

Advances in PLGA-Based Drug Delivery Systems for Glioblastoma Treatment

Salona Roy, Daniel Alday, Qi Cai 

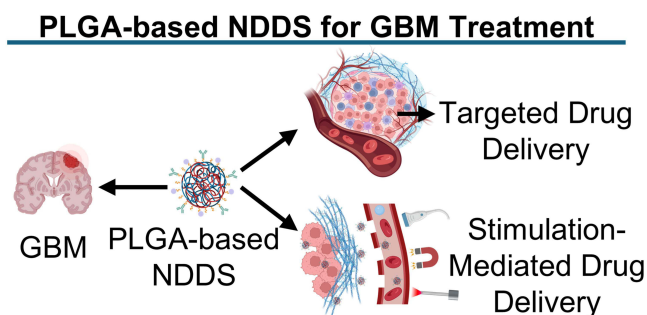
Department of Biological and Agricultural Engineering, Louisiana State University, Baton Rouge, LA, 70803, USA

Correspondence: Qi Cai, Department of Biological and Agricultural Engineering, Louisiana State University, Baton Rouge, LA, 70803, USA, Email qcai@lsu.edu

Abstract: Glioblastoma (GBM) is the most aggressive primary brain tumor, with median survival rates remaining dismally low despite standard-of-care therapies including maximal resection, radiation, and chemotherapy. A significant challenge in GBM therapy is the inability of conventional drugs to achieve therapeutic concentrations in the tumor due to the restrictive nature of the blood-brain barrier (BBB) and the complex tumor microenvironment (TME), which includes high interstitial pressure, abnormal vasculature, and dense extracellular matrix that together hinder drug penetration and distribution. Nanoparticle-based drug delivery systems have emerged as promising tools to circumvent the BBB and enhance drug delivery for GBM treatment. Among these, poly(lactic-co-glycolic acid) (PLGA) formulations stand out as one of the most widely used biodegradable carriers, which have been approved by the FDA for drug delivery applications. This review provides a comprehensive evaluation of the challenges and opportunities arising from the GBM microenvironment and their implications for the development of PLGA nanoparticle-based drug delivery systems. We compare commonly used PLGA nanoparticle synthesis techniques and analyze key GBM characteristics that impede drug transport, highlighting how tumor microenvironmental constraints govern nanoparticle engineering and delivery efficiency. We further evaluate the integration of multimodal therapies that affect both therapeutic delivery and outcomes. Critically, we identify persistent translational bottlenecks and outline specific research and engineering solutions to bridge preclinical efficacy and clinical translation. By integrating current evidence through a translational perspective, this review offers researchers and clinicians a strategic roadmap to guide future efforts toward more rational nanoparticle design and successful clinical translation for GBM therapy.

Keywords: PLGA nanoparticles, glioblastoma, blood-brain barrier, targeted therapy, tumor microenvironment, drug delivery

Graphical Abstract



Introduction

Glioblastoma (GBM) is the most severe and lethal malignant brain tumor, categorized as grade IV (most malignant) astrocytic glioma in the World Health Organization (WHO) classification of brain tumors.¹ GBM accounts for approximately 54% of all gliomas and 16% of primary malignant brain tumors, with an annual incidence rate of approximately 3.19 per 100,000 cases.² The prognosis for GBM remains poor, with the 5-year survival rate in grade IV patients less than 5%.³ The standard therapy for GBM includes maximal safe resection followed by adjuvant radiation and oral temozolomide (TMZ).⁴ However, the highly invasive nature of gliomas leads to extensive tumor infiltration, making complete surgical removal infeasible for most GBM cases, which are prone to relapse.⁵ Moreover, the blood-brain barrier (BBB), characterized by its high selectivity and low permeability, poses a significant challenge by blocking nearly all macromolecules and 98% of small molecules from accessing the tumor site.^{6,7} These challenges underscore the urgent need for innovative therapeutic strategies that can address the limitations of current treatments.

The nanoparticle-based drug delivery system (NDDS) has emerged as a promising approach with the ability to enhance drug solubility, stability, bioavailability, and tumor targeting while minimizing systemic toxicity.⁸ Over the past decade, a diverse spectrum of nanocarriers has been engineered to meet the distinct physicochemical and biological requirements of drug delivery to the central nervous system, including lipid-based carriers, polymeric NPs, dendrimers, and inorganic NPs.⁹ Among the various NDDS, poly(lactic-co-glycolic acid) nanoparticle (PLGA NP)-based drug delivery systems have gained significant attention due to their biodegradability, bioavailability, and reduced systemic toxicity.¹⁰ PLGA is one of the most extensively studied polymers in controlled-release systems and is widely regarded as the gold standard for biodegradable drug-delivery platforms.¹¹ They serve as versatile delivery vehicles for a range of therapeutics, including small-molecule drugs and proteins, as well as macromolecules such as DNA and RNA.^{11–14} A variety of PLGA formulations have been approved by the FDA for medical and healthcare applications (Table 1). PLGA NPs can be formed by condensing two monomers, lactic acid (LA) and glycolic acid (GA) (Figure 1A). The ratio of these components can be adjusted to fine-tune properties such as degradation rate, drug release kinetics, and particle stability.¹⁵ PLGA NPs demonstrate numerous merits as drug carriers. First, PLGA NPs can readily integrate functionalization agents, such as hydrophilic or hydrophobic drug molecules, photosensitizers, photothermal agents, therapeutic genes, and imaging probes, thereby preventing degradation and uncontrolled release.^{16–21} Second, PLGA NPs can be engineered for targeted delivery to specific cells or tissues.^{11,15,22} Moreover, PLGA naturally degrades into LA and GA, both of which are non-toxic and metabolized into water and carbon dioxide.^{18,23} These properties have made it a preferred choice for fabricating nanocarriers for GBM therapy.^{24,25} Despite promising preclinical results with PLGA-based NDDS for GBM treatment, clinical translation has remained limited (Table 2), creating an urgent need for a systematic analysis of this translation gap.

Table 1 Summary of FDA-Approved PLGA-Based Formulations

Brand Name	Active Pharmaceutical Ingredient	Therapeutic Indication	Dosage Form	Initial FDA Approval Year
Lupron Depot	Leuprolide acetate	Prostate cancer	PLGA microspheres	1989
Sandostatin LAR	Octreotide acetate	Acromegaly, neuroendocrine tumors	PLGA microspheres	1998
Nutropin Depot	Somatropin	Growth hormone deficiency	PLGA microspheres	1999
Trelstar Depot	Triptorelin pamoate	Prostate cancer	PLGA microspheres	2002
Risperdal Consta	Risperidone	Schizophrenia, bipolar disorder	PLGA microspheres	2003
Vivitrol	Naltrexone	Alcohol and opioid dependence	PLGA microspheres	2006
Ozurdex	Dexamethasone	Macular edema, noninfectious posterior uveitis	Biodegradable PLGA-based ocular implant	2009
Durysta	Bimatoprost	Open-angle glaucoma or ocular hypertension	Biodegradable PLGA-based ocular implant	2020

