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Nanotechnology Applications for Glioblastoma

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Synopsis

Glioblastoma remains one of the most difficult cancers to treat and represents the most common primary malignancy of the brain. While conventional treatments have found modest success in reducing the initial tumor burden, infiltrating cancer cells beyond the main mass are responsible for tumor recurrence and ultimate patient demise. Targeting the residual infiltrating cancer cells requires the development of new treatment strategies. The emerging field of cancer nanotechnology holds much promise in the use of multifunctional nanoparticles for the imaging and targeted therapy of GBM.. Nanoparticles have emerged as potential “theranostic” agents that can permit the diagnosis and therapeutic treatment of GBM tumors. A recent human clinical trial with magnetic nanoparticles has provided feasibility and efficacy data for potential treatment of GBM patients with thermotherapy. Here we examine the current state of nanotechnology in the treatment of glioblastoma and interesting directions of further study.

Keywords

Malignant Brain Tumors; Glioblastoma; Magnetic Nanoparticles; Nanoparticles; Convection-Enhanced Delivery; MRI; EGFR; Thermotherapy

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].

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Cancer nanotechnology has recently emerged as a field which 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 treatment of various cancers [8]. The use of biocompatible nanomaterials have 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 after systemic administration or be distributed in the brain by convection-enhanced delivery (CED) to target GBM cells therapeutically while harboring elements which may enable imaging of the particle and the target. The field has been moving at a rapid pace, enabling nanoparticles to be utilized in recent clinical trials [9]. While not exhaustive, the list of nanoparticles being 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, being used to create structures that can trap diagnostic or therapeutic modalities within a cage. We will discuss the use of different nanoparticle formulations in strategies to image and treat GBM, including delivery schemes.

1.0 Magnetic Nanoparticles (MNPs)

Tags: Malignant Brain Tumors, Glioblastoma, GBM, Magnetic Nanoparticles, Nanoparticles, Convection-Enhanced Delivery, MRI, EGFR, Thermotherapy

1.1 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. Magnetic nanoparticles (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 imaging [16,17], with superparamagnetic iron oxide-based nanoparticles (SPIOs) as the most commonly investigated type of MRI contrast agents [18]. Since 1990, ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs), smaller than 50nm, have been considered as 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], as compared to 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 (e.g., microglia) found in brain tumors. The USPIOs can reside within brain tumors much longer than Gd-based agents, with a peak enhancement noted at 24–28 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, as preliminary studies have shown no adverse renal effects [27,28].

1.1.1 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 (Figure 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 binds to the epidermal growth factor receptor deletion mutant, EGFRvIII, 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 over-expressed 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 over-expressed 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 non-coated F3 nanoparticles, when administered intravenously [44].

A molecular MRI contrast agent, consisting of superparamagnetic iron-oxide nanoparticle coated with dextran, was functionalized with an anti-insulin-like-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].

Gadolinium has also been incorporated into some some therapeutic nanoparticles to enable them to be tracked using MRI. One group has designed nanoparticles containing gadolinium which are rapidly taken up by the GL-261 tumor cell line and show MRI contrast when these cells are then cultured in a chick embryo host[46]. Gadolinium nanoparticles functionalized with diethylenetriaminepentaacetic acid (DTPA) can also be used as a radiosensitizing agent [47]. Fullarene magnetic nanotubes have been made such that gadolinium 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 iron-oxide nanoparticles in these larger nanotube structures so that the magnetic properties of iron-oxide can be utilized, allowing the clinician 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].

1.2 MNPs for Optical Delineation of Brain Tumors

While surgical intervention is not curative in GBM, obtaining a maximal resection is important for survival [51]. The use of intraoperative MRI and neuronavigation have increased extent of resection and outcome [52–54]. Recently, fluorescence-guided surgery after oral administration of 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 sucessfully incorporated into several nanoparticles. An IONP-Cy5.5 molecule has been used in many pre-clinical 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 which could be injected pre-operatively to outline malignant tissue which would need to be resected at surgery.

1.3 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 (NSCs) have tropism for GBM tumors, making them attractive for tumor-targeting gene therapy [63, 64,65]. Mesenchymal stem cells (MSCs) 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].

1.4 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 and 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 (HSP) 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, 100–103].

