Volume 4 (2014) // Issue 1 // e-ISSN 2224-3453

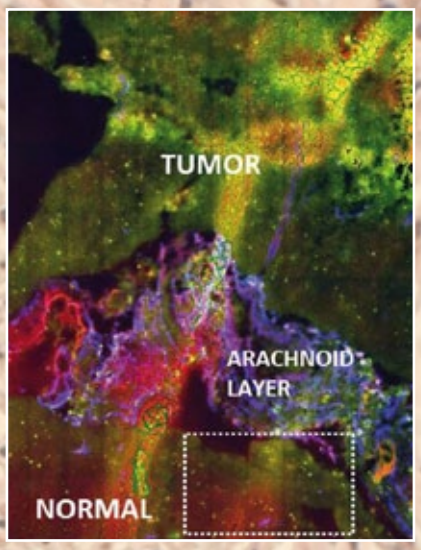
European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Applications of Multifunctional Nanoparticles in Malignant Brain Tumours

Hadjipanayis CG, Bouras A, Chang S

European Association of NeuroOncology Magazine 2014; 4 (1) 9-15



Homepage

www.kup.at/journals/eano/index.html

Online Database Featuring Author, Key Word and Full-Text Search

THE EUROPEAN ASSOCIATION OF NEUROONCOLOGY

Member of the DOAJ

Indexed in EMBASE

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz, Austria

Applications of Multifunctional Nanoparticles in Malignant Brain Tumours

Costas G Hadjipanayis[1], Alexandros Bouras[1], Susan Chang[2]

Abstract: Malignant brain tumours are one of the most devastating human cancers associated with high mortality and morbidity rates. Clinical management of these tumours remains challenging despite recent advances in current treatment strategies. Difficulties in early detection, local recurrence, and resistance to conventional therapies are the major reasons for failure in malignant brain tumour treatment. Nanoparticles have drawn increased interest in treating malignant brain tumours due to their potential to act as a vector for brain delivery and to provide tumour-specific detection and treatment. Multitasking nanoparticles can be engineered into a single nanoplatform and hold great promise for brain tumour diagnosis and treatment. Currently, magnetic nanoparticles are being used for the imaging and treatment of malignant brain tumours in humans. This review article summarizes different types of multifunctional nanoparticles that have been used both preclinically and in humans for nanoparticle-based brain tumour imaging and therapy. **Eur Assoc NeuroOncol Mag 2014; 4 (1): 9–15.**

Key words: malignant brain tumours, nanoparticles, drug delivery, magnetic resonance imaging, thermotherapy, theranostics, glioblastoma

Introduction

Malignant brain tumours remain a major clinical problem despite improvements in surgery and multimodal adjuvant therapies. Malignant gliomas represent the most common and aggressive malignant brain tumours. The median survival of malignant glioma patients ranges between 3 and 16 months and has virtually remained unchanged during the last 3 decades [1, 2]. Management of malignant gliomas poses a surgical challenge due to their proximity to eloquent anatomical structures within the brain and also their diffuse infiltrative nature which precludes complete surgical resection. The therapy of malignant gliomas is further limited by the inadequate delivery of therapeutic agents to the brain due to the presence of the blood-brain barrier (BBB) as well as non-specificity targeting. The application of novel therapeutic agents for the treatment of malignant brain tumours is urgently needed.

Among different therapeutic approaches, nanotechnology appears to be a promising tool for advancing cancer therapies. Nanotechnology is defined as the manufacturing and construction of materials in the nanometer scale size range of 1–100 nm [3, 4]. Nanomedicine is the use of nanotechnology in medicine and health care [3, 4]. Cancer nanotechnology is the application of nanotechnology toward various aspects of detection, imaging, treatment, and monitoring of cancer [5]. Current innovations in nanotechnology hold great promise in changing the foundations of cancer diagnosis and therapy. The potential application of nanoparticles (NP) to the diagnosis and treatment of malignant brain tumours is now being explored. Various nanotechnology platforms have been used for improving malignant brain tumour imaging, drug delivery to brain tumours, and therapeutic efficacy. One of the most promising aspects of NP-based cancer therapy is multifunctionality. NPs can be attached to different types of small molecules such as targeting ligands, imaging, and therapeutic agents to serve as diagnostic and therapeutic agents simultaneously [6–12]. The integrated diagnostic and therapeutic capability of nanotechnology has attracted particular attention for diagnosing and treating brain tumours. This review article focuses on different types of multifunctional NPs that have been studied in the management of brain tumours in preclinical models as well as human patients.

NPs and Brain Tumours

The unique properties of NPs offer several advantages over conventional malignant brain tumour therapeutic agents. One advantage may be more effective delivery of compounds to the brain tumour site in comparison to conventional drug delivery systems [13–15]. The flow of NPs through blood capillaries and uptake by cancer cells can be facilitated by their small size [13, 14]. The NPs can be engineered to contain small molecules such as contrast agents and drugs [13]. Multiple types of small ligands with different functions, such as MRI contrast enhancement or therapeutic agents, can be incorporated into a nanoparticle and delivered to the brain tumour site. The specificity of the delivery can be achieved by adding targeting ligands, such as monoclonal antibodies, to the nanoparticle surface in order to ensure targeted delivery of the agents to the brain tumour site. The ability of nanoplatform-based targeted delivery of imaging or therapeutic regimens to the brain tumour site at effective concentrations is the fundamental principle of multifunctionality of NPs and the key factor for efficient cancer diagnosis and therapy.