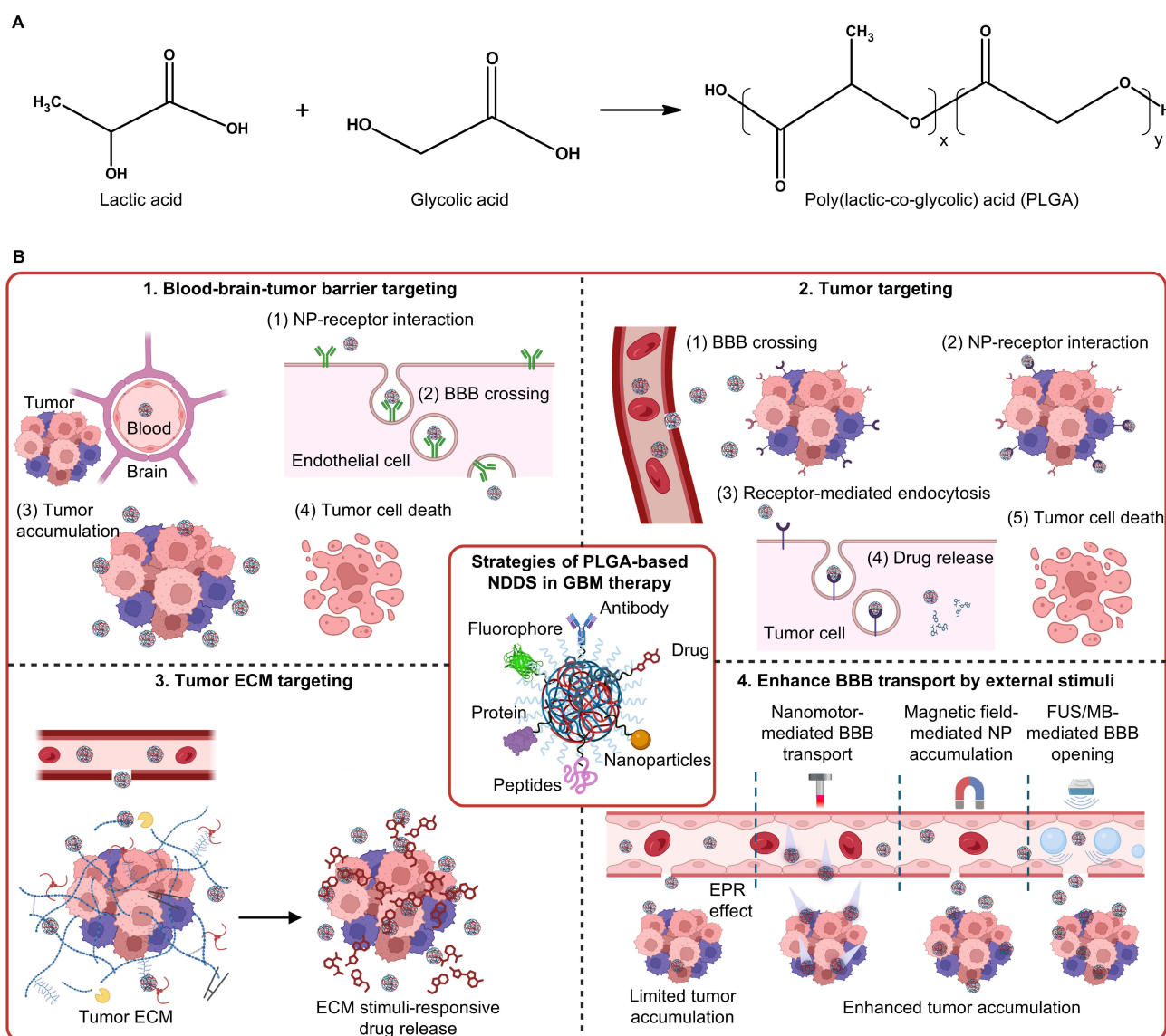


Figure 1 PLGA and its application in GBM therapy. **(A)** A graphical representation illustrating the chemical structure of PLGA molecules, where x and y denote the number of repeating units for each component. The Figure was created with ChemSketch. **(B)** A summary of strategies of PLGA-based NDDS in GBM therapy. The Figure was created with BioRender.

This review provides a timely and comprehensive analysis of the current state and prospects of PLGA-based NDDS for GBM treatment. Distinct from earlier work, this review systematically links the unique features and therapeutic challenges of GBM with the rational design of PLGA-based NDDS, integrating insights from tumor biology and material engineering (Figure 1B). Moreover, we provide a thorough analysis of translational barriers that impede successful clinical adoption and offer suggestions for addressing these challenges through improved design, evaluation, regulation, and delivery strategies. Together, these insights offer a critical foundation for guiding the next generation of PLGA-based NDDS and accelerating progress toward more effective, clinically translatable treatments for this devastating disease. The databases of Google Scholar, PubMed, ScienceDirect, SpringerLink, and ClinicalTrials were searched for literature published between 2015 and 2025. Older papers outside the inclusion window remain valuable references for establishing conceptual foundations, methodological background, or historical context. This dual approach enriches both scientific depth and the comprehensive scope of the review.

Table 2 Pilot Studies and Phase I/II Clinical Trials of PLGA for GBM Drug Delivery

Phase	Dosage Form	Drug	Outcomes	Ref
Pilot Study	PLGA microspheres	5-Fluorouracil	The overall median survival time was 98 weeks from the time of implantation and 2 patients had achieved disease remission at 139 and 153 weeks, respectively	[26]
I	PLGA microspheres	5-Fluorouracil	The median overall survival was 40 weeks, with 2 patients who had longer survival (71 weeks and 89 weeks, respectively)	[27]
II	PLGA microspheres	5-Fluorouracil	The overall survival was 15.2 months in patients in the intervention group, compared to 13.5 months in the control group. However, these differences were not significant	[28]

Synthesis, Characterization, and Biodegradation of PLGA NPs

Various synthesis techniques have been employed to develop PLGA-based NDDS. In this section, we highlight the most used methods, including single and double emulsification, nanoprecipitation, and advanced microfluidic engineering techniques. Representative examples of drug-encapsulated PLGA nanoparticle synthesis and characterization are summarized in Table 3, given the wide range of reported formulations. Additionally, we discussed the drug-release profile and the biodegradation of PLGA, key factors that govern the overall efficacy and biocompatibility of PLGA-based NDDS.

Single and Double Emulsification Method

Emulsification is one of the most straightforward and widely employed techniques for synthesizing PLGA nanoparticles. This technique involves dispersing a volatile, non-water-miscible solvent into an aqueous solution and then emulsifying the mixture using high shear forces. Subsequently, the volatile solvent evaporates, forming NPs.^{20,62,63} Oil-water emulsion (O/W, or single-emulsion) is where oil is the dispersed phase dispersed within the continuous water phase. Water-oil-water emulsion (W/O/W, or double-emulsion) occurs when internal aqueous droplets are dispersed within larger oil droplets, which are then dispersed in an external aqueous continuous phase.⁶⁴ Hydrophobic or hydrophilic drugs can be encapsulated into PLGA nanocarriers using single or double emulsification methods, respectively, as shown in Figure 2A and B.

Table 3 Representative Examples of the Synthesis and Characterization of PLGA Particle-Based Drug Delivery Systems Using the Emulsion Approach, Nanoprecipitation Approach, and Microfluidic Approach

Synthesis Method	Drug Type	Drug	Particle Diameter	Zeta Potential (mV)	Encapsulation Efficiency	Ref
Single-Emulsion	Small Molecule	Rutin	252.6 ± 2.85 nm	−23.7 ± 1.36	81%	[29]
		TMZ16e	121.4 ± 1.8 nm	−23.05 ± 1.48	95.72 ± 1.50%	[30]
		PTX	154 ± 22.19 nm	−23.7 ± 2.71	79.41%	[31]
	Protein/Peptide	LpanUA.27.1260, LpanUA.22.1860	15.35 ± 44.97 μm, 20.31 ± 43.29 μm	N.A.	94.66 ± 4.86%, 89.03 ± 4.91%	[32]
		CCL22	20.2 ± 6.0 μm	N.A.	N.A.	[33]
	Nucleic Acid	pEGFP-C1	507.8 ± 170.2 nm	N.A.	62.8 ± 8.2%*	[34]
	Other Bioactive Materials	PTX, SPIO	250 ± 20 nm	−18 ± 5	30 ± 6% (PTX) 3 ± 1% (Iron)**	[35]
		SPIO, DOX	205.5 ± 3.2 nm	−14	>80%	[36]
		CQD	150 ± 23 nm	−27.3 ± 0.6	N.A.	[37]

(Continued)

Table 3 (Continued).

Synthesis Method	Drug Type	Drug	Particle Diameter	Zeta Potential (mV)	Encapsulation Efficiency	Ref
Double-Emulsion	Small Molecule	I7-DMAG	305.5 nm	−28.7	17%	[38]
		Gemcitabine	163 ± 14 nm	22 ± 4	33 ± 3%	[39]
		Curcumin	128.6 ± 15.8 nm	−32.4	23.2 ± 5.3%	[40]
	Protein/Peptide	αCT1	186 nm	−23	0.000966 ± 0.00049%	[41]
		CCL22	17.4 ± 7.0 μm	N.A.	N.A.	[33]
		LRP	390 ± 88.5 nm	N.A.	72%	[42]
	Nucleic Acid	siOPN	180.7 ± 3.6 nm	−1.31 ± 0.2	58.93 ± 1.1%	[43]
		siRNA	475.9 nm	−23.87	79.65%	[44]
		NNV CP-targeting siRNA	110 nm	30.91	N.A.	[45]
	Other Bioactive Materials	DOX, SPIO	209.4 ± 2.4 nm	−25.3 ± 2.4	26.66 ± 2.41% (DOX)	[46]
		Epirubicin, SPION	226 ± 101 nm	−30	20.00 ± 2.35% (Epirubicin)	[47]
Nanoprecipitation	Small Molecule	Curcumin	254 ± 10 nm	−6.6 ± 4.1	27%	[48]
		MTX, PTX	117 ± 20 nm, 215 ± 41 nm	−29.3 ± 1, −18.4 ± 1	70.66 ± 7.57%, 89.33 ± 3.78%	[37]
		Indomethacin	160.6 ± 25.0 nm	−23.9 ± 2	8.0 ± 0.2%***	[49]
	Protein/Peptide	Insulin	65.2 nm	−22.03	8.95 ± 1.44%	[50]
		Ovalbumin	500 nm	N.A.	11 μg of OVA per mg of polymer vesicle	[51]
	Nucleic Acid	DOX, EGFR siRNA	190.5 nm	30.2 ± 3.6	75.2 ± 3.9% (DOX)	[52]
		CRISPR Cas-9 DNA	182 nm	−26	80%	[53]
		CpG DNA	500 nm	N.A.	150 pg of CpG DNA per mg of vesicle	[51]
	Other Bioactive Materials	Coenzyme Q10, QD	153 ± 3.24 nm	N.A.	Approx. 25% RFU/mass (QD), approx., 0.09 Co-Q10 ABS/mg [#]	[54]
		CQD	163 - 375 nm	−12.9 to −21	61.1–87.4%	[33]
Microfluidics	Small Molecule	Rapamycin	40 - 160 nm	N.A.	67.15%	[55]
		MMC, DOX	160 - 200 nm	−5 to −8	65 - 73% (dox), 62–71% (MMC)	[56]
		Curcumin, C ₈ G ₂	155 nm	10	60% (Curcumin)	[57]
	Protein/Peptide	Ovalbumin, Lysozyme	90 - 180 nm	< −16 or −5 to 0 [§]	44-78% (ovalbumin), 58–85% (lysozyme)	[58]
		CCL22	23.3 ± 4.1 μm	N.A.	N.A.	[33]
		Ovalbumin, lysozyme	90 - 110 nm (Ovalbumin), 100 nm - 180 nm (lysosome)	−2 to −3 (ovalbumin); −1 to −2 (lysosome);	50 - 80% (ovalbumin); 60 –80% (lysosome);	[58]
	Nucleic Acid	GapmeR oligonucleotides	179.8 ± 6.3 nm	32.25 ± 1.36	91 ± 7%	[59]

(Continued)

Table 3 (Continued).