Hyperthermia can be induced in MNPs through the use of an appropriate alternating magnetic field (AMF) of the right amplitude and frequency to heat up the nanoparticles. A predictable and sufficient amount of heat known as the specific absorption rate (SAR) is produced. The MNPs utilize 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 (Figure 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 [75–77]. MNPs suitable for thermotherapy can be made from a combination of various metals, including manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), zinc (Zn), magnesium (Mg) and their oxides [78–85]. 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 [81–87]. There are also ferromagnetic NPs that are iron-based and have greater magnetic properties than IONPs [75]. These Fe-based NPs produce greater hyperthermia effects at much lower concentrations than IONPs. FeNPs are comprised of an Fe 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 [88–90], 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- or aminosilane-coated IONPs have been used for thermotherapy in a rodent GBM model [91] and in a human clinical trial in patients with recurrent GBM [9,92]. Intratumoral injection of aminosilane-coated IONPs (core size 12 nm) and application of an AMF (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 as compared to a reference population. Further randomized studies will be required to validate the promise of this treatment modality.

2.0 Nanoparticlized Chemotherapeutic Agents

Tags: Malignant Brain Tumors, Glioblastoma, GBM, Nanoparticles, Convection-Enhanced Delivery, Chemotherapy

While few conventional chemotherapeutics have been proven 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 can potentially cross the BBB better then standard chemotherapy agents. Polyethylene glycol-coated (PEG) coated paclitaxel (taxol) nanoparticles have been shown to offer superior bioavailability as compared to free paclitaxel with a survival advantage shown in a rodent glioma model [93]. Poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles are another form of biocompatible nanoparticles. Convection-enhanced delivery of these nanoparticles, loaded with camptothecin, has been shown to be efficacious in a rodent glioma model [94]. While 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 which are thermosensitive, releasing their drug preferentially when the temperature has been increased [95]. When delivered with gold nanorods, concurrent photothermal hyperthermia can release the drug from the heat sensitive nanoparticle, thus increasing efficacy.

3.0 Gene delivery with Nanoparticles

Tags: Malignant Brain Tumors, Glioblastoma, GBM, Nanoparticles, Convection-Enhanced Delivery, Gene therapy

The TCGA has revealed the multiple genetic aberrations in GBM tumors that can serve as therapeutic targets provide targets [96]. Cationic solid lipid nanoparticles can be conjugated to PEGylated therapeutic *c-Met* siRNA and reduce human GBM tumor growth in a rodent model without significant toxicity [97]. Another nanoparticle, containing the integrin binding motif, RGD, together with the PEG-PEI non-viral gene carrying nanoparticle, was able to deliver pORF-hTRAIL with increased efficiency and increase survival in a rodent glioma model [98].

4.0 Nanoparticles for Brachytherapy

Tags: Malignant Brain Tumors, Glioblastoma, GBM, Nanoparticles, 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 [99]. 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.[100]

5.0 Gold Nanoparticle Phototherapy

Tags: Malignant Brain Tumors, Glioblastoma, GBM, Nanoparticles, Phototherapy, Gold nanoparticles

Gold nanoparticles can be designed as nanoshells, consisting of a spherical dielectric core nanoparticle surrounded by thin sheet metal [101]. The size of each layer of the nanoshell can be tailored to enable it to have a peak light absorption at 800nm, in the near infrared range. Light in this region of the electromagnetic spectrum has minimal absorption by water and biological 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 biological chromophores. Thus, light of this wavelength may penetrate deep into tissues with minimal disruption. This has enable researchers to produce such gold nanoparticles which can be activated by light and kill glioblastoma cells in vitro [102]. 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 [103].

6.0 Malignant Brain Tumor Delivery of Nanoparticles

Tags: Malignant Brain Tumors, Glioblastoma, Magnetic Nanoparticles, Nanoparticles, Convection-Enhanced Delivery, Blood-brain barrier

Delivery of therapeutic agents to GBM tumors remains a formidable challenge. Systemic delivery is limited by the blood-brain barrier (BBB), non-specific uptake, nontargeted distribution, and systemic toxicity. We will examine the benefits and drawbacks of the use of systemic delivery, systemic delivery augmented by magnetic targeting, and direct infusion in the brain known as convection enhanced delivery (CED).