Another advantage of nanotechnology compared to conventional imaging and therapeutic agents is the tendency of NPs to accumulate within the brain tumour site via the enhanced permeability and retention effect (EPR). The growth of the tumour results in neoangiogenesis in order to provide cancer cells with oxygen and nutrients for rapid proliferation [16]. The defective architecture of the neovascularization resulting in leaky vasculature, along with the expression of vascular mediators of extravasation (eg, nitric oxide, VEGF) are thought to be responsible for the EPR effect and selective retention of NPs at the brain tumour site [17–19]. In con-

Received on February 2, 2013; accepted on February 6, 2013; Pre-Publishing Online on March 1, 2013

From the [1]Brain Tumor Nanotechnology Laboratory, Department of Neurosurgery, Emory University, School of Medicine, Winship Cancer Institute of Emory University, Atlanta, GA; [2]Division of Neuro-Oncology, Department of Neurological Surgery, University of California, San Francisco, CA, USA

Correspondence to: Costas G Hadjipanayis, MD, PhD, Dept of Neurosurgery, Emory University School of Medicine, Winship Cancer Institute of Emory University, 1365B, Suite 6200, Clifton Road, Atlanta, GA 30322, USA; e-mail: chadjip@emory.edu

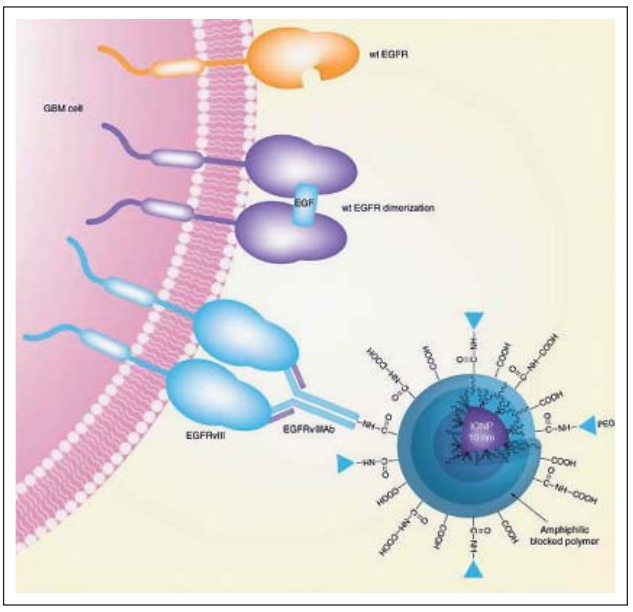


Figure 1. Illustration of an EGF receptor vIII-expressing glioblastoma cell bound by an EGF receptor vIII antibody-conjugated magnetic nanoparticle construct. Reproduced from [Expert Review of Clinical Pharmacology, March 2012, vol 5, no 2, pp 173–86] with permission from Expert Reviews Ltd. The wt EGFR dimerizes upon ligand binding. The truncated EGFRvIII deletion mutant, which does not require a ligand for activation, is bound by an EGFRvIII antibody-conjugated magnetic nanoparticle conjugate (EGFRvIIIAb-iron oxide nanoparticle). The EGFRvIIIAb-iron oxide nanoparticle is comprised of a 10-nm iron oxide core surrounded by an amphiphilic triblock copolymer, which is covalently conjugated to the EGFRvIIIAb.
Ab: antibody; EGFR: EGF receptor; GBM: glioblastoma; IONP: iron oxide nanoparticle; wt: wild-type.

trast, small molecules, such as conventional chemotherapeutic agents, diffuse freely across the tissues and the EPR effect is not observed.

In regards to treatment toxicity, the payload of the NPs can be isolated from the surrounding normal tissues by the addition of biocompatible polymers, preventing the release of the loaded agents within those normal tissues. The result is increased maximum tolerated dose of the therapeutic agent and reduced systemic toxicity. Moreover, targeted delivery of therapeutic agents encapsulated into NPs in conjunction with retention of NPs within the brain tumour site can lead to higher localized concentrations of the agents within the tumour mass, while preventing the undesired systemic consequences of the therapeutic agents [20, 21].

Taking into account the above advantages of nanotechnology, many different types of NPs have been examined in malignant brain tumour research. These include magnetic iron oxide (Fe_3O_4) NPs [22–33], gadolinium (Gd) NPs [34, 35], gold NPs (AuNPs) [36], quantum dots (QDs) [37, 38], dendrimers [39–42], carbon nanotubes (CNTs) [43–45] and polymer-based NPs [46–61].

Magnetic NPs

MRI Contrast Effect

Magnetic NPs (MNPs) have been studied as potential diagnostic and therapeutic tools in malignant brain tumours. The unique paramagnetic properties of MNPs enable their detection by magnetic resonance imaging (MRI), and have been used as both T_1 and T_2 MRI contrast agents [62–65]. Most MNP formulations are comprised of iron-oxide nanoparticles (IONPs). Superparamagnetic iron-oxide NPs (SPIOs) have most commonly been used as MRI contrast agents [66, 67]. Ultrasmall SPOIs (USPOIs) with size < 50 nm have also been examined as potential MRI contrast agents [68]. The MRI contrast effect can occur in both T_2-weighted MRI sequences, where they produce a hypointense (dark) signal (negative contrast enhancement), and in T_1-weighted images, where they produce a hyperintense (bright) signal (positive contrast enhancement) [69–71]. The major advantage of USPOIs, compared to conventional Gd- (gadolinium-) based contrast agents, is their prolonged MRI contrast effect due to uptake by tumour cells and microglia (reactive phagocytic cells in the brain) and retention within the brain [72]. Administration of USPOIs leads to an observed peak enhancement for approximately 24 hours that can persist for up to 72 hours in contrast to Gd-based contrast agents which are rapidly cleared by the kidneys [34, 73–75]. In an attempt to overcome the rapid elimination of conventional Gd and increase its retention within brain tumours, Gd NPs have also been reported. Incorporation of Gd into therapeutic NPs has been utilized to track them by using MRI [76]. Functionalized Gd NPs have also been reported as radiosensitizing agents [77]. Gd NPs can be better visualized in T_1-weighted MRI sequences [35]. SPIOs and USPIOs have been shown to have a relatively safe toxic profile with no evidence of brain toxicity [67, 78]. These agents can be served as an alternative in patients at high risk for Gd-induced nephrogenic systemic fibrosis [79, 80].