Synthesis Method	Drug Type	Drug	Particle Diameter	Zeta Potential (mV)	Encapsulation Efficiency	Ref
	Other Bioactive Materials	Carbon QD, VEGF	16 - 36 μm	N.A.	51 - 69% (VEGF) ^{###}	[60]
		Fe ₃ O ₄	319 $\pm$ 14 μm	N.A.	>94%	[61]

Note: *DNA loading efficiency; **iron loading efficiency; ***, IND loading percentage; #QD encapsulation within PLGA NP was determined by measuring the fluorescence intensity of the resuspended pellets, and CoQ10 encapsulation was confirmed by spectrophotometrically measuring CoQ10 absorbance. ^{###}VEGF loading efficiency. [§]Depends on the aqueous phase.

Abbreviations: TMZ16e, temozolomide hexadecyl ester; SPION, superparamagnetic iron oxide nanoparticle; PTX, paclitaxel; SPIO, superparamagnetic Iron Oxide; DOX, doxorubicin; CQD, carbon quantum dots; 17-DMAG, 17-Dimethylaminoethylamino-17-Demethoxygeldanamycin; α CT1, Connexin43 mimetic peptide; LRP, laminin receptor precursor; siOPN, siRNA against osteopontin; NNV CP-targeting siRNA, Nervous necrosis virus capsid protein-targeting siRNA; MTX, Methotrexate; EGFR, Epidermal Growth Factor Receptor; CPG DNA, TLR9 agonist CpG motif DNA; QD, quantum dots; MMC, mitomycin C; C₈G₂, cationic amphiphilic anti-cancer peptide CH₃(CH₂)₆CO-GIIKKIHKI-NH₂.

In single-emulsion processes, PLGA and the hydrophobic drug are first dissolved in a water-immiscible, volatile organic solvent, such as dichloromethane (DCM), chloroform, or ethyl acetate (EtOAc).⁶⁴ This solution is then mixed with the aqueous phase, which contains a stabilizer such as polyvinyl alcohol (PVA), dodecyl dimethyl ammonium bromide (DMAB), sodium dodecyl sulfate (SDS), and Polyvinyl pyrrolidone (PVP).^{62,65,66} The emulsion is sonicated, during which intense shear forces generate NPs that solidify upon removal of the organic solvent through continuous

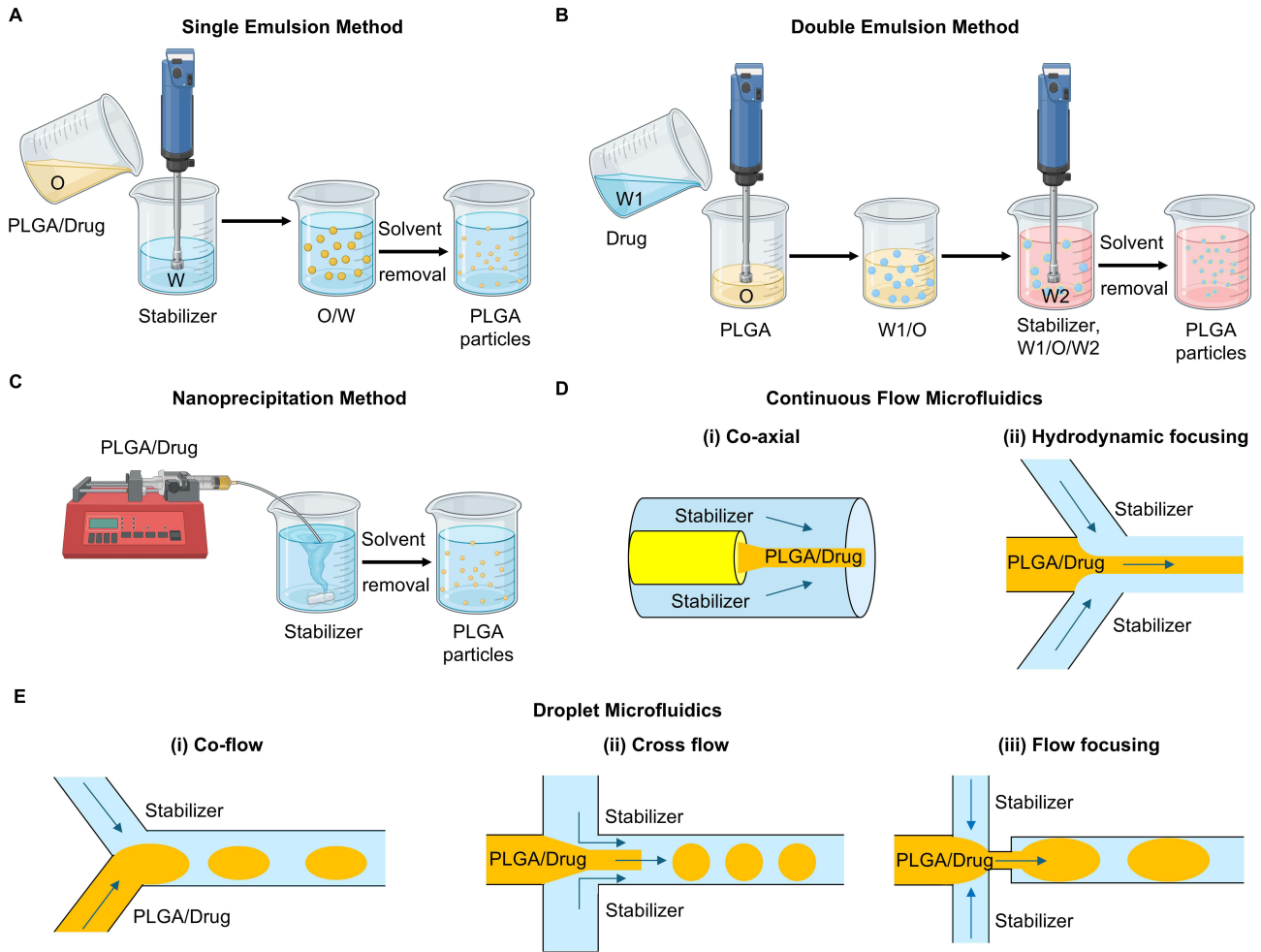


Figure 2 Schematics of synthesis approaches of PLGA NPs. (A) Single emulsion approach. (B) Double emulsion approach. (C) Nanoprecipitation approach. (D) Continuous flow microfluidics approach, with (i) co-axial device and (ii) hydrodynamic focusing device. (E) Droplet microfluidics approach, with (i) co-flow device, (ii) cross flow device, and (iii) flow focusing device. (A–C) were created with BioRender.

stirring.²⁰ Hydrophilic drugs, on the other hand, are encapsulated using the double emulsion method, in which the drug is first dissolved in an aqueous phase and then emulsified into an organic phase containing PLGA (W/O emulsion). Subsequently, this primary emulsion is added to an aqueous phase containing surfactant, followed by homogenization to obtain a W/O/W emulsion. The organic solvent is then evaporated to form the NPs.^{64,67}

The physical properties of the NPs, such as size, polydispersity index (PDI), morphology, and surface charge, are influenced by numerous parameters, including PLGA and drug concentrations, surfactant type and concentration, organic solvent ratios, agitation speed, sonication amplitude, and evaporation conditions. These factors ultimately affect drug loading efficiency and encapsulation profiles.^{20,62,66,68,69} While emulsification techniques are advantageous for encapsulating both hydrophobic and hydrophilic drugs, they involve solvent evaporation through heating and pose challenges related to the removal of residual solvent and stabilizer. Nevertheless, their scalability makes them attractive for industrial applications.⁷⁰

Nanoprecipitation Method

The nanoprecipitation approach, also known as the solvent displacement method, is depicted in Figure 2C. This one-step approach involves gradually adding a polar, water-miscible organic solvent, such as acetone, ethanol, or acetonitrile, that contains the PLGA and the hydrophobic drug to an aqueous solution under high-speed agitation.^{20,71,72} The organic phase rapidly disperses into the aqueous phase, leading to NPs precipitation. This process is followed by the evaporation of the solvent to form solid NPs. The formation of NPs occurs in three phases: supersaturation, nucleation, and growth. First, polymer nucleation is initiated by local supersaturation of the polymer solution at the interface between the organic and aqueous phases, resulting in the formation of numerous small nuclei. Then, the concentration of the polymeric solution (at the local supersaturation interface) decreases, making it less favorable to produce further nuclei. Subsequently, polymer molecules are added to the nuclei until the solution achieves equilibrium. A higher nucleation rate typically results in smaller NPs. Moreover, the size of the NPs is determined by formulation variables, including polymer concentration, solvent-to-water ratio, the diffusion coefficient of the organic solvent in water, and mixing speed.^{71,73} This method effectively traps hydrophobic drugs within the hydrophobic polymeric cores, resulting in high encapsulation efficiencies.²⁰

Nanoprecipitation offers several advantages, including low energy requirements, minimal use of toxic solvents, and ease of scale-up with high reproducibility.⁷⁴ However, it is less suitable for hydrophilic drugs, which tend to diffuse into the aqueous phase during preparation, thereby reducing encapsulation efficiency. Controlling particle size and uniformity also remains a challenge.^{20,71}

Microfluidic Technology

While conventional methods are widely used, microfluidics technology has emerged as an advanced alternative that offers superior control over particle formation. Microfluidics technology controls mixing by regulating fluid flow dynamics at the microscale, thereby improving the controllability, reproducibility, and homogeneity of NPs.^{75,76} The high surface-to-volume ratio in these devices enables efficient mixing and excellent heat and mass transfer.⁷⁷ The microchannels can be made of various materials such as polydimethylsiloxane (PDMS), aluminum, glass capillaries, silicon, and phenol formaldehyde resin.^{75,78,79} Microfluidic flows have been divided into two types based on the flow configuration in microchannels: continuous phase flow microfluidics and droplet phase flow microfluidics. Continuous flow microfluidics typically generate PLGA NPs in the submicron range, whereas droplet-based microfluidics produce particles in the micrometer range.⁷⁹

In continuous flow microfluidics, PLGA and the drug are dissolved in a water-miscible organic solvent, such as acetone, acetonitrile, ethanol, or methanol, and then introduced through a central microchannel, with aqueous streams containing surfactant flowing on both sides. The formation of PLGA NPs is achieved through the nanoprecipitation process (Figure 2D).⁷⁹ In droplet microfluidics, PLGA and the drug are first dissolved in a volatile organic solvent, such as dimethyl carbonate (DMC), chloroform, or toluene. Monodisperse polymer droplets are subsequently formed through shear-driven emulsification in an immiscible aqueous phase containing a stabilizer (Figure 2E). Then, the solvent is

evaporated to collect the particles. The particle size can be tuned by adjusting the concentrations of PLGA and the stabilizer, the organic-to-aqueous phase flow rate ratio, the mixing time, and the microchannel size.^{79–81}

Microfluidic-based PLGA NP synthesis allows the production of NPs with high batch-to-batch consistency, narrow size distribution, and scalability. However, this approach also presents limitations, including difficulties in online purification and characterization, as well as susceptibility to channel clogging and fouling.^{20,79}

PLGA-Based NDDS Biodegradation and Drug Release

PLGA can degrade into two by-products (LA and GA) that can be broken down by enzymes and eliminated from the body.⁸² The rate of PLGA biodegradation depends on several factors that affect hydrolytic degradation processes, including water permeability and solubility, chemical composition, molecular weight (MW), the mechanism of hydrolysis, additives incorporated, polymer crystallinity, and glass transition temperature.^{83,84} Among the various factors, MW and co-polymer composition play the most critical roles. PLGA with higher MW degrades more slowly, as the extensive chain entanglement between long backbones increases resistance to chain scission.⁸⁴ The LA-to-GA ratio in the polymer influences the degradation rate. Generally, a higher LA content leads to slower degradation and more sustained release due to increased hydrophobicity. The ratio also affects the crystallinity of the copolymer, as LA is crystalline, whereas GA is amorphous. A higher amorphous GA content results in faster particle hydrolysis. However, the 50:50 polymer ratio is generally regarded as having the fastest degradation rate.⁸⁵

In PLGA-based NDDS, PLGA primarily controls drug release kinetics. Drugs may exit delivery systems by diffusing through the pores, a process influenced by random molecular motion and driven by chemical potential gradients as well as osmotic pressure-induced convection. Moreover, drug release can occur through polymer degradation, in which matrix erosion generates new pores and accelerates drug release, typically following an initial lag phase dominated by diffusion.⁸³ A typical characteristic of polymer-based carriers, including PLGA-based NDDS, is the initial burst in drug release. In this phase, a large fraction of the loaded drug is discharged rapidly over a short duration. Several factors are known to primarily control the initial burst release of the drug from PLGA-based NDDS, including particle size, porosity, and polymer MW.^{85,86} Chen et al demonstrated that PLGA with larger sizes (>100 μm and 50–100 μm) exhibited slower release compared to those with smaller sizes (20–50 μm and <20 μm). Furthermore, particle size influences release behavior: larger particles exhibit a sigmoidal release profile, whereas smaller particles show a biphasic pattern with an early burst phase.⁸⁷ The results were in agreement with other studies.^{88–90} Kim et al demonstrated that drug release from the porous system was significantly faster than that from the nonporous analogue, the phenomenon has also been observed by others.^{91,92} Since the porous microparticles have larger surface areas and shorter diffusion distances, they also exhibited an intense initial burst release of the drug.⁹³ Mylonaki et al demonstrated that low MW PLGA microparticles exhibited a burst biphasic drug release profile. In contrast, higher MW PLGA microparticles exhibited triphasic drug release behavior.⁹⁴ In designing a PLGA-controlled release system, comprehensively considering the above factors is essential to achieve the desired release profile.

Glioblastoma Microenvironment: Challenges and Opportunities in Designing PLGA-Based NDDS

Blood-Brain Barrier and Blood-Brain-Tumor Barrier

The BBB is located at the interface between blood circulation and brain parenchyma, which is composed of brain microvascular endothelial cells (ECs), astrocytes, pericytes, and junctional complexes that seal the ECs, including tight junctions and adherens junctions.⁶ Due to the presence of these junctional complexes, EC connections at the BBB are 50–100 times tighter than those at the peripheral microvascular wall.⁹⁵ Brain microvascular ECs at the BBB exhibit low levels of transcytosis, thereby restricting molecular exchange. They also feature specialized tight junctions that limit paracellular passage between the blood and the brain.⁹⁶ Additionally, primary efflux transport proteins embedded within the endothelial layer play a crucial role in regulating the concentrations of foreign substances in the brain and cerebrospinal fluid.⁹⁷ Consequently, the BBB is essential in maintaining brain physiology by regulating the exchange of ions and molecules between the bloodstream and brain tissue. However, it also poses a significant challenge for drug

delivery into the brain, as it effectively excludes or limits the penetration of 98% of small-molecule drugs and nearly all large-molecule drugs to sub-therapeutic levels.⁹⁵ This restrictive nature of the BBB thus represents a substantial barrier to the effective treatment of many neurological disorders.

The organization and function of the BBB can be altered under pathological conditions, such as GBM, resulting in the blood-brain-tumor barrier (BBTB).⁹⁸ BBTB disruption varies with disease stage and is primarily observed in the tumor core, where microvascular proliferation leads to the formation of newly formed, leaky blood vessels.⁹⁹ Moreover, tumor progression leads to changes in BBTB structure, including neuronal death, displacement of astrocyte endfeet by cancer cells, and heterogeneous pericyte and astrocyte subpopulations, all of which can compromise endothelial barrier function.¹⁰⁰ The variably disrupted and leaky blood vessels, along with impaired lymphatic drainage in the GBM, give rise to the enhanced permeability and retention (EPR) effect, allowing therapeutics to access and accumulate within the GBM.¹⁰¹ However, it is unlikely that the BBB breakdown is homogeneous or that the magnitude of this local disruption is sufficient to allow drug penetration in meaningful quantities for GBM treatment.^{7,102} On the other hand, most GBMs have an intact BBB that extends beyond the contrast-enhancing tumor volume.^{103,104} Therefore, drugs with poor BBB permeability do not provide therapeutically adequate exposure to this fraction of tumor cells. Furthermore, GBM may develop chemoresistance due to the overexpression of ATP-binding cassette transporters, which regulate the transport of multiple compounds, including chemotherapeutic agents, through biological membranes.¹⁰⁵ Therefore, by blocking the delivery of adequate amounts of potentially effective treatment drugs, the BBB and the BBTB constitute a significant barrier in GBM therapy.

