrasmall Gold NPs	Doxorubicin	T98GBM cells	Increased NPs uptake	[44]
PEtOz[2] conjugated micelle	Temozolomide	C6 in mice	Extended circulation time and inhibited glioblastoma growth	[45]
Chitosan-PLGA NPs	Gemcitabine	U215 and T98G cells	Antiproliferative effect enhancing TMZ sensitivity	[46]
PAMAM denderimer+protoporphyrin IX dendrimer	Etoposide	U87-MG cells	Enhanced cellular uptake	[47]
PAMAM dendrimers	Doxorubicin	U-118 MG cell	Induced G2/M cell cycle arrest	[48]
PAMAM-OH dendrimer	Rapamycin	GL261 cells in C57BL/6 mice	Enhanced tumor burden reduction	[49]
Hydroxyl-terminated PAMAM dendrimers	BLZ945	GL261 in C57BL/6 mice	Extended survival and reduced tumor size	[50]
Gold@ polydopamine NPs	Pifithrin-μ, PES[3]	SW1783 tumor-bearing nude mice	Activated pro-apoptotic cascades, enhancing radiotherapy and photothermal therapy efficacy	[51]
Aptamer conjugated to AuNPs	-	U87-MG, U87EGFR and U87-EGFRvIII cells	Inhibited proliferation and invasion of cells and extended survival in vivo	[52]
AgNPs	-	U-118MG cells	Enhanced anti-tumor activity	[53]
Iron oxide NPs	Paclitaxel	U251 in BALB/c-nude mice	Reduced tumor volume in GBM model	[26]
Zeolite NPs	O2, CO_2	U87-MG in Athymic nude rats	Enhanced oxygenation and blood volume within GBM	[29]
Folic acid modified mesoporous silica NPs	Cisplatin	LN18	Suppressed GBM cell proliferation	[32]
Ultra-small silica NPs	Doxorubicin	3D spheroids of U87-MG	Enhanced NPs penetration into spheroids and promoted GBM cell apoptosis	[54]
PLGA/gambojic acid Nanobubbles	-	U87-MG and U251 cells and U87-MG carrying luciferase gene fragments in BALB/c nude mice	Combined with FUS, enabled BBB opening and targeted GBM therapy	[55]
Nanobubble targeted with transferrin	Doxorubicin, Pt, Fe NPs	D54MG in mice (subcutaneous and orthotopic)	Improved T2-weighted MRI image resolution in GBM imaging	[56]
ApoE, or RVG -conjugated liposomes	Oligonucleotide miRNA inhibitors, Au NPs	GL261 cells in C57BL/6 mice	Enhanced systemic delivery and higher accumulation in brain tumor tissues	[57]
Nanocomplex modified with angiopep-2 peptides	Cisplatin, Cu^{2+}	GL261-luc in GBM murine model	Improved tumor targeting and inhibition of tumor proliferation	[58]
Membrane-coated NPs	Doxorubicin	U87-MG cells in BABL/c nude mice	Enhanced cellular uptake and in vivo distribution	[59]
Iron–nitrogen-doped mesoporous carbon nanospheres coated with cell membrane	Doxorubicin	GSC and U87-MG cells in BABL/c nude mice	Enhanced anti-tumor efficacy	[60]

[1] Apolipoprotein E
[2] Poly(2-ethyl-2-oxazoline)
[3] Photothermal conversion agent

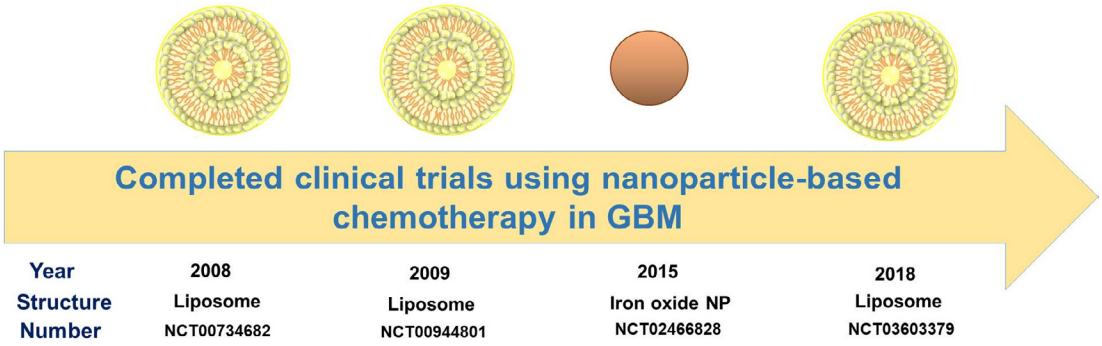

Fig. 1. Schematic overview of completed clinical trials using NPs for chemotherapy in GBM. Three trials employed liposomal carriers for chemotherapeutic delivery, while one utilized iron oxide NPs to enhance tumor oxygenation.

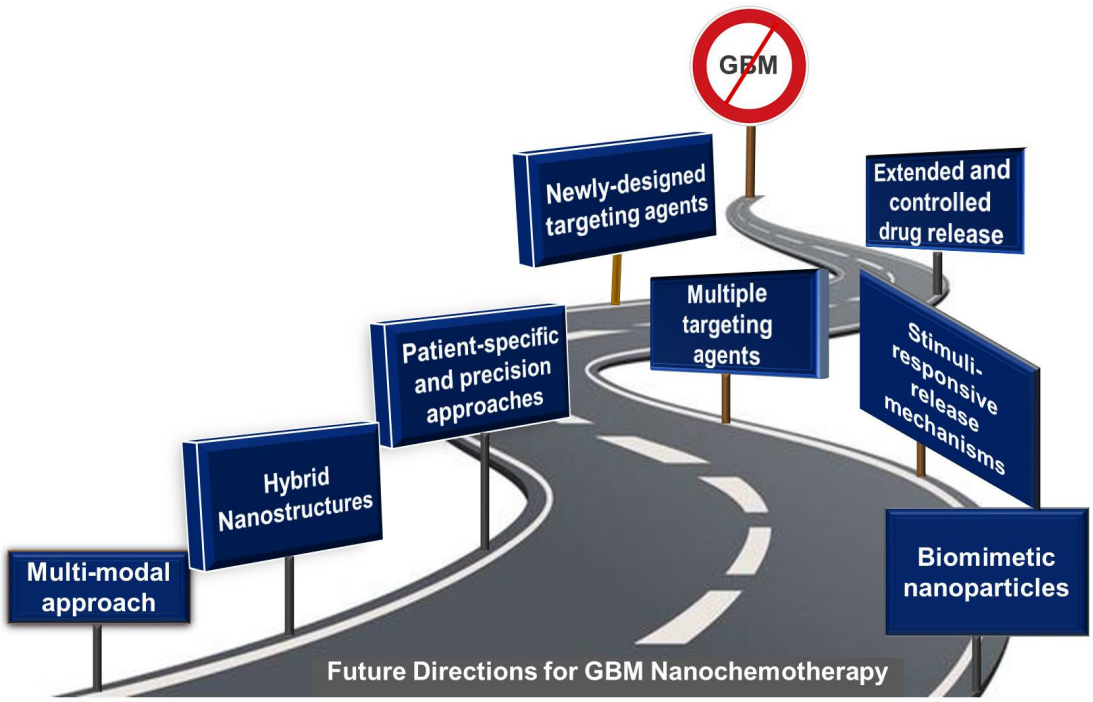

Fig. 2. Strategic advancements in GBM therapy that may pave the way toward achieving more effective and potentially curative treatment.

can be engineered to carry chemotherapeutic agents, genetic materials, or imaging agents, enabling combinational therapy and real-time monitoring of treatment response. Despite these advantages, clinical translation has faced challenges, including limited intratumoral penetration, off-target effects, heterogeneity of GBM, and variability in patient responses. To overcome these obstacles, future research should focus on optimizing NPs design through surface modification, active targeting, and stimuli-responsive systems, as well as developing reliable preclinical models that better mimic the human GBM microenvironment. By addressing these issues, nanomedicine has the potential to substantially improve therapeutic outcomes, offering safer, more effective, and personalized treatment strategies for GBM patients.

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CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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