Tumour Targeting

MNPs specifically targeted to tumour cells can further increase their imaging benefits by enhancement of their uptake by the targeted tumour cells [81]. Multiple types of compounds, such as peptides and antibodies, have been reported as potential MNP targeting ligands [82].

Chlorotoxin, a peptide derived from scorpion venom, has been described as a targeting motif for brain tumour cells. Chlorotoxin inhibits tumour infiltration by specific binding and inhibition of matrix metalloproteinase-2 (MMP-2), which is overexpressed on the surface of glioma cells and responsible for the degradation of extracellular matrix during tumour invasion [83–85]. Conjugation of chlorotoxin to MNPs has been reported as a method for targeted brain tumour imaging [24] by MRI in addition to inhibition of tumour cell invasion [86]. Furthermore, incorporation of the fluorescent Cy5.5 molecule to the conjugated chlorotoxin-MNPs allows for simultaneous MRI and intraoperative optical imaging [22, 25, 87]. Chlorotoxin-labelled MNPs have also been utilized for targeted gene delivery to glioma cells [32].

Attachment of another small peptide, called F3, to the MNP surface has also been used for the targeting of brain tumours. F3 targets endothelial cells by specific binding to nucleolin, which is over-expressed on the surface of proliferating vascular endothelial cells of tumour-associated vasculature [88]. Intravenous injection of IONPs coated with F3 has provided more persistent and profound MRI contrast enhancement of intracranially implanted rodent tumours compared to identical non-F3-targeted IONPs [48].

Polymer-coated IONPs have been conjugated to a purified antibody that selectively binds to the epidermal growth factor receptor deletion mutant, EGFRvIII (Figure 1), which is a tumour-specific mutation present on the surface of glioblastoma (GBM) cells. The bioconjugated IONPs can provide simultaneous MRI contrast enhancement, as well as targeted therapy of intracranial human GBM xenografts implanted in rodents after convection-enhanced delivery (CED) [26]. Recent toxicity testing of cetuximab-conjugated IONPs has been reported in healthy canines after CED in the brain [89].

Conjugation of a tumour-specific monoclonal antibody known as L6 to IONPs can provide targeted MRI enhancement of the neovasculature of malignant brain tumours after their uptake by tumour cells [90]. Dextran-coated SPIOs functionalized with an antibody against an insulin-like growth factor domain have also been used for targeted MRI and fluorescent imaging of the GBM vasculature [91].

Cytokines can be utilized for the targeted imaging of malignant brain tumours. Gd-containing metallofullerenes functionalized and conjugated to IL-13 peptides have the ability to specifically bind to glioma cells over-expressing the IL-13 receptor providing targeted imaging of these cells in vitro [92].

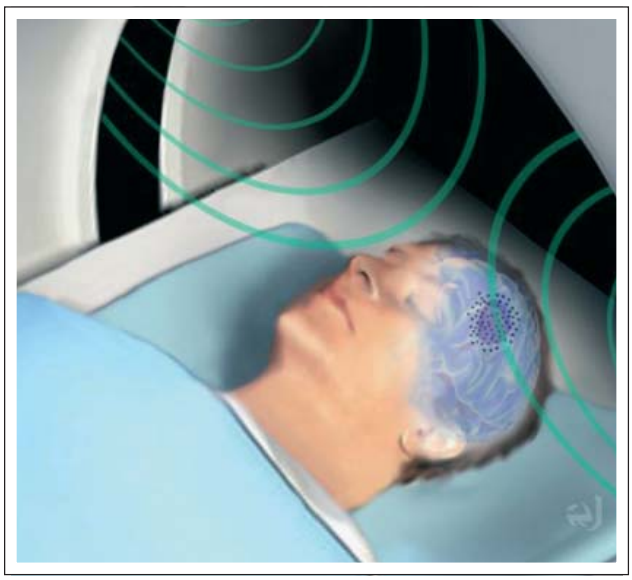


Figure 2. Intratumoural thermotherapy of a malignant brain tumour with magnetic nanoparticles. Reproduced from [Expert Review of Clinical Pharmacology, March 2012, vol 5, no 2, pp 173–86] with permission from Expert Reviews Ltd. A patient who has undergone intratumoural implantation of magnetic nanoparticles is depicted undergoing an alternating magnetic field session for treatment of his malignant brain tumour by thermotherapy.

Neural Stem Cells

MNPs can also be used for tracking stem cell tropism to malignant gliomas in vivo. Neural stem cells are brain tumour targeting tools as they exhibit tropism for GBM tumours after intracranial administration [93]. This striking characteristic makes neural stem cells a potential candidate for tumour-targeted gene delivery and therapy [94, 95]. IOPNs can label neural stem cells enabling visualization of their migration into the brain [96, 97].