Molecular and Cellular Characteristics in the GBM Microenvironment

Unlike normal brain tissue, the GBM microenvironment is markedly more complex and heterogeneous, comprising glioma cells, glioma stem cells, infiltrating immune cells, neural components, the cerebral microvasculature, and the extracellular matrix (ECM).¹⁰⁶ Key features of this intricate microenvironment include hypoxia, which contributes to a more acidic tumor microenvironment; limited nutrient availability; immune suppression; stromal impediments; elevated interstitial fluid pressure; and the restrictive BBB/BBTB, all of which often undermine the effectiveness of otherwise promising therapies.^{107,108}

In GBM, rapid tumor growth increases oxygen and nutrient requirements, leading to the formation of new blood vessels and, consequently, angiogenesis.¹⁰⁹ During rapid tumor growth, tumor cells express and release pro-angiogenic factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hypoxia-inducible factor 1 α (HIF-1 α), fibroblast growth factor (FGF), angiopoietin-1 (Ang-1), and angiopoietin-2 (Ang-2).¹¹⁰ These angiogenic factors bind to their receptors on the EC membrane, leading to the dissolution of the vessel wall and degradation of the EC basement membrane and ECM. Subsequently, specific proteases, such as matrix metalloproteinases (MMPs), remodel the ECM components to facilitate the migration and proliferation of ECs, leading to the sprouting of new blood vessels from pre-existing ones.¹¹¹

In addition to the vascular abnormalities and EC markers, GBM cells themselves exhibit distinct molecular features, including the overexpression of specific surface biomarkers that further define the tumor microenvironment (TME). Over the years, several targets have been identified that are overexpressed on GBM cells, including the transferrin receptor (TfR), lipoprotein receptor-related protein (LRP), connexin 43 (Cx43), α v β 3 integrin, epidermal growth factor receptor (EGFR), and EGFR variant III (EGFRvIII).¹¹²

The ECM provides structural support essential for maintaining tissue and organ homeostasis, while within the TME, it plays a pivotal role in facilitating tumor development.¹¹³ In GBM, the ECM becomes abnormally dense and tense, with dysregulated production of elements including hyaluronic acid, tenascin-C, fibronectin, proteoglycans, and matricellular proteins, ultimately resulting in a stiffer ECM. As ECM stiffens, mechanotransductive signaling enhances MMP secretion from both malignant and stromal cells, thereby accelerating ECM degradation and remodeling.^{114,115} Hence, ECM stiffness may be highly dynamic in cancer. The tumor ECM creates physical barriers that surround and protect the tumor, thus limiting the capacity of chemotherapeutics to reach and infiltrate tumor tissue, reducing overall treatment effectiveness.^{116–118}

Moreover, the GBM TME sustains a highly immunosuppressive state that severely impairs immune cell activity and prevents effective recognition and elimination of malignant cells.¹¹⁹ TME is enriched with immunosuppressive cells, including tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs).¹²⁰ Cytokines and chemokines secreted by tumor cells, such as CXCL2, EGFR, and VEGF, recruit and polarize TAMs to promote glioma growth and invasion. Tregs effectively inhibit anti-tumor responses and promote tumor immune escape by secreting Th2-polarized immunomodulatory cytokines TGF- β and IL-10.^{121,122} Together, these mechanisms create a profoundly immunosuppressive microenvironment that limits the effectiveness of current immunotherapies for GBM.

Engineering PLGA-Based NDDS to Increase BBB/BBTB Transport and GBM Targeting

Non-modified NPs internalize BBB/BBTB mainly via the EPR effect and are highly dependent on NP size. Moreover, NPs that rely on passive entry show markedly lower brain accumulation efficiency.¹²³ Consequently, various strategies have been employed to enhance the efficiency of PLGA-based NDDS for GBM therapy by modifying the NPs with functional groups that target overexpressed receptors on brain microvascular ECs and GBM cells (Table 4). PLGA NPs functionalized with such receptors can facilitate both drug transport across the BBB/BBTB and subsequent internalization into the tumor, representing a simple strategy for sequential, dual-site targeting.

Hao et al designed brain-targeted multifunctional PLGA NPs for the systematic delivery of docetaxel (DTX) and indocyanine green (ICG) for imaging and chemo-photothermal therapy. They first prepared PLGA (LA/GA = 50:50, MW: 17 kDa)/DTX/ICG NPs using the single-emulsion method and further conjugated angiopep-2 (ANG) to the NPs (ANG/PLGA/DTX/ICG NPs). ANG targets lipoprotein receptor-related protein 1 (LRP-1) on brain capillary ECs and GBM cells. Therefore, these NPs can readily undergo receptor-mediated endocytosis, enabling efficient uptake by tumor cells and

Table 4 Functionalization of PLGA-NDDS for BBB Targeting, GBM Targeting, and ECM Targeting

Targeting Approach	Mechanism	PLGA	Functional Group	Drug	Model	Outcomes	Ref
BBB Targeting	Electrostatic interaction	PLGA-COOH	PAMAM	PTX	U87 mouse model	Median survival increased to 38 days compared with 31 days in the untreated group and 32 days in the free-drug group	[124]
	Apolipoprotein E binding	50:50, 24–38 kDa	Polysorbate 80	PTX	U87 cell line, U87 mouse model	Improved BBB permeability; inhibited tumor growth; the median survival time increases to 37 days compared with 26 days for the control group	[125]
	LDL binding	50:50, 30 kDa	Poloxamer 188	MTX, PTX	C6 cell line, C6 rat model	Increased cytotoxicity, decreased tumor volume; increased mean survival values (59 days compared to 38, 39, and 54 days for the control groups)	[37]
	P-gp inhibition	Resomer® 502, 503, 752 with free carboxylic or ester end groups	Tween 80, Brij-35, Pluronic F68 and Vitamin E-TPGS	DOX, SPION	9L/LacZ, U87, NSC-23 cell lines	Demonstrate therapeutic effects not only in normal population glioma cells but also in neuronal cells with stem cell properties	[126]
GBM Targeting	Folate receptor binding	50:50, 5–15 kDa	Folic acid	ICG, RSV	U87 cell line, U87 mouse model	Increased tumor cell inhibition ($81.4 \pm 2.1\%$) compared to the control group ($53.1 \pm 1.1\%$); increased tumor targeting; decreased tumor volume	[127]
	EGFRvIII receptor binding	75:25, 65 kDa	A-EGFRvIII-f	Curcumin	DKMG/EGFRvIII cell line	Demonstrate more effective photodynamic toxicity (56%) compared to the control group (24%)	[48]
	$\alpha_v\beta_3$ binding	50:50, ester-terminated	RGD	Docetaxel	C6 cell line, C6 rat model	Increased anti-proliferative activity (2.69- and 4.13-fold compared with the control group); The median survival time (57 days) increased 1.43, 1.78, 3.35, and 3.56-fold compared with the control groups	[128]

(Continued)

Table 4 (Continued).

Targeting Approach	Mechanism	PLGA	Functional Group	Drug	Model	Outcomes	Ref
	SSTR2 binding	50:50, 7–17 kDa	SSTR2 peptides	3,3' Diindolylmethane	C6, DBTRG-05, and U87 cell lines, C6 rat model	Enhanced antiproliferative and apoptotic effect; decreased tumor volume; improved survival (2–3 times compared to the control group)	[129]
	Interleukin 13 receptor $\alpha 2$ binding	MePEG-PLGA (40 kDa), Male-PEG-PLGA (41.5 kDa)	Pep-I	Coumarin-6	C6 spheroids, C6 mouse model	Enhanced cellular uptake than the control group; exhibited a desirable brain biodistribution profile with significantly increased delivery in vivo glioma region	[130]
	Cell-penetrating peptide	PLGA, PLGA-PEG-MAL	P28 peptide	Fatostatin	U87 cell line, U87 mouse model	Inhibited cell viability and cell invasion; promoted the production of lipid ROS; inhibited tumor growth; enhanced survival time	[131]
	CD133 binding	PLGA (73 kDa), PLGA-NH ₂ (30–40 kDa), PLGA-NHS (50–80 kDa)	CD133 aptamer	TMZ, RG7388	Human GBM cancer stem cells	Increased GBM cancer stem cells targeting; increased cytotoxicity	[132]
	Electrostatic interaction	N.A.	Chitosan	PTX, FLUR	RG2 cell line, RG2 rat model	Increased cellular uptake; decreased tumor area	[133]
	Hypoxia-induced targeting	N.A.	Disulfiram	Disulfiram	U87, U251, U373 spheroids, U87 rat model	Selective toxicity to GBM cells, eradicates GBM stem cells, and blocks migration and invasion at very low concentration; inhibits orthotopic and subcutaneous U87MG xenograft in mouse models with no toxicity to vital organs	[134]
BBB-GBM dual Targeting	Transferrin receptor binding	MePEG 2000-PLGA 20000 (50: 50), Mal-PEG2000-PLGA 20000 (50: 50)	Transferrin	DOX, THC	C6 cell line, U251 cell line, C6 mouse model	Increased cellular uptake, increased cytotoxicity; showed the lowest tumor weight (0.19 ± 0.07 g) and highest tumor inhibition rate (94.49%) compared with other treatments	[135]
	Nucleolin binding	50:50, PLGA-COOH, 15 kDa	AS1411	PTX	C6 cell line, C6 mouse model	Increased cellular uptake (about 2-fold); enhanced cytotoxicity (IC ₅₀ is 2–4 times lower than the control group); decreased tumor size; increased tumor inhibition rate (81.68%) compared to the control groups; prolonged animal survival	[136]
	Glycosphingolipid GMI binding	45 kDa	CTB	PTX	U87 cell line, U87 mouse model	Effective BBB penetration and tumor targeting in vitro; induce apoptosis of intracranial glioma cells and ablate neovasculature in vivo; prolongation of survival of nude mice bearing intracranial glioma (34 days) compared to the control groups (21–29 days)	[137]
	LRP-1 receptor binding	50:50	Angiopep-2	DOX, PTX	U87 cell line	Enhanced the cellular uptake and increased cytotoxicity	[138]
	Lactoferrin and folate receptor binding	85:15, 58 kDa	Lactoferrin, folic acid	Etoposide	U87 cell line	Increased cytotoxicity ($18.94 \pm 5.4\%$ survival rate) compared to the control group ($37.3 \pm 3.2\%$)	[139]
	OCTN2 binding	75:25, 38 kDa	L-carnitine	PTX	T98G cell line, T98G spheroids	Enhanced the cellular uptake and increased cytotoxicity	[140]
	^D WSV peptide: BBB penetration, NGR: GBM targeting	75:25, 5.6 kDa	^D WSV/NGR-RBCNPs	EFLI	C6 cell line, C6 mouse model	Enhanced brain-targeting and tumor-targeting; increased cytotoxicity; decreased tumor volume; the median survival time (36 days) is 1.8-, 1.6-, 1.5-, 1.3-, and 1.2-fold longer compared to the control groups	[141]

(Continued)

Table 4 (Continued).

Targeting Approach	Mechanism	PLGA	Functional Group	Drug	Model	Outcomes	Ref
TME targeting	Stimuli-homing of macrophage, inflammatory chemotaxis of neutrophils	50:50, 90 kDa	NMm	Rapamycin	C6 cells, C6 mouse model	Efficiently transmigrate across the BBB, respond to inflammatory stimuli, and specifically accumulate within the inflammatory site; enhanced tumor-targeting; capable of eliminating glioma cells and inducing durable tumor regression	[142]
	CD44 binding, magnetic field-guided targeting	50:50, 15–30 kDa	Hyaluronic acid, IOMNP	Cisplatin	U87 cell line, U87 mouse model	Increased tumor targeting efficiency; increased cytotoxicity (IC ₅₀ value is only 46% that of the free drug); decreased tumor growth rate and prolonged survival time;	[143]

Abbreviations: PAMAM, poly(amidoamine); PTX, paclitaxel; LDL, low-density lipoprotein; MTX, Methotrexate; aDCM, activated mature dendritic cell membrane; DOX, doxorubicin; SPION, superparamagnetic iron oxide NPs; ICG, Indocyanine green; RSV, Resveratrol; RGD, arginineglycine-aspartic acid (RGD) peptide; SSTR2, somatostatin receptor 2; Pep-1, a specific ligand of IL-13R α 2; RG7388, mouse double minute 2 (MDM2) antagonist; TMZ, temozolomide; FLUR., R-flurbiprofen; ASI411, a DNA aptamer specifically binding to nucleolin; THC, Tetrahydrocurcumin; CTB, Cholera toxin subunit B; LRP-1, low-density lipoprotein receptor-related protein 1; OCTN2, Na⁺-coupled carnitine transporter 2; ⁵¹WSW/NGR-RBCNPs, erythrocyte membranes dual-modified with ⁵¹WSW and NGR peptide ligands; EFL1, Euphorbia factor 1; NMm, neutrophil and macrophage membrane; EGFRvIII, Epidermal growth factor receptor variant III; IOMNP, oleic acid-coated iron oxide magnetic nanoparticles.

selective delivery of the encapsulated drug. These NPs had a hydrodynamic size of 221.7 ± 1.6 nm (PDI: 0.233 ± 0.02) and a zeta potential of -22.2 ± 2.1 mV. The encapsulation efficiency for ICG and DTX was $42.3 \pm 2.4\%$ and $93.1 \pm 2.2\%$, respectively. DTX showed a sustained release from the NPs over 200 hours. The study further demonstrated that NIR image-guided chemo-phototherapy of these NPs could inhibit U87 tumor growth and prolong the lifespan of the orthotopic mouse GBM model.¹⁴⁴

Kang et al functionalized paclitaxel (PTX)-loaded PLGA NPs with iNGR moiety (iNGR-NP-PTX) to achieve tumor vascular recognition and tumor penetration. The PLGA (PLGA-COOH, 20 kDa)-PTX was synthesized using the emulsion/solvent evaporation method and further conjugated with iNGR peptide. The recognition of blood vessels was achieved through the interaction between iNGR and aminopeptidase N (APN/CD13), which is selectively overexpressed in angiogenic blood vessels and pericytes. Upon binding to the vasculature, iNGR is proteolytically cleaved into CRNGR, which can then bind neuropilin-1 to facilitate deep penetration into the tumor parenchyma. The hydrodynamic diameter of iNGR-NP-PTX was 127.8 ± 4.1 nm, and the zeta potential was -18.6 ± 3.0 mV. The PTX encapsulation efficiency was 48.05%, and the drug loading efficiency was 1.43%. The PTX release data indicate a slight burst release of approximately 43% within the first 24 hours in PBS, followed by a sustained release pattern reaching around 73% at 96 hours. Moreover, when the release medium contained 10% rat plasma, a faster release was observed, with cumulative release reaching 88% in 96 hours. In vivo GBM penetration analysis data showed that coumarin-6-labeled iNGR-NPs had the highest accumulation and deepest penetration at the tumor site compared to the control groups, with $25.4 \pm 5.2\%$ of total fluorescent signals detected within a distance of 0–10 μ m, and $46.4 \pm 7.3\%$ at penetration distances over 20 μ m from vessels. iNGR-NP-PTX demonstrated enhanced tumor-inhibition efficacy in the U87 cell line and significantly prolonged survival in the U87 mouse GBM model.¹⁴⁵

Engineering PLGA-Based NDDS to Enhance the ECM Targeting

Functionalized PLGA NPs targeting specific ECM proteins can enhance drug delivery and improve tumor treatment efficiency. Incorporating stimuli-responsive materials further enhances NP performance by enabling controlled drug release or ECM modulation in response to local environmental cues, such as the upregulated tumor-associated proteins. Different strategies for engineering PLGA-based NDDSs to target GBM ECM are listed in Table 4.

Agarwal et al developed chlorotoxin (CTX) conjugated morusin-PLGA NP (PLGA-MOR-CTX) for GBM therapy. Morusin is a naturally derived chemotherapeutic drug. CTX is a peptide derived from scorpion venom, highly specific for chloride channels (CIC-3) expressed in GBM cells, as well as for MMP-2, which is upregulated in TME. PLGA (LA/GA = 50:50, 7–17 kDa)-MOR-CTX NPs were synthesized by the single-emulsion solvent evaporation method, followed by biofunctionalization with CTX via EDC-NHS reaction. The NPs had a hydrodynamic size of 242.9 nm (PDI = 0.209) and a zeta potential of -10.51 mV. Cell viability in human GBM cell lines (U87 and GI-1) and the human cortical neuron cell

line (HCN-1A) after NP treatment was 39.67%, 27.9%, and 61.4%, respectively, demonstrating high selectivity for cancer cells. Moreover, PLGA-MOR-CTX NPs induced tumor cell death by multiple mechanisms, including autophagy, caspase activation, MMP inhibition, cytoskeletal degeneration, and reactive oxygen species generation.¹⁴⁶

Cantisani et al developed PLGA NPs that can detect MMP-2 and release Dox on demand for GBM treatment. The MW of the PLGA was 12 kDa. They synthesized tumor-activated prodrugs (TAPs) composed of MMP-2-sensitive peptides bound to doxorubicin (DOX) and polyethylene glycol (PEG). The resulting TAP-conjugated NPs (PELGA-TAP NPs) could trigger DOX release only in the presence of MMP-2. PELGA-TAP NP was synthesized by the nanoprecipitation method. The average particle hydrodynamic size was 75.1 ± 0.5 nm, and the zeta potential was -29.5 ± 14.8 mV. The release kinetic study showed that approximately 40% was released within 24 hours in the presence of MMP-2, whereas approximately 25% was released in its absence. Their results further demonstrated that PELGA-TAP NPs release DOX upon enzymatic cleavage and facilitate deeper drug diffusion within the 3D U87 spheroid.¹⁴⁷

Engineering PLGA-Based NDDS to Enhance Immunotherapy

Effective immunotherapy depends on accurately delivering therapeutic agents to specific tissues and immune cells to maximize efficacy while minimizing off-target effects. Ma et al developed an activated, mature dendritic cell membrane (aDCM)-coated, rapamycin (RAPA)-loaded PLGA nanoplatform, a simple, efficient, and individualized strategy for crossing the BBB and improving the immune microenvironment. PLGA (50:50, 9 kDa)/RAPA NPs were prepared by nanoprecipitation, followed by mixing with aDCM and extrusion to generate aDCM@PLGA/RAPA. These nanoparticles can assist RAPA in penetrating the BBB, facilitating intratumoral accumulation, and stimulating T cell activation. aDCM@PLGA/RAPA was 127.9 ± 1.5 nm and with an average zeta potential of -23.2 ± 1.0 mV. The drug loading efficiency and drug encapsulation efficiency of PLGA/RAPA were 11.39% and 57.55%, respectively. The in vitro release rate of RAPA was 21.88% at pH 5.5 but less than 8.97% at pH 7.4, indicating the pH responses of the nanoparticles. The results also suggest that mice treated with aDCM@PLGA/RAPA demonstrated continuous inhibition of tumor growth and a significantly increased median survival (29 days compared to 14–22 days in the control groups). This nanoplatform offers several advantages: (1) aDCM retains antigen-presenting capability to activate native CD8⁺ T cells, enabling direct tumor killing and acting as an immunotherapeutic adjuvant; (2) aDCM preserves membrane protein activity of aDCs and can cross the BBB to reach tumor sites; (3) tumor-homing is enhanced through recognition of tumor antigens acquired via endocytosis of tumor cell lysate by DCs; (4) aDCM@PLGA helps remodel the tumor microenvironment, suppressing tumor recurrence and metastasis; and (5) the immunotherapeutic effects of aDCM@PLGA synergize with the cytotoxic activity of RAPA to further enhance antitumor efficacy.¹⁴⁸

Zhang et al described a novel Trojan-horse NP system, which encapsulates PLGA-coated TMZ and IL-15 nanoparticles with cRGD-decorated natural killer (NK) cell membrane (R-NKm@NP), to elicit the immunostimulatory TME for GBM chemo-immunotherapy. The PLGA had a 50:50 LA:GA ratio, was ester-terminated, and had a molecular weight of 7–17 kDa. NPs were prepared via nanoprecipitation, followed by coating the NPs with NKm via direct extrusion. The hydrodynamic diameter of these NPs was 125.6 nm, and the zeta potential was -14 mV. The results also demonstrated that R-NKm@NPs achieve efficient delivery across the BBB and target the GBM, further stimulating an immunostimulatory TME and enhancing NK cell activation, DC maturation, and CD8⁺ T-cell infiltration, resulting in prolonged survival and effective tumor suppression in orthotopic GL261 GBM-bearing mice.¹⁴⁹

Brain Modulation: Increasing Drug Delivery into GBM

External stimuli-mediated brain modulation has emerged as a widely explored approach to enhance the delivery of PLGA-based NDDS into the brain. These strategies can be implemented using various external stimuli, such as light stimulation, magnetic targeting, and ultrasound stimulation.

Light Stimulation

Nanomotors are self-propelled nanoscale robots that convert chemical fuels (eg, hydrogen peroxide, glucose) or physical stimuli (eg, light, ultrasound, magnetic fields) into mechanical motion, enabling them to perform complex tasks in

diverse biological environments. In GBM therapy, tumor-targeted nanomotors offer a promising active drug-delivery strategy by autonomously navigating and penetrating the BBB/BBTB, thereby enhancing drug permeability and tumor accumulation.¹⁵⁰ Li et al developed a calabash-like nanomotor using PLGA (LA:GA = 65:35, 40–75 kDa) and Polycaprolactone (PCL) scaffolds, employing a double-emulsion technique to enhance the efficacy of chemo-photothermal therapy in treating GBM. This method efficiently and simultaneously loads two drugs, the photothermal agent ICG and the chemotherapeutic drug DOX, into biocompatible polymeric scaffolds. The surfactant PB80 in the corona of the motor enabled it to pass through the BBB. The hydrodynamic diameter of the NP was 122.7 ± 4.4 nm (PDI = 0.122 ± 0.023). The loading efficiency of ICG and DOX was 67.1 ± 1.3 $\mu\text{g}/\text{mg}$ and 79.8 ± 2.6 $\mu\text{g}/\text{mg}$, respectively. NIR laser irradiation enables both nanomotor propulsion and photothermal antitumor effects. The results show that nanomotors can cross the blood-brain barrier and reach the brain parenchyma more effectively than their counterparts upon intravenous (i.v.) administration in a GL261-Luc orthotopic mouse model. This dual-drug-loaded nanomotor exhibited superior in vivo chemo-photothermal efficacy, as indicated by reduced tumor volumes and a promoted survival rate without apparent toxicity.¹⁵¹

Magnetic Targeting

Several studies have shown that magnetic polymeric NPs, when guided by an external magnetic field, exhibit improved permeability across the BBB. By further functionalizing their surfaces with ligands that specifically recognize GBM cells, these NPs can serve as dual-targeting systems, achieving both BBB penetration and selective GBM drug delivery.^{143,152,153} For example, Dash et al developed cetuximab (CET)-conjugated magnetic PLGA NPs as a dual-targeting system for GBM therapy. They first encapsulated the chemotherapeutic agent irinotecan (CPT-11) and an oleic acid-coated iron oxide magnetic NP (OMNP) in PLGA (LA:GA = 50:50, 15–30 kDa), followed by conjugation with the EGFR monoclonal antibody CET to form PLGA@OMNP@CPT-11-CET. These NPs could be guided to the tumor site through magnetic localization using a permanent magnet. CET-mediated targeting further enhanced intracellular uptake by specifically binding to EGFR receptors overexpressed on GBM cells. These particles had an average particle size of 245.2 ± 5.1 nm, with a PDI of 0.29 ± 0.02 . The zeta potential was -13.0 ± 0.4 mV. At 37 °C, the cumulative release percentage of CPT-11 in 48 hours from PLGA@OMNP@CPT-11-CET was 20.7% (pH 7.4) and 79.9% (pH 5), respectively, indicating a more efficient release of the drug in the acidic TME. In vitro studies demonstrated that PLGA@OMNP@CPT-11-CET had the highest cytotoxic effect on U87 GBM cells ($\text{IC}_{50} = 2.5$ $\mu\text{g}/\text{mL}$) when compared to PLGA@OMNP@CPT-11 (8.8 $\mu\text{g}/\text{mL}$) and CPT-11 (9.3 $\mu\text{g}/\text{mL}$), alone. In an orthotopic U87 xenograft model, the combination of magnetic targeting and EGFR targeting yielded the most effective treatment outcome, as evidenced by the lowest tumor-associated signal intensity observed by bioluminescence imaging.¹⁵²

Focused Ultrasound-Mediated BBB Modulation

Focused ultrasound (FUS) can locally, transiently, and reversibly increase BBB permeability in the presence of circulating microbubbles (MBs), demonstrating tremendous potential for targeted delivery of chemotherapeutic agents for GBM therapy. Upon exposure to low-intensity ultrasonic pulses, MBs oscillate through repeated expansion and contraction, temporarily and reversibly opening the BBB at speeds of tens to hundreds of meters per second by inducing mechanical and functional changes in blood vessels. At the same time, millions of MBs can burst under the action of the FUS beam, which can increase the permeability of the cell membrane and open the BBB and BBTB noninvasively and reversibly.^{154,155}

Wang et al developed negatively charged gambogic acid-loaded PLGA nanobubbles and conjugated them to the surface of cationic lipid microbubbles (CMBs) via electrostatic interactions for ultrasound-triggered drug delivery in GBM therapy. The PLGA has a 50:50 LA:GA composition and an MW of 30 kDa. The hydrodynamic size of the gambogic acid/PLGA-CMBs was 869.7 ± 79.50 nm, and the zeta potential was 7.22 ± 1.87 mV. The gambogic acid entrapment efficiency was $96.81 \pm 1.63\%$, with a loading efficiency of $7.75 \pm 0.13\%$. I.V. administration of gambogic acid/PLGA-CMBs followed by low-intensity FUS markedly increased gambogic acid delivery to the brain, as cavitation of the CMBs transiently disrupted the BBB. Leveraging this temporary opening, gambogic acid/PLGA nanobubbles were

subsequently delivered into the tumor. A second, higher-energy FUS exposure was then applied to trigger cavitation of the gambogic acid/PLGA nanobubbles, generating a localized destructive effect on tumor cells and further promoting gambogic acid penetration into tumor tissue, thereby enhancing its antitumor efficacy.¹⁵⁶

While active-targeting drug delivery approaches provide inherent biological specificity, they are constrained by manufacturing complexity, biological heterogeneity, and limited spatial-temporal control. Conversely, brain stimulation strategies offer complementary advantages: (1) tunable, externally controlled spatial selectivity. The stimulation parameters can be adjusted to target localized tumor regions or expand to whole-brain delivery, providing flexibility that formulation-based targeting cannot achieve; (2) simplified PLGA formulation design that eliminates the need for targeting ligand engineering, cell membrane sourcing, or sophisticated conjugation chemistry, thereby reducing manufacturing burden and batch variability; (3) precise temporal control over barrier permeability and drug release kinetics, synchronized to clinical decision-making or optimized dosing schedules rather than constrained by baseline receptor saturation, heterogeneous ECM composition, or inconsistent cell membrane coating efficiency; and (4) enhanced safety through externally gated modulation of BBB permeability, which minimizes systemic drug exposure and reduces the risk of uncontrolled off-target accumulation.

Conclusion and Outlook

PLGA-based drug delivery platforms have demonstrated notable regulatory and translational success in several cancers using diverse delivery strategies, such as local depots or implants (eg, Ozurdex™ for ocular melanoma, NCT04082962) and localized biodegradable membranes (eg, CEB-01 for retroperitoneal sarcoma, NCT04619056; and pancreatic cancer, NCT06538857). These successes largely benefit from favorable formulation attributes, including excellent stability, biocompatibility, and controlled drug release. In contrast, although extensive preclinical studies demonstrate that PLGA-based NDDS engineered with specialized surface functionalization can cross the BBB, target GBM tissue, and penetrate the tumor ECM, translation into clinical applications in GBM has been limited. This gap reflects multiple barriers to clinical translation, including manufacturing and scale-up challenges, safety assessment limitations, GBM TME-specific obstacles, rapid *in vivo* opsonization and clearance of PLGA nanocarriers, and complexities related to personalized medicine.

- (1) Manufacturing and scale-up barriers: The intricate challenges of scale-up manufacturing remain the most significant barrier in translating benchtop-scale formulations into larger clinical-scale batches.¹⁵⁷ Even minor variations in formulation composition or processing parameters during scale-up can markedly alter NPs' performance. Although many PLGA-based NDDS are relatively easy to synthesize on a laboratory scale, their structural complexity demands precise engineering, robust characterization techniques, and highly reproducible scale-up and manufacturing processes. To address this challenge, innovative approaches such as inline sonication processes have been developed for industrial-scale production.¹⁵⁸ Moreover, future development should explicitly incorporate Good Manufacturing Practice (GMP)-compliant production with validated aseptic processing or terminal sterilization, predefined critical quality attributes (eg, size, PDI, encapsulation efficiency, residual solvent, endotoxin burden), and in-process controls that ensure batch-to-batch consistency at clinically relevant scales. In parallel, establishing scalability metrics, such as target production throughput, acceptable variability limits for key Critical Quality Attributes (CQAs), and demonstrable process robustness across equipment scales, will be essential to align PLGA-based NDDS manufacturing with regulatory expectations for safety, quality, and reproducibility.
- (2) Safety assessment challenges: Comprehensive toxicological assessment of PLGA-based NDDS remains critical, particularly for nanomedicines, as the nanoscale nature introduces risks beyond those associated with conventional drug delivery matrices. Small variations in NP formulation parameters can significantly alter their biodistribution, immune responses, and overall safety. Moreover, the initial burst drug release from PLGA-based NDDS is generally unfavorable, as it can shorten the sustained therapeutic window of the drug. Excessive bursts may even lead to toxic effects, posing a safety risk.⁸⁶ Various strategies have been developed to overcome the burst effect, including modifying interactions between the drug and the polymer, altering polymer surface permeability, controlling monomer sequence distribution, and adjusting drug spatial distribution.⁸⁶ However, to date, a lack of established scientific paradigms persists, hindering the ability to fully predict or understand their biological

interactions and potential adverse effects. To mitigate these challenges, standardized toxicity evaluation criteria should be established across preclinical and translational studies to enable consistent safety assessment and regulatory decision-making. Furthermore, harmonized protocols for assessing the immunogenicity, systemic toxicity, pharmacokinetics, and biodistribution of the nanocarriers across regulatory agencies will accelerate clinical translation.

- (3) GBM-specific clinical translation barriers: Due to the restrictive nature of the BBB, most therapeutic agents are unable to reach GBM tissues effectively. The prolonged underdevelopment of BBB-targeting strategies has been a key factor underlying the high rate of clinical trial failures in brain disorder therapeutics.¹⁵⁹ This limitation underscores the necessity for further investigation into the combination of PLGA-based NDDS with advanced BBB opening techniques, with a special focus on controlling drug release spatially and temporally while reducing drug- and surgery-related adverse effects.^{7,160,161} As an alternative approach, intranasal delivery is a promising non-invasive method for bypassing the BBB and delivering therapeutics directly to the brain. The intranasal route offers several advantages over conventional systemic delivery, including rapid and targeted drug delivery to brain tissues via the olfactory and trigeminal nerve pathways, minimized systemic side effects, avoidance of first-pass hepatic metabolism, and the convenience of patient self-administration.^{162–164} Successful intranasal PLGA formulations should incorporate mucoadhesive surface coatings, permeation enhancers, and optimized nanoparticle size to extend mucosal residence time, prevent degradation, and facilitate epithelial transport.^{165,166} On the other hand, ECM stiffness is a critical factor in cancer progression and represents a promising therapeutic target for GBM treatment. In GBM, the dense ECM establishes a physical barrier that impedes the diffusion of oxygen, therapeutic agents, and immune effector cells, thereby contributing to resistance against various clinical treatment modalities.^{167,168} Therefore, ECM normalization may act as a powerful adjuvant for conventional chemotherapy and immunotherapy.
- (4) Opsonization and clearance of PLGA nanocarriers in vivo: Upon i.v. injection, the hydrophobic and negatively charged PLGA nanoparticles rapidly adsorb plasma proteins, forming a protein corona that changes their surface properties and prompts opsonization. This leads to two major barriers for drug delivery: (1) masking of targeting ligands, which hinders the nanoparticles' ability to localize to diseased tissue, and (2) accelerated immune clearance, as opsonins trigger phagocytosis by neutrophils and monocytes, resulting in off-target or incomplete drug release. To address these challenges, surface modification with PEG imparts a near-neutral charge, forms a hydrated steric barrier, and improves stability in biological media. Optimal PEG coatings (typically 2–5 kDa) provide stealth from opsonins, prolonging circulation. Other alternatives, such as chitosan, albumin, or cell membrane coatings, are also being explored to further enhance the longevity and targeting of PLGA nanocarriers.¹⁶⁹
- (5) Personalized medicine challenges: While PLGA-based NDDS have shown promise in preclinical GBM therapy, current designs are largely standardized and do not support personalized treatment approaches. Given the high heterogeneity of GBM, individualized strategies are critical for achieving better therapeutic outcomes. In this context, artificial intelligence (AI) offers a powerful tool for optimizing PLGA-based NDDS design, which can integrate multi-dimensional patient data, including genomic profiles, tumor characteristics, and imaging information, to guide the design of PLGA-based NDDS tailored to each patient's unique needs. By leveraging machine learning algorithms and predictive modeling, AI can optimize key NP parameters (eg, size, surface charge, drug release kinetics, and ligand functionalization) to enhance tumor targeting, drug penetration, and treatment efficacy. AI can analyze large datasets from preclinical studies to identify patterns linking NP design to therapeutic performance and immune responses, enabling rapid iteration and data-driven refinement of nanocarrier systems. Moreover, AI algorithms can analyze nanoparticle drug-release kinetics, generate predictive models for different physiological conditions, and predict bio-nano interactions. These predictions help design individualized treatment plans and maintain therapeutic drug levels at the tumor site. By integrating patient-specific data, AI can simulate personalized pharmacokinetic responses, enabling optimized dosing and treatment schedules for improved outcomes.^{170,171} Ultimately, integrating AI into PLGA-based NDDS development holds great promise for advancing precision medicine in GBM, offering a path toward safer, more effective, and patient-specific treatments.

In summary, GBM remains one of the most aggressive and treatment-resistant brain tumors, and PLGA-based NDDS show great promise for overcoming key therapeutic barriers such as poor BBB penetration, limited tumor targeting, and suboptimal drug distribution, as evidenced by preclinical studies. Despite these advances, bridging the gap between preclinical success and clinical application presents complex challenges related to scalability, safety assessments, and disease-specific translational obstacles. The integration of AI-driven approaches into PLGA-based NDDS development offers a transformative pathway toward patient-specific therapies. Short-term priorities should include establishing standardized toxicity, biodistribution, and pharmacokinetic evaluation protocols, while optimizing nanoparticle surface modifications to integrate PLGA-based NDDS with BBB- and ECM-targeting strategies and to enhance immunotherapy efficacy. Long-term research needs include developing scalable manufacturing processes for clinical translation and integrating AI and machine learning to achieve personalized, patient-specific nanomedicine designs for GBM. With continued innovation, interdisciplinary collaboration, and the strategic application of AI, the clinical potential of PLGA-based NDDS for GBM therapy may soon be realized, ushering in a new era of precision, safety, and efficacy in brain tumor treatment.

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Disclosure

The authors declare no conflict of interest in this work.

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