6.1 Systemic Delivery

The reticulo-endothelial system (RES) can significantly reduce the amount of nanoparticle available to treat the lesion by non-specific 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. However, it is well-known that the vasculature in GBM is not phenotypically normal, due to open endothelial gaps and atypical angiogenesis, allowing more efflux of intravascular material into the tumor mass [107, 108,109]. The enhanced permeability retention (EPR) effect is used to describe the selective extravasation of macromolecules, into the tumor interstitium through the hyper-permeable tumor vasculature [110]. By attaching tumor-specific targeting ligands, delivery has been shown to be increased in a rodent model, as the extravasated treatment is more likely to be taken up by the lesion [44,111].

Integrins are over-expressed in GBM at the brain tumor border, and one of the integrin binding motifs is RGD. Conjugating this peptide to PEG and polyethylenimine (PEI) creates a nanoparticle which is targeted to GBM and was found to prolong survival in rodents implanted with human intracranial GBM xenografts [98]. This same group was able to use their polyethylenimine-conjugated to DNA and myristic acid, a hydrophobic molecule which can enhance the ability of the polyethylenimine/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 [117].

6.2 Magnetic Targeting

The concept of magnetic targeting of malignant brain tumors has also been demonstrated in preclinical rodent models [118,119] 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 [120]. There are concerns in how efficacious the translation of this technique will be to human studies, as the depth of the lesions in the human brain will limit the ability to precisely target a lesion with a magnetic field[119]. 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 (FUS) represents a non-invasive technique which can selectively disrupt the BBB and increase the EPR effect in a targeted region of the brain [121, 122,123]. FUS 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 FUS/magnetic targeting approach of epirubicin-MNPs [124].

6.3 Convection-Enhanced Delivery (CED)

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[125]. This 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 in order 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 [126].

The size of nanoparticles makes them optimal to be delivered with CED. Penetration of nanoparticles through the extracellular matrix (ECM) in the brain is possible due to the larger effective pore size of the ECM (50 nm) [127]. CED of dextran-coated maghemite MNPs have recently been depicted by MRI in a normal rat brain model [128], 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 leakback.

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 [129,130]. 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 [131]. While progress has been made using surrogate tracers such as Gd-DTPA[132], directly imaging the therapeutic particle would provide even more accurate information.

We have studied the CED of theranostic MNPS in mice (Figure 3) [35]. This particle consisted of an IONP core, coated by polymer and conjugated to an EGFRvIII antibody, specific for a subset of GBM tumors. We both assessed the ability of the nanoparticles to localize to and image the lesion treated as well as its treatment effect. 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

While researchers have made great strides in developing nanoparticles that address the difficulties in treating GBM, many challenges still remain. In the use of magnetic nanoparticles for thermotherapy and magnetic targeting, clinical equipment needs to be further developed and improved[133] to make these cost effective and freely available for further clinical trials. Phase III studies will 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 particles will be enhanced, further expanding their possible effectiveness.

Conclusions

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

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Key Points

- GBM remains a difficult tumor to treat due to its infiltrative nature
- Nanoparticles present a new way to approach infiltrating cells
- Magnetic nanoparticles can be used as magnetic resonance imaging contrast agents and therapeutic agents, including the use of thermotherapy
- Nanoparticlized chemotherapeutics can be more efficacious than conventional chemotherapeutic agents due to their ability to target GBM cells
- 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 directly to the tumor
- Magnetic targeting can be used to enhance the delivery of magnetic nanoparticles, by directing the delivered particles to the area of interest

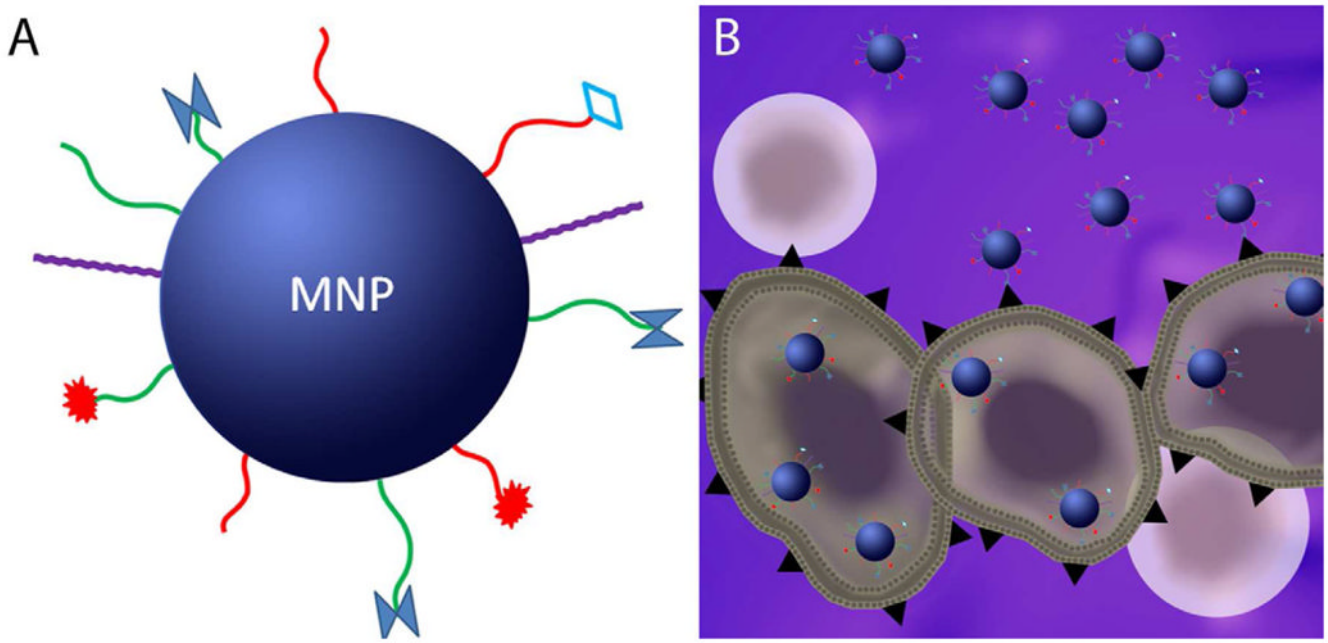

Figure 1. Theranostic magnetic nanoparticles (MNPs) and tumor targeting

A., Illustration of a 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 (in pink). Internalization of MNPs is shown in cancer cells as well.

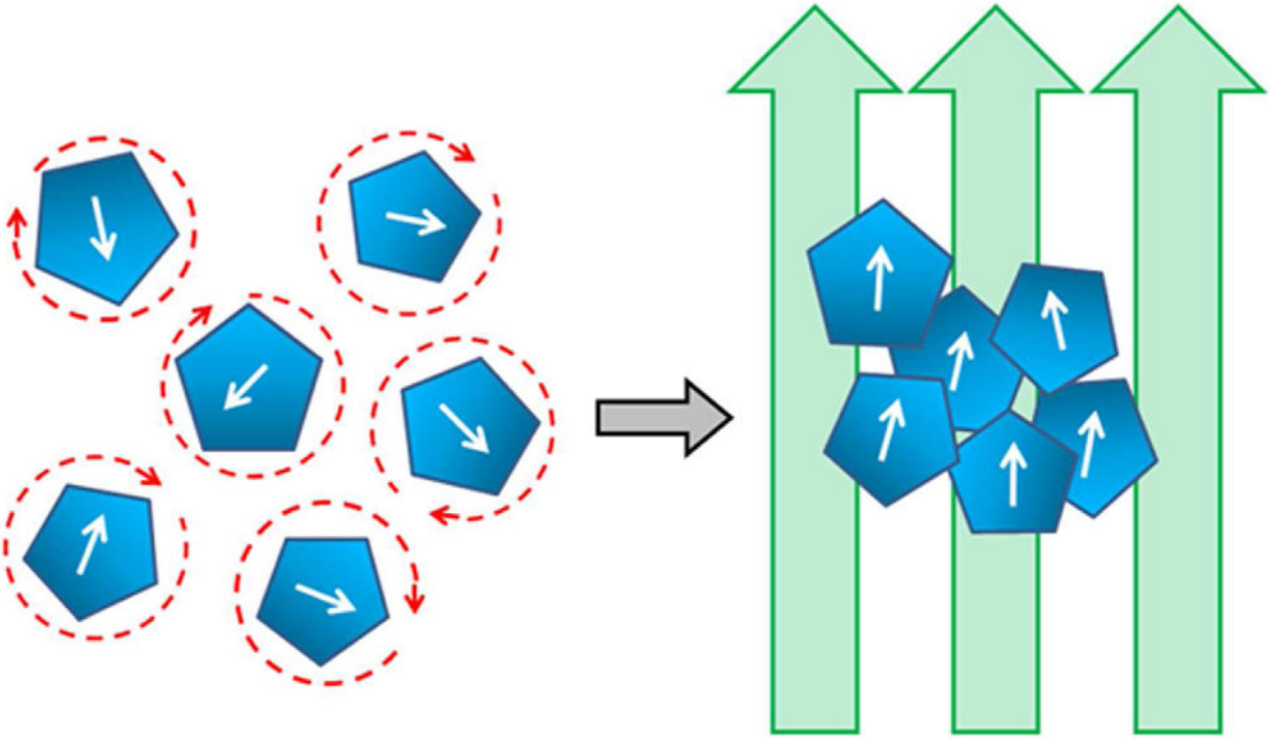

Figure 2. Magnetic nanoparticle (MNP) response to alternating magnetic fields and thermotherapy

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.

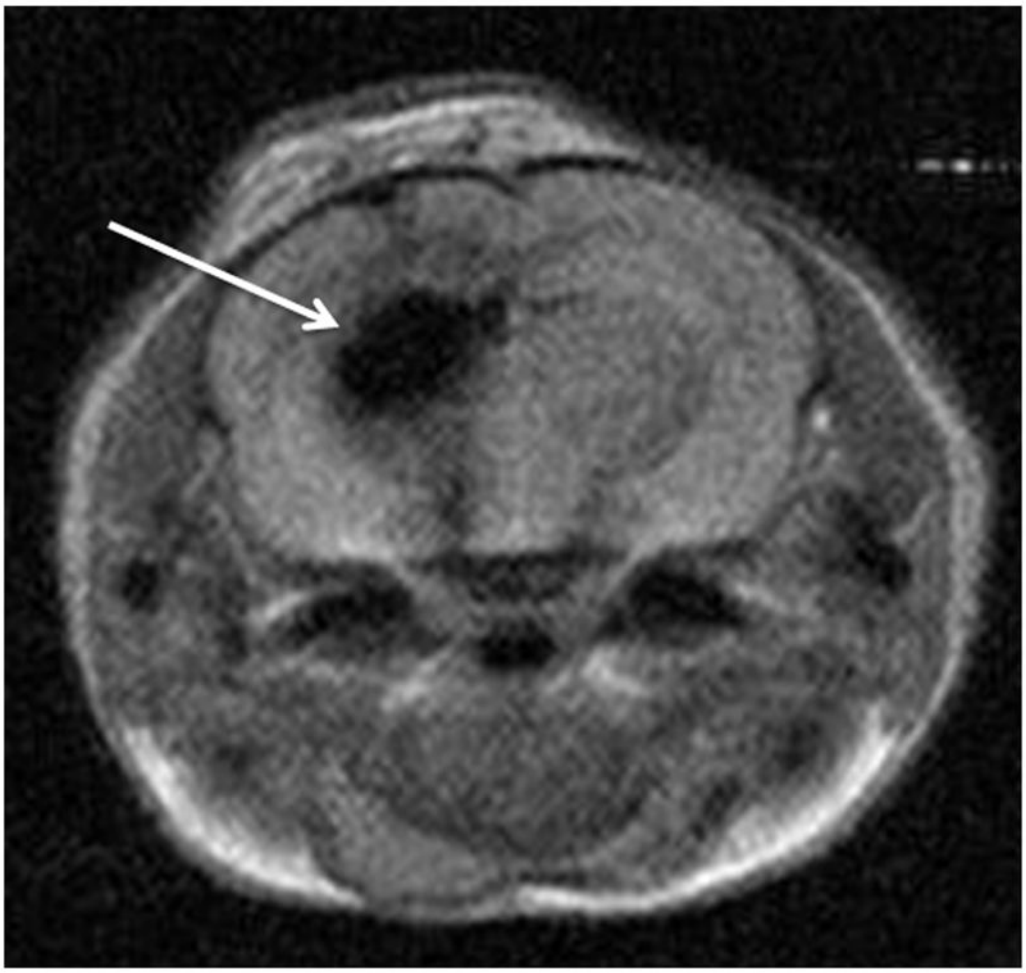

Figure 3. Convection-enhanced delivery (CED) of magnetic nanoparticles (MNPs) in the rodent brain

Magnetic resonance imaging of a rodent brain depicting the hypointense (dark) area in the brain that represents distribution of MNPs after CED with no leakback.