Nanotechnology Applications for Glioblastoma

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KEYWORDS

• Malignant brain tumors • Glioblastoma • Magnetic nanoparticles • Nanoparticles
• Convection-enhanced delivery • MRI • EGFR • Thermotherapy

KEY POINTS

- GBM remains a difficult tumor to treat due to its infiltrative nature.
- Nanoparticles present a new way to target infiltrating cells.
- Magnetic nanoparticles (MNPs) can be used as MRI contrast agents as well as therapeutic agents by the use of thermotherapy.
- In a nanoparticle formulation chemotherapeutics can be more efficacious than conventional chemotherapeutic agents due to their ability to target GBM cells and release drug.
- Gene delivery through the use of nanoparticles may be a safe option to deliver therapeutic genes to tumor cells.
- Brachytherapy delivered by radioactive nanoparticles can provide long-term focused radiation therapy to these lesions.
- Gold nanoparticles can be used to treat tumors through phototherapy, where deep penetrating near-infrared light can be used to inhibit tumor growth.
- Nanoparticles can be delivered safely systemically or by bulk flow using convection-enhanced delivery (CED) directly to the tumor.
- Magnetic targeting can be used to enhance the delivery of MNPs by directing the delivered particles to the area of interest.

INTRODUCTION

Glioblastoma (GBM) is the most common primary malignancy of the brain as well as its most malignant.[1] The median survival after radiation and chemotherapy ranges from 12 to 15 months, despite advances in surgery, radiation, and chemotherapy.[2] GBM tumors are nearly uniformly fatal due to local recurrence.[3–5] Even for lesions amenable to gross surgical resection, infiltrating cancer cells beyond the boundaries of the enhancing lesion are responsible for tumor recurrence as well as radiation and chemotherapy resistance.[6,7]

Cancer nanotechnology has recently emerged as a field that may provide answers to some of the difficulties encountered in treating GBM. Nanoparticles, defined as particles less than 100 nm in hydrodynamic size, have been used in the

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treatment of various cancers.[8] The use of biocompatible nanomaterials has permitted the fabrication of nanoparticles with capabilities that surpass those of conventional agents. Chemotherapy-loaded nanoparticles have resulted in sustained-release formulations that can lower systemic toxicity and produce greater antitumor effects. Recently developed nanoparticles can cross the blood-brain barrier (BBB) after systemic administration or be distributed in the brain by CED to target GBM cells therapeutically while harboring elements that may enable imaging of the particle and the target. The field has been moving at a rapid pace, enabling nanoparticles to be used in recent clinical trials.[9] Although not exhaustive, the list of nanoparticles used in the treatment of experimental GBM includes polymeric particles, micelles,[10] nanoshells,[11] quantum dots,[12] and magnetic iron oxide nanoparticles (IONPs).[13] Nanotubes are another formulation of nanoparticle, used to create structures that can trap diagnostic or therapeutic modalities within a cage. This article discusses the use of different nanoparticle formulations in strategies to image and treat GBM, including delivery schemes.

MAGNETIC NANOPARTICLES

MRI Contrast Properties of MNPs

The base of the promise for theranostic nanoparticles with both therapeutic and diagnostic ability hinges on the idea that such nanoparticles will be able to image where the lesion is and treat it. MNPs have attracted particular interest in this respect due to their unique paramagnetic properties that enable their detection by MRI.[14,15] These MNPs have shown great potential as T_1 or T_2 contrast agents in MRI,[16,17] with superparamagnetic iron oxide–based nanoparticles (SPIOs) as the most commonly investigated type of MRI contrast agents.[18] Since 1990, ultrasmall SPIOs (USPIOs), smaller than 50 nm, have been considered an MRI contrast agent,[19] and most of the MRI data regarding nanoparticles references these particles. USPIOs can be visualized in T_2-weighted MRI sequences (T_2 contrast agents) as a hypointense (dark) signal (negative contrast enhancement) or with T_1-weighted MRI sequences (T_1 contrast agents) as a hyperintense (bright) signal (positive contrast enhancement).[20–22]

USPIOs can provide contrast for a longer period of time[23] compared with gadolinium (Gd)-based contrast agents that are rapidly eliminated by the kidney.[24,25] USPIOs are also taken up by tumor cells as well as by reactive phagocytic cells (eg, microglia) found in brain tumors. The USPIOs can reside within brain tumors much longer than Gd-based agents, with a peak enhancement noted at 24 to 28 hours and persisting up to 72 hours after administration.[26,27] These agents may provide a safe alternative for patients at risk for nephrogenic systemic fibrosis, because preliminary studies have shown no adverse renal effects.[27,28]

MNPs for Targeted Brain Tumor Imaging

Targeting of tumor cells can increase the benefits provided by nanoparticles as contrast agents. IONPs are taken up by GBM cells both in vivo and in vitro.[29,30] Surface functionalization further enhances tumor uptake of these particles.[31] Tumor-specific ligands conjugated to MNPs can further enhance the uptake within targeted tumor tissue (**Fig. 1**).[32,33] Antibodies, peptides (including toxins), cytokines, and chemotherapeutic agents have been reported as possible MNP ligands.[34] Amphiphilic triblock copolymer IONPs can be conjugated with a purified antibody that selectively

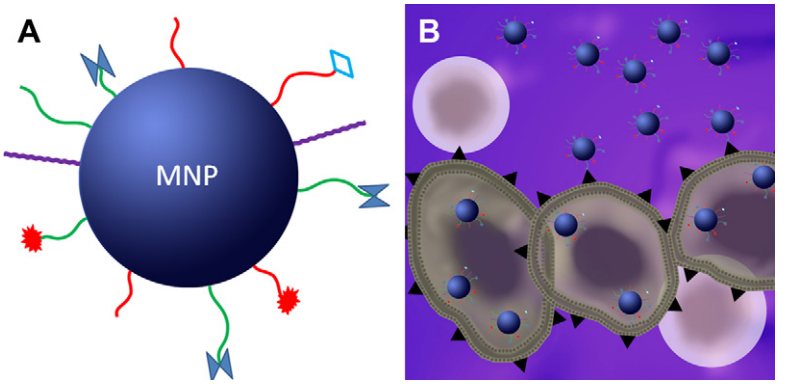

Fig. 1. Theranostic MNPs and tumor targeting. (*A*) Illustration of an MNP with different functional groups on the surface, which permit molecular targeting, imaging, enhanced plasma circulation times, and/or therapy. (*B*) Illustration of MNPs functionalized with tumor cell–specific ligands binding cancer cells (*large irregular cells*) instead of normal cells (*pink*). Internalization of MNPs is shown in cancer cells as well.

binds to the epidermal growth factor receptor (EGFR) deletion mutant, EGFR vIII, which is solely expressed by a population of GBM tumors.[35] Such nanoparticles exhibit MR contrast enhancement of GBM cells and can target these therapy-resistant cancer cells in vitro and in vivo.

Chlorotoxin, derived from scorpion venom, specifically binds to matrix metalloproteinase 2 (MMP-2), which is overexpressed on the surface of GBM cells.[36,37] MMP-2 degrades the extracellular matrix during tumor invasion, and chlorotoxin can be used to bind the MMP-2 and inhibit infiltration.[38,39] Chlorotoxin conjugated to MNPs can act as MRI contrast agents and the addition of a Cy5.5 molecule makes these suitable for use as an intraoperative fluorescent dye as well.[40–42]

F3 is a small peptide that specifically binds to nucleolin overexpressed on proliferating endothelial cells of tumor cells and the associated vasculature.[43] F3-coated IONPs can provide significant MRI contrast enhancement of intracranial rat-implanted tumors, compared with noncoated F3 nanoparticles, when administered intravenously.[44]

A molecular MRI contrast agent, consisting of SPIO coated with dextran, was functionalized with an anti–insulinlike growth factor binding protein 7 (anti-IGFBP7) single-domain antibody and was found by both MRI and in vivo fluorescent imaging to target the vasculature of GBM cells.[45]

Gd has also been incorporated into some therapeutic nanoparticles to enable them to be tracked using MRI. One group has designed nanoparticles containing Gd, which are rapidly taken up by the GL261 tumor cell line and show MRI contrast when these cells are then cultured in a chick embryo host.[46] Gd nanoparticles functionalized with diethylenetriaminepentaacetic acid (DTPA) can also be used as a radiosensitizing agent.[47] Fullerene magnetic nanotubes have been made such that Gd can be trapped within these structures to make them an effective contrast agent, along with whatever therapeutic modality is also associated with the fullerene cage.[48,49] It is also possible to internalize IONPs in these larger nanotube structures so that the magnetic properties of iron oxide can be used, allowing clinicians to localize these particles to a particular area. This, together with surface targeting, can greatly increase the amount of intake and resultant therapeutic effect of these particles.[50]

MNPs for Optical Delineation of Brain Tumors

Although surgical intervention is not curative in GBM, obtaining a maximal resection is important for survival.[51] The use of intraoperative MRI and neuronavigation has increased extent of resection and outcome.[52–54] Recently, fluorescence-guided surgery after oral administration of 5-aminolevulinic acid (5-ALA) has resulted in more complete resection of malignant gliomas.[55,56] Laboratory studies have attempted to find ways to use optical aides to increase the contrast between normal and tumor tissue,[57–59] and these methods have shown improvement in the extent of tumor resection in clinical use.[60,61]

Fluorescent molecules have already been successfully incorporated into several nanoparticles. An IONP-Cy5.5 molecule has been used in many preclinical studies,[40,41,62] giving it the dual benefits of MRI detection and possibly enhanced surgical contrast using the fluorescent properties of the particle. This also could lead to theranostic particles that could be injected preoperatively to outline malignant tissue that would need to be resected at surgery.

MNPs for Stem Cell Tracking

The ability of MNPs to act as MRI contrast agents can be used to track stem cell tropism to malignant brain tumors in vivo. Intracranially administered neural stem cells have tropism for GBM tumors, making them attractive for tumor-targeting gene therapy.[63–65] Mesenchymal stem cells have also been found to migrate to tumor cells.[66] By labeling these cells with IONPs, this migration can be visualized on MRI.[67,68] Magnetically labeled hematopoietic stem cells can also be tracked to gliomas in this fashion.[69]

MNPs for Thermotherapy of GBM

One of the more unique features of MNPs is the ability to induce hyperthermia when exposed to alternating magnetic fields. Temperature elevations in the range of 41°C to 46°C can cause cells to undergo heat stress, resulting in protein denaturation, protein folding, aggregation, and DNA cross-linking.[70] This process can induce apoptosis and heat shock protein expression. At the tissue level, moderate hyperthermia causes changes in pH, perfusion, and oxygenation of the tumor microenvironment.[71–74] These effects, combined with chemotherapy and radiation, can have a synergistic effect.[74–78]

Hyperthermia can be induced in MNPs through the use of an appropriate alternating magnetic field of the right amplitude and frequency to heat up the nanoparticles. A predictable and sufficient amount of heat known as the specific absorption rate is produced. The MNPs use several different mechanisms to convert the magnetic energy into heat energy. Néel relaxation is caused by rapidly occurring changes in the direction of magnetic

moments relative to crystal lattice. Brownian relaxation results from the physical rotation of MNPs within the medium in which they are placed. Both internal (Néel) and external (brownian) sources of friction lead to a phase lag between applied magnetic field and the direction of magnetic moment, producing thermal losses (**Fig. 2**).

MNPs can be specifically engineered to maximize their suitability for hyperthermia by producing greater saturation magnetization, optimal anisotropy, and larger size within the constraints of nanoparticle production.[79–81] MNPs suitable for thermotherapy can be made from a combination of various metals, including manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), zinc (Zn), and magnesium (Mg) and their oxides.[82–89] Ferrites of the various metals are frequently used in these settings, such as cobalt ferrites ($CoFe_2O_4$), manganese ferrites ($MnFe_2O_4$), nickel ferrites ($NiFe_2O_4$), lithium ferrites ($Li_{0.5}Fe_{2.5}O_4$), mixed ferrites of nickel–zinc–copper, and cobalt–nickel ferrites.[85–91] There are also ferromagnetic nanoparticles that are iron based and have greater magnetic properties than IONPs.[79] These cobalt ferrites–based nanoparticles produce greater hyperthermia effects at much lower concentrations than IONPs. FeNPs are comprised of an iron core surrounded by an iron oxide layer to permit stability. Nevertheless, owing to their lack of toxicity, excellent biocompatibility, and their capacity to be metabolized,[92–94] iron oxide–based MNPs are actively being studied for thermotherapy of brain tumors.

MNP-based hyperthermia has been evaluated for feasibility in animal models and in human patients with malignant brain tumors. Dextran-coated or aminosilane-coated IONPs have been used for thermotherapy in a rodent GBM model[95] and in a human clinical trial in patients with recurrent GBM.[9,96] Intratumoral injection of aminosilane-coated IONPs (core size 12 nm) and application of an alternating magnetic field (100 kHz) in several sessions before and after adjuvant fractionated radiation therapy was given. With a high concentration of IONPs (>100 mg/mL), this achieved effective thermotherapy with a median peak temperature within the tumor of 51.2°C. This phase II clinical trial successfully demonstrated safety and efficacy of thermotherapy of malignant brain tumors with MNPs in humans, with a significant increase in overall survival compared with a reference population. Further randomized studies will be required to validate the promise of this treatment modality.

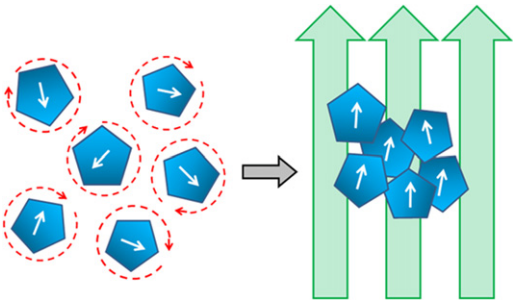

Fig. 2. MNP response to alternating magnetic fields and thermotherapy. Application of applied magnetic fields (*arrows*) orients the MNPs on the right from their random orientation on the left in the absence of magnetic fields. Random orientation on the left produces thermal losses, allowing for hyperthermia generation by the MNPs.

NANOPARTICALIZED CHEMOTHERAPEUTIC AGENTS

Although few conventional chemotherapeutics have been proved effective in GBM, chemotherapeutics in a nanoparticle formulation offer possible advantages. These often can be targeted, evade the reticuloendothelial system for prolonged circulatory time, and potentially cross the BBB better then standard chemotherapy agents. Polyethylene glycol (PEG)-coated paclitaxel (taxol) nanoparticles have been shown to offer superior bioavailability compared with free paclitaxel with a survival advantage shown in a rodent glioma model.[97] Poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles are another form of biocompatible nanoparticles. CED of these nanoparticles, loaded with camptothecin, has been shown efficacious in a rodent glioma model.[98] Although the controlled release offered by nanoparticles can reduce systemic toxicity and allow drug to be slowly released only when it has reached its target, there is also a need to ensure that an adequate dose is delivered to the lesion being treated. Nanoparticles have been developed that are thermosensitive, releasing their drug preferentially when the temperature has been increased.[99] When delivered with gold nanorods, concurrent photothermal hyperthermia can release the drug from the heat sensitive nanoparticle, thus increasing efficacy.

GENE DELIVERY WITH NANOPARTICLES

The Cancer Genome Atlas has revealed the multiple genetic aberrations in GBM tumors that can serve as therapeutic targets provide targets.[100] Cationic solid lipid nanoparticles can be conjugated to PEGylated therapeutic *c-Met* small interfering RNA and reduce human GBM tumor growth in a rodent model without significant toxicity.[101] Another nanoparticle, containing the integrin-binding motif RGD, together with the PEG-polyethylenimine (PEI) nonviral gene carrying

nanoparticle, was able to deliver a plasmid expressing the tumor necrosis factor-related apoptosis-inducing ligand with increased efficiency and increase survival in a rodent glioma model.[102]

NANOPARTICLES FOR BRACHYTHERAPY

Brachytherapy, where localized radiotherapy is delivered directly to a tumor, has been explored as a strategy with nanoparticles. In an orthotopic xenograft brain tumor model, a functionalized fullerene nanoparticle (^{177}Lu-DOTA-f-$Gd_3N@C_{80}$), with radiolabeled lutetium 177 (^{177}Lu) and tetraazacyclododecane tetraacetic acid (DOTA), provided an anchor to deliver effective brachytherapy and longitudinal imaging of the tumor.[103] Internal fractionated radiation has also been achieved using a lipid nanoparticle formulation of radionucliides, such as ^{188}Re-SSS in the 9L rat glioma cell line.[75]

GOLD NANOPARTICLE PHOTOTHERAPY

Gold nanoparticles can be designed as nanoshells, consisting of a spherical dielectric core nanoparticle surrounded by thin sheet metal.[76] The size of each layer of the nanoshell can be tailored to enable it to have a peak light absorption at 800 nm, in the near infrared range. Light in this region of the electromagnetic spectrum has minimal absorption by water and biologic chromophores, allowing it to pass deep into tissues without losing much of its energy. This region of the electromagnetic spectrum is notable for minimal absorption by water and biologic chromophores. Thus, light of this wavelength may penetrate deep into tissues with minimal disruption. This has enabled researchers to produce these gold nanoparticles, which can be activated by light and kill GBM cells in vitro.[77] One group has used macrophages loaded with gold nanoshells to deliver these particles to glioma spheroids to then be activated by near infrared light, inhibiting growth.[78]

MALIGNANT BRAIN TUMOR DELIVERY OF NANOPARTICLES

Delivery of therapeutic agents to GBM tumors remains a formidable challenge. Systemic delivery is limited by the BBB, nonspecific uptake, nontargeted distribution, and systemic toxicity. The benefits and drawbacks of the use of systemic delivery, systemic delivery augmented by magnetic targeting, and direct infusion in the brain known as CED are examined.

Systemic Delivery

The reticuloendothelial system can significantly reduce the amount of nanoparticle available to treat the lesion by nonspecific uptake in the liver, kidney, spleen, and circulating macrophages.[104,105] This can be addressed by biocompatible surface coating of nanoparticles, which can increase their circulation time.[106] The BBB further obstructs delivery by preventing the entry of most particles from the circulation into the interstitial space of the brain. It is well known that the vasculature in GBM, however, is not phenotypically normal, due to open endothelial gaps and atypical angiogenesis, allowing more efflux of intravascular material into the tumor mass.[107–109] The enhanced permeability and retention effect is used to describe the selective extravasation of macromolecules into the tumor interstitium through the hyperpermeable tumor vasculature.[110] By attaching tumor-specific targeting ligands, delivery has been shown to be increased in a rodent model, because the extravasated treatment is more likely to be taken up by the lesion.[44,111]

Integrins are overexpressed in GBM at the brain tumor border, and one of the integrin-binding motifs is RGD. Conjugating this peptide to PEG and PEI creates a nanoparticle, which was targeted to GBM and found to prolong survival in rodents implanted with human intracranial GBM xenografts.[102] Meng and colleagues used PEI conjugated to DNA and myristic acid, a hydrophobic molecule, can enhance the ability of the PEI/DNA complexed nanoparticles to cross the BBB, thus showing a treatment effect in GBM tumor models.[112]

PLGA nanoparticles have been shown to cross the BBB. The use of surfactants, such as poloxamer 188 (Pluronic F-68) or polysorbate 80 (Tween 80), can enhance the transport of the particles and increase the delivery of drugs conjugated to them and increase intracellular uptake.[113–115] A recent study demonstrated that conjugating transferrin, a protein known to be actively transported across the BBB, enhances the delivery of these particles to the brain, with an intact BBB as well as a disrupted BBB with an intracranial lesion.[116]

The α-helical amphipathic peptide $_D$[KLAKLAK]$_2$ was originally designed as a synthetic antibacterial peptide that disrupts the bacterial cell membrane but is less toxic to eukaryotic cells. When conjugated to a mitochondrial peptide, CGKRK, IONP-derived nanoworms (due to their elongated shape), these particles localize to the mitochondria of tumor cells and cure tumors in a rodent tumor model. The nanoparticles could be seen to localize to the tumor on MRI.[111]

Magnetic Targeting

The concept of magnetic targeting of malignant brain tumors has also been demonstrated in

preclinical rodent models[117,118] as a method to enhance the systemic delivery of MNPs to malignant brain tumors. By using a magnetic field targeted to the region of interest, it has been shown that delivery of MNPs can be increased over the delivery to lesions when a magnetic field is not used.[119] There are concerns in how efficacious the translation of this technique will be to human studies, because the depth of the lesions in the human brain limit the ability to precisely target a lesion with a magnetic field.[118] Nevertheless, this remains an area for increased study.

In an effort to enhance the delivery and deposition of MNPs into malignant brain tumors, many studies have examined using strategies to open the BBB. Focal ultrasound represents a noninvasive technique, which can selectively disrupt the BBB and increase the enhanced permeability and retention effect in a targeted region of the brain.[120–122] Focal ultrasound and magnetic targeting have been used synergistically to enhance the delivery and the deposition of chemotherapy (epirubicin)-loaded MNPs into tumor-bearing animals. Epirubicin delivery and brain tumor accumulation was significantly enhanced by the combined focal ultrasound/magnetic targeting approach of epirubicin-MNPs.[123]

Convection-Enhanced Delivery

CED, where bulk flow is used to distribute infusate throughout the brain with a pressure gradient, is a well-established technique for delivery of molecules to the brain.[124] CED bypasses the BBB, allowing targeted delivery of infusate to the parenchyma of a region of interest through a catheter. A pump is connected to each infusion catheter to ensure a positive pressure gradient during delivery for convection of molecules through the interstitium of the brain. The pressure gradient created by the pump greatly augments the delivery that would be achieved by the use of simple diffusion alone.[125]

The size of nanoparticles makes them optimal to be delivered with CED. Penetration of nanoparticles through the extracellular matrix in the brain is possible due to the larger effective pore size of the extracellular matrix (50 nm).[126] CED of dextran-coated maghemite MNPs have recently been depicted by MRI in a normal rat brain model,[127] showing that these particles could be directly imaged and tracked. They also showed that increased viscosity of the infusate increased efficacy of delivery and reduced leak back.

Imaging the infusate in CED is critical for ensuring adequate drug delivery to regions of interest. Valuable feedback can be gained from tracking infusate delivered into the brain to enable clinicians to properly plan further treatments and avoid pitfalls, such as placement of catheters near sulci or ventricles.[128,129] Trials of conventional chemotherapeutics have failed to show significant benefit with CED, and lack of adequate drug delivery is often cited as the reason for this.[130] Although progress has been made using surrogate tracers, such as Gd-DTPA,[131] directly imaging the therapeutic particle would provide even more accurate information.

The authors have studied the CED of theranostic MNPS in mice (**Fig. 3**).[35] This particle consisted of an IONP core, coated by polymer and conjugated to an EGFR vIII antibody, specific for a subset of GBM tumors. The ability of the nanoparticles to localize to and image the lesion treated and its treatment effect were assessed. CED enabled a broad distribution of the nanoparticles in the region of the tumor and the surrounding brain, and repeat imaging showed that this effect remained for days after the nanoparticle delivery.

FUTURE STUDIES

Although researchers have made great strides in developing nanoparticles that address the difficulties in treating GBM, many challenges remain. In the use of MNPs for thermotherapy and magnetic targeting, clinical equipment needs to be further developed and improved[132] to make these cost effective and freely available for further clinical trials. Phase III studies need to be undertaken to prove their effectiveness. In addition, drug delivery remains an issue with nanoparticles, and as further targeting motifs are studied, delivery of these

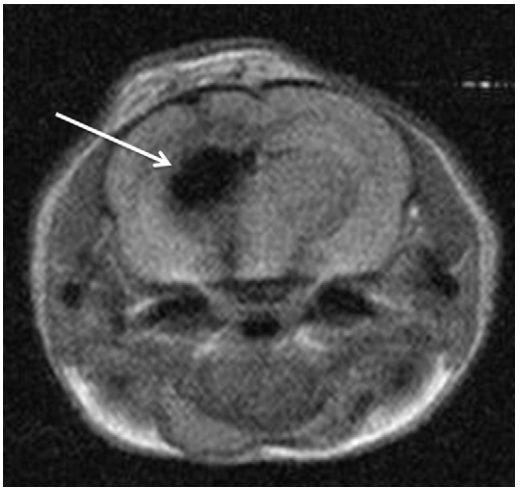

Fig. 3. CED of MNPs in the rodent brain. MRI of a rodent brain depicting the hypointense (*white arrow*) area in the brain that represents distribution of MNPs after CED with no leak back.

particles will be enhanced, further expanding their possible effectiveness.

SUMMARY

Nanotechnology has quickly become a promising tool in the ongoing research to tackle the difficulties in treating GBM. The authors expect translational research to continue to elucidate further uses for this technology as these various particles come into widespread clinical use.

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