Chemotherapeutics and MNPs

MNPs can also be utilized to deliver chemotherapeutic agents to the brain tumour site while simultaneously tracking them by MRI. IONPs coated with a polymer have been used for both delivery of the chemotherapeutic agent epirubicin and monitoring of their distribution in vivo by MRI [29]. Paclitaxel-loaded MNPs have been utilized to deliver the chemotherapeutic agent paclitaxel in a rat glioma model. Increased drug uptake by the brain tumour cells resulted in enhanced therapeutic efficacy and effective MRI contrast enhancement [30].

Magnetic Targeting and Focal Ultrasound

In an attempt to enhance the delivery of MNPs to malignant brain tumours after systemic administration, magnetic targeting has been described. Magnetic targeting is the application of a magnetic field to enhance accumulation of MNPs within the brain tumour site [98–100]. Another concept that has been described in an effort to increase the systemic delivery and deposition of MNPs into malignant brain tumours is disruption of the BBB. Many strategies have been examined in order to facilitate opening of the BBB. Focal ultrasound is a non-invasive technique that can be utilized for selective BBB disruption in a targeted brain region [101–103]. The synergistic effect of focal ultrasound and magnetic targeting has been demonstrated in a study where both systemic delivery and deposition of epirubicin-loaded MNPs into tumour-bearing animals were significantly increased [29].

Thermotherapy

Another function of MNPs is their ability to produce heat with the application of an alternating magnetic field (AMF). Use of hyperthermia for the treatment of cancer, known as thermotherapy, has been demonstrated in patients with human GBM [104, 105] (Figure 2). Temperatures above 41 °C cause heat stress with resultant protein denaturation and DNA cross-linking within the cell, leading to cell apoptosis [106]. Alterations of the tumour microenvironment can also occur [107]. The above changes have a synergistic effect when combined with chemotherapy and radiation [108]. Engineering of MNPs plays a crucial role in maximizing the hyperthermia response [109, 110]. MNPs that can be used for thermotherapy are combinations of various metals such as manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), zinc (Zn), and magnesium (Mg) [111–114]. Iron oxide-based MNPs have been extensively examined for thermotherapy application in brain tumours due to their biocompatibility and safe toxicity profile [115, 116]. Animal models and human patients with malignant brain tumours have been used to evaluate feasibility and safety of MNP-based thermotherapy [104, 105, 117]. Safety and efficacy have been demonstrated holding great promise of this cancer treatment modality.

Polymer-Based NPs

A vast amount of research has been made exploring polymer-based NPs in brain tumour diagnosis and therapy. Varying core polymer compositions have been examined with the most popular being the polysorbate 80-coated poly(butyl cyanoacrylate) and poly(ε caprolactone) [46, 50, 51, 53, 54]. Drug delivery to brain tumours is the main application of polymer-based NPs

with doxorubicin, paclitaxel, and camptothecin being used [46, 50, 51, 53, 57, 58, 118]. Polymer-based NPs have been used in clinical trials as vehicles for drug delivery, but the results were discouraging as 1 % or even less of the injected dose was delivered to the brain with most of the nanoparticle-drug conjugate being trapped in the liver [119]. The incorporation of a small peptide sequence known as angiopep has been used for improved targeted delivery to brain tumours [55]. Dual targeting by using 2 different moieties has also been reported. Incorporation of both a small peptide accounting for BBB targeting and an additional small aptamer targeting cancer cells onto a polymer-based nanoparticle has been described [59]. Dual targeting resulted in enhanced tumour distribution of the dual targeted NPs [59]. Furthermore, polymer-based NPs have been successfully used for gene therapy of brain tumours [49, 120]. In one study, incorporation of the integrin-binding motif RDG into a polymer-based nanoparticle enabled efficient targeted delivery of a plasmid expressing an apoptosis ligand in a rat glioma model resulting in increased survival [120]. Moreover, polymer-based NPs have also been utilized for both MRI and drug delivery by loading of both a magnetic contrast agent and a fluorescent drug [48]. Polymer-based NPs can also be encapsulated by both iron oxide and photodynamic therapy (PDT) drugs for both MRI contrast enhancement and PDT of brain tumours, respectively [48].

Gold NPs

Gold NPs comprised of a silica core and coated with a gold shell have received increased attention as potential vehicles for delivery of therapeutic agents to the brain, as well as for imaging. Their small size, surface chemistry available for functionalization, and biocompatibility make them strong candidates for biological and medical applications [36, 121–125]. Gold NPs with sizes up to 50 nm are able to cross through the disrupted blood-brain tumour barrier [121, 123, 124, 126]. Gold NPs have been utilized to deliver gadolinium for enabling preoperative detection and surgical planning through MRI, as well as to simultaneously deliver photoacoustic and Raman imaging agents for tumour margin delineation during surgery [127]. Fluorescent imaging agents can also be incorporated into gold NPs for purely diagnostic purposes [36]. Another application of gold NPs is phototherapy. Gold NPs can be designed as nanoshells enabling light absorption in the near-infrared range of the light spectrum which has minimal absorption by water, thus allowing for passage deep into tissues with minimal energy loss. Design of these gold NPs has been achieved and their activation by light has enabled killing of medulloblastoma and glioma cells in vitro by phototherapy [128]. Loading of gold nanoshells into macrophages can lead to efficient delivery of the NPs to gliomas and their subsequent activation by near infrared light can result in growth inhibition [129].

Quantum Dots

QDs are nanocrystals made of semiconductors with unique optical and electronic properties [130]. They are advantageous for in vivo imaging due to the fact that they can emit fluorescence light from 400–2000 nm. Their increased fluorescence emission spectrum allows for enhanced brightness and simultaneous multicolour detection [131]. Due to their heavy metal content, toxicity issues are a concern with normal surrounding tissues [131]. QDs can be loaded with contrast agents, such as gadolinium, in order to provide further imaging capabilities in addition to inherent fluorescent properties [37, 132]. However, the above capabilities have not been applied to brain tumours at this point. QDs have also been used for targeted delivery of siRNA for selective inhibition of EGFRvIII expression in human GBM cells [38]. Conjugation of epidermal growth factor (EGF) or EGF receptor antibody to QDs has been attempted and has led to successful specific labelling of human glioma cells in vitro, glioma mouse models, and in human brain tumour biopsies by the fluorescent emission of QDs [133].

Dendrimers

Dendrimers have been examined as NPs with the potential of delivering agents to brain tumours by crossing the BBB. It has been shown that dendrimers with size < 20 nm can cross the BBB [41]. Dendrimers are spherical molecules formed from repetitively monomeric or oligomeric organic molecule branching units. Their structure, specifically the degree of branching, allows for encapsulation of molecules in the interior as well as on the surface [39, 40, 42]. Dual targeting can be performed with dendrimers [40, 134]. A dendrimer-based nanoprobe has been labelled with both angiopep-2, for higher BBB transcytosis efficacy, and RGD peptides for targeting of the brain tumour vasculature [40]. The near-infrared fluorophore Cy5.5 and rhodamine were added to the dendrimer in order to create a multifunctional nanoprobe allowing for non-invasive preoperative localization of brain tumours, as well as possible intraoperative image-guided tumour resection [40]. A tolerable toxicity after using dendrimers has been reported [39, 40].

Carbon Nanotubes

CNTs are formed of graphite sheets assuming a cylinder-shaped configuration. They possess electrical properties and heat conductivity [135]. They have been used as nanovectors for targeted drug and gene delivery into tumours. CNTs can be packaged with siRNA molecules for targeting tumour cells by exerting RNA interference on target gene expression and suppressing tumour growth [136]. CNTs can potentially be used as a nanovector delivery system for targeted delivery of agents into phagocytic cells in vivo for modulating macrophage function in brain tumours. Selective uptake by tumour macrophages labelled with non-toxic hydrophobic fluorescent dye multi-walled CNTs has been shown in a murine glioma model [45]. In another study, conjugation of an immunopotent oligodeoxynucleotide to single-walled CNTs has been described. Enhanced targeted delivery and uptake of the immunopotent compound by glioma cells both in vitro and in vivo has been demonstrated resulting in potentiation of anti-glioma immunity and inhibition of glioma tumour growth [44]. CNTs can also be utilized for thermal ablation therapy. Photothermolysis of GBM stem-like cells by CNTs targeted with CD133 monoclonal antibody has been reported [43]. Both GBM-CD133$^+$ and GBM-CD133$^-$ cells were treated in vitro with single-walled CNTs functionalized with a CD133 monoclonal antibody (CD133Ab-CNT) and subsequent irradiation with near-infrared laser light. The GBM-CD133$^+$

cells were selectively targeted and eradicated, whereas GBM-CD133$^-$ cells were unaffected [43]. Moreover, GBM-CD133$^+$ cells pre-treated in vitro with the CD133Ab-CNTs were injected subcutaneously into mice and then near-infrared laser-induced photothermolysis was applied. Significant inhibition of both tumour growth rate and tumour progression was observed [43]. This study has demonstrated the potential utilization of CNTs as a thermal-coupling agent for effective targeting and inhibition of growth of GBM stem-like cells.

Human Clinical Translation of NPs

Although the benefits of NPs in cancer diagnosis and therapy have been widely explored, their potential effects in humans are still unclear. The translation of NPs into clinical use remains challenging. Various issues, such as pharmacokinetics, biodistribution, side effects, potential toxicity, and the immune system reaction to NPs, remain to be addressed and are of great importance in order to establish whether and which NPs can be used in humans. The recent advances of cancer nanotechnology are necessary to proceed in parallel with bioactivity and toxicity assessment studies before clinical application. Numerous nanoparticle platforms are currently under different stages of preclinical and clinical development. However, in the brain tumour field, investigation of potential clinical use of NPs remains limited. MNPs, specifically IONPs, are the most advanced NPs in terms of translation into clinical application for brain tumours. Ferumoxytol, a USPIO that targets phagocytic cells, has been used in the imaging of patients with malignant brain tumours. Patients underwent serial MRI up to 72 hours after a single dose of ferumoxytol and the time course of enhancement was compared with baseline Gd scan [73]. Maximal ferumoxytol-induced enhancement intensity was observed at 24–28 hours after administration and enhancement was expanded into non-Gd enhancing regions of infiltrating brain [73]. The use of IONPs as MRI contrast agents can provide visualization of brain tumours that is not apparent with conventional Gd. Furthermore, the delayed peak enhancement provided after IONP administration compared to Gd can allow for assessment of postoperative residual tumour without the need of re-administration of a contrast agent. In another study, intraoperative MRI (iMRI) with ferumoxtran-10, also a USPIO, was used in patients who underwent malignant brain tumour surgical resection [137]. Less confounding (non-tumoural) contrast enhancement was observed during iMRI compared to iMRI after Gd administration [137]. IONPs have also been used for hyperthermia-induced tumour ablation, known as thermotherapy, in patients with recurrent GBM. In a phase-II clinical trial, aminosaline-coated IONPs have been used for hyperthermia induction after intratumoural injection in patients with recurrent GBM and application of AMF in combination with fractionated external beam radiotherapy (EBRT) [104, 105]. Direct inoculation of IONPs into tumours using stereotactic-guided injections was used, followed by multiple thermotherapy sessions, demonstrating safety and efficacy in combination with EBRT [104, 105].

Conclusion

Effective treatment of malignant brain tumours poses a significant challenge. Recent advances in microsurgery and multimodal adjuvant therapy have only resulted in a modest improvement in patient prognosis. Novel technologies are therefore needed to be applied to the management of malignant brain tumours. Nanotechnology has quickly emerged as a promising tool having the potential to change multiple aspects of malignant brain tumour diagnosis and treatment. Several types of NPs have been described providing MRI contrast enhancement, intra-operative tumour delineation, and targeted delivery of chemotherapy or gene therapy, as well as thermotherapy. Currently, NPs are being used in humans for imaging and thermotherapy of malignant brain tumours. Multifunctional NPs, which have the potential for simultaneous targeted cancer cell delivery, imaging, and therapy, form the basis for new approaches combating malignant brain tumours. Additional improvements in the design and surface chemistry of NPs will permit better delivery and penetration within brain tumours. The comprehensive assessment of the toxicological effects of NPs remain to be further determined in the future management of brain tumour patients.

Conflict of Interest

The authors report no conflict of interest with the material presented in this manuscript.

References:

1. Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg 2003; 99: 467–73.
2. Stupp R, Hegi ME, van den Bent MJ, et al. Changing paradigms – an update on the multidisciplinary management of malignant glioma. Oncologist 2006; 11: 165–80.
3. Sandhiya S, Dkhar SA, Surendiran A. Emerging trends of nanomedicine – an overview. Fundam Clin Pharmacol 2009; 23: 263–9.
4. Webster TJ. Nanomedicine: what's in a definition? Int J Nanomedicine 2006; 1: 115–6.
5. Grobmyer SR, Iwakuma N, Sharma P, et al. What is cancer nanotechnology? Methods Mol Biol 2010; 624: 1–9.
6. Liong M, Lu J, Kovochich M, et al. Multifunctional inorganic nanoparticles for imaging, targeting, and drug delivery. ACS Nano 2008; 2: 889–96.
7. Kumar A, Jena PK, Behera S, et al. Multifunctional magnetic nanoparticles for targeted delivery. Nanomedicine 2010; 6: 64–9.
8. Blanco E, Kessinger CW, Sumer BD, et al. Multifunctional micellar nanomedicine for cancer therapy. Exp Biol Med (Maywood) 2009; 234: 123–31.
9. Guo R, Zhang L, Qian H, et al. Multifunctional nanocarriers for cell imaging, drug delivery, and near-IR photothermal therapy. Langmuir 2010; 26: 5428–34.
10. Bhaskar S, Tian F, Stoeger T, et al. Multifunctional nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging. Part Fibre Toxicol 2010; 7: 3.
11. Gindy ME, Prud'homme RK. Multifunctional nanoparticles for imaging, delivery and targeting in cancer therapy. Expert Opin Drug Deliv 2009; 6: 865–78.
12. Masotti A. Multifunctional nanoparticles: preparation and applications in biomedicine and in non-invasive bioimaging. Recent Pat Nanotechnol 2010; 4: 53–62.
13. Koo YE, Reddy GR, Bhojani M, et al. Brain cancer diagnosis and therapy with nanoplatforms. Adv Drug Deliv Rev 2006; 58: 1556–77.
14. Moghimi SM, Hunter AC, Murray JC. Nanomedicine: current status and future prospects. FASEB J 2005; 19: 311–30.
15. Moffat BA, Reddy GR, McConville P, et al. A novel polyacrylamide magnetic nanoparticle contrast agent for molecular imaging using MRI. Mol Imaging 2003; 2: 324–32.
16. Jain RK. Transport of molecules, particles, and cells in solid tumors. Annu Rev Biomed Eng 1999; 1: 241–63.
17. Greish K. Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. Methods Mol Biol 2010; 624: 25–37.
18. Maeda H, Bharate GY, Daruwalla J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. Eur J Pharm Biopharm 2009; 71: 409–19.
19. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul 2001; 41: 189–207.
20. Crowder KC, Hughes MS, Marsh JN, et al. Sonic activation of molecularly-targeted nanoparticles accelerates transmembrane lipid delivery to cancer cells through contact-mediated mechanisms: implications for enhanced local drug delivery. Ultrasound Med Biol 2005; 31: 1693–700.
21. Van Vlerken LE, Duan Z, Seiden MV, et al. Modulation of intracellular ceramide using polymeric nanoparticles to overcome multidrug resistance in cancer. Cancer Res 2007; 67: 4843–50.
22. Veiseh O, Sun C, Gunn J, et al. Optical and MRI multifunctional nanoprobe for targeting gliomas. Nano Lett 2005; 5: 1003–8.
23. Anderson SA, Glod J, Arbab AS, et al. Noninvasive MR imaging of magnetically labeled stem cells to directly identify neovasculature in a glioma model. Blood 2005; 105: 420–5.

24. Sun C, Veiseh O, Gunn J, et al. In vivo MRI detection of gliomas by chlorotoxin-conjugated superparamagnetic nanoprobes. Small 2008; 4: 372–9.

25. Veiseh O, Sun C, Fang C, et al. Specific targeting of brain tumors with an optical/magnetic resonance imaging nanoprobe across the blood-brain barrier. Cancer Res 2009; 69: 6200–7.

26. Hadjipanayis CG, Machaidze R, Kaluzova M, et al. EGFRvIII antibody-conjugated iron oxide nanoparticles for magnetic resonance imaging-guided convection-enhanced delivery and targeted therapy of glioblastoma. Cancer Res 2010; 70: 6303–12.

27. Hua MY, Liu HL, Yang HW, et al. The effectiveness of a magnetic nanoparticle-based delivery system for BCNU in the treatment of gliomas. Biomaterials 2011; 32: 516–27.

28. Xie H, Zhu Y, Jiang W, et al. Lactoferrin-conjugated superparamagnetic iron oxide nanoparticles as a specific MRI contrast agent for detection of brain glioma in vivo. Biomaterials 2011; 32: 495–502.

29. Liu HL, Hua MY, Yang HW, et al. Magnetic resonance monitoring of focused ultrasound/magnetic nanoparticle targeting delivery of therapeutic agents to the brain. Proc Natl Acad Sci USA 2010; 107: 15205–10.

30. Dilnawaz F, Singh A, Mewar S, et al. The transport of non-surfactant based paclitaxel loaded magnetic nanoparticles across the blood brain barrier in a rat model. Biomaterials 2012; 33: 2936–51.

31. Kumar M, Medarova Z, Pantazopoulos P, et al. Novel membrane-permeable contrast agent for brain tumor detection by MRI. Magn Reson Med 2010; 63: 617–24.

32. Kievit FM, Veiseh O, Fang C, et al. Chlorotoxin labeled magnetic nanovectors for targeted gene delivery to glioma. ACS Nano 2010; 4: 4587–94.

33. Mejias R, Perez-Yague S, Roca AG, et al. Liver and brain imaging through dimercaptosuccinic acid-coated iron oxide nanoparticles. Nanomedicine (Lond) 2010; 5: 397–408.

34. Varallyay P, Nesbit G, Muldoon LL, et al. Comparison of two superparamagnetic viral-sized iron oxide particles ferumoxides and ferumoxtran-10 with a gadolinium chelate in imaging intracranial tumors. AJNR Am J Neuroradiol 2002; 23: 510–9.

35. Park JY, Baek MJ, Choi ES, et al. Paramagnetic ultrasmall gadolinium oxide nanoparticles as advanced T1 MRI contrast agent: account for large longitudinal relaxivity, optimal particle diameter, and in vivo T1 MR images. ACS Nano 2009; 3: 3663–9.

36. Cheng Y, Meyers JD, Agnes RS, et al. Addressing brain tumors with targeted gold nanoparticles: a new gold standard for hydrophobic drug delivery? Small 2011; 7: 2301–6.

37. Jackson H, Muhammad O, Daneshvar H, et al. Quantum dots are phagocytized by macrophages and colocalize with experimental gliomas. Neurosurgery 2007; 60: 524–9.

38. Jung J, Solanki A, Memoli KA, et al. Selective inhibition of human brain tumor cells through multifunctional quantum-dot-based siRNA delivery. Angew Chem Int Ed Engl 2010; 49: 103–7.

39. Yan H, Wang L, Wang J, et al. Two-order targeted brain tumor imaging by using an optical/paramagnetic nanoprobe across the blood brain barrier. ACS Nano 2012; 6: 410–20.

40. Yan H, Wang J, Yi P, et al. Imaging brain tumor by dendrimer-based optical/paramagnetic nanoprobe across the blood-brain barrier. Chem Commun (Camb) 2011; 47: 8130–2.

41. Sarin H, Kanevsky AS, Wu H, et al. Effective transvascular delivery of nanoparticles across the blood-brain tumor barrier into malignant glioma cells. J Transl Med 2008; 6: 80.

42. He H, Li Y, Jia XR, et al. PEGylated poly(amidoamine) dendrimer-based dual-targeting carrier for treating brain tumors. Biomaterials 2011; 32: 478–87.

43. Wang CH, Chiou SH, Chou CP, et al. Photothermolysis of glioblastoma stem-like cells targeted by carbon nanotubes conjugated with CD133 monoclonal antibody. Nanomedicine 2011; 7: 69–79.

44. Zhao D, Alizadeh D, Zhang L, et al. Carbon nanotubes enhance CpG uptake and potentiate antiglioma immunity. Clin Cancer Res 2011; 17: 771–82.

45. Vanhandel M, Alizadeh D, Zhang L, et al. Selective uptake of multi-walled carbon nanotubes by tumor macrophages in a murine glioma model. J Neuroimmunol 2009; 208: 3–9.

46. Gelperina SE, Khalansky AS, Skidan IN, et al. Toxicological studies of doxorubicin bound to polysorbate 80-coated poly(butyl cyanoacrylate) nanoparticles in healthy rats and rats with intracranial glioblastoma. Toxicol Lett 2002; 126: 131–41.

47. Steiniger SC, Kreuter J, Khalansky AS, et al. Chemotherapy of glioblastoma in rats using doxorubicin-loaded nanoparticles. Int J Cancer 2004; 109: 759–67.

48. Reddy GR, Bhojani MS, McConville P, et al. Vascular targeted nanoparticles for imaging and treatment of brain tumors. Clin Cancer Res 2006; 12: 6677–86.

49. Lu W, Sun Q, Wan J, et al. Cationic albumin-conjugated pegylated nanoparticles allow gene delivery into brain tumors via intravenous administration. Cancer Res 2006; 66: 11878–87.

50. Ambruosi A, Khalansky AS, Yamamoto H, et al. Biodistribution of polysorbate 80-coated doxorubicin-loaded [14C]-poly(butyl cyanoacrylate) nanoparticles after intravenous administration to glioblastoma-bearing rats. J Drug Target 2006; 14: 97–105.

51. Petri B, Bootz A, Khalansky A, et al. Chemotherapy of brain tumour using doxorubicin bound to surfactant-coated poly(butyl cyanoacrylate) nanoparticles: revisiting the role of surfactants. J Control Release 2007; 117: 51–8.

52. Ren WH, Chang J, Yan CH, et al. Development of transferrin functionalized poly(ethylene glycol)/poly(lactic acid) amphiphilic block copolymeric micelles as a potential delivery system targeting brain glioma. J Mater Sci Mater Med 2010; 21: 2673–81.

53. Xin H, Chen L, Gu J, et al. Enhanced antiglioblastoma efficacy by PTX-loaded PEGylated poly(varepsilon-caprolactone) nanoparticles: In vitro and in vivo evaluation. Int J Pharm 2010; 402: 238–47.

54. Gelperina S, Maksimenko O, Khalansky A, et al. Drug delivery to the brain using surfactant-coated poly(lactide-co-glycolide) nanoparticles: influence of the formulation parameters. Eur J Pharm Biopharm 2010; 74: 157–63.

55. Xin H, Jiang X, Gu J, et al. Angiopep-conjugated poly(ethylene glycol)-co-poly(epsilon-caprolactone) nanoparticles as dual-targeting drug delivery system for brain glioma. Biomaterials 2011; 32: 4293–305.

56. Wohlfart S, Khalansky AS, Gelperina S, et al. Kinetics of transport of doxorubicin bound to nanoparticles across the blood-brain barrier. J Control Release 2011; 154: 103–7.

57. Sawyer AJ, Saucier-Sawyer JK, Booth CJ, et al. Convection-enhanced delivery of camptothecin-loaded polymer nanoparticles for treatment of intracranial tumors. Drug Deliv Transl Res 2011; 1: 34–42.

58. Geldenhuys W, Mbimba T, Bui T, et al. Brain-targeted delivery of paclitaxel using glutathione-coated nanoparticles for brain cancers. J Drug Target 2011; 19: 837–45.

59. Gao H, Qian J, Cao S, et al. Precise glioma targeting of and penetration by aptamer and peptide dual-functioned nanoparticles. Biomaterials 2012; 33: 5115–23.

60. Gao H, Qian J, Yang Z, et al. Whole-cell SELEX aptamer-functionalised poly(ethyleneglycol)-poly(epsilon-caprolactone) nanoparticles for enhanced targeted glioblastoma therapy. Biomaterials 2012; 33: 6264–72.

61. Chang J, Paillard A, Passirani C, et al. Transferrin adsorption onto PLGA nanoparticles governs their interaction with biological systems from blood circulation to brain cancer cells. Pharm Res 2012; 29: 1495–505.

62. Jain TK, Richey J, Strand M, et al. Magnetic nanoparticles with dual functional properties: drug delivery and magnetic resonance imaging. Biomaterials 2008; 29: 4012–21.

63. Sun C, Lee JS, Zhang M. Magnetic nanoparticles in MR imaging and drug delivery. Adv Drug Deliv Rev 2008; 60: 1252–65.

64. Corot C, Robert P, Idee JM, et al. Recent advances in iron oxide nanocrystal technology for medical imaging. Adv Drug Deliv Rev 2006; 58: 1471–504.

65. Lodhia J, Mandarano G, Ferris N, et al. Development and use of iron oxide nanoparticles (Part 1): Synthesis of iron oxide nanoparticles for MRI. Biomed Imaging Interv J 2010; 6: e12.

66. Thorek DL, Chen AK, Czupryna J, et al.. Superparamagnetic iron oxide nanoparticle probes for molecular imaging. Ann Biomed Eng 2006; 34: 23–38.

67. Muldoon LL, Sandor M, Pinkston KE, et al. Imaging, distribution, and toxicity of superparamagnetic iron oxide magnetic resonance nanoparticles in the rat brain and intracerebral tumor. Neurosurgery 2005; 57: 785–96.

68. Weissleder R, Elizondo G, Wittenberg J, et al. Ultrasmall superparamagnetic iron oxide: characterization of a new class of contrast agents for MR imaging. Radiology 1990; 175: 489–93.

69. Pan D, Caruthers SD, Hu G, et al. Ligand-directed nanobialys as theranostic agent for drug delivery and manganese-based magnetic resonance imaging of vascular targets. J Am Chem Soc 2008; 130: 9186–7.

70. Na HB, Lee JH, An K, et al. Development of a T1 contrast agent for magnetic resonance imaging using MnO nanoparticles. Angew Chem Int Ed Engl 2007; 46: 5397–401.

71. Bridot JL, Faure AC, Laurent S, et al. Hybrid gadolinium oxide nanoparticles: multimodal contrast agents for in vivo imaging. J Am Chem Soc 2007; 129: 5076–84.

72. Bourrinet P, Bengele HH, Bonnemain B, et al. Preclinical safety and pharmacokinetic profile of ferumoxtran-10, an ultrasmall superparamagnetic iron oxide magnetic resonance contrast agent. Invest Radiol 2006; 41: 313–24.

73. Neuwelt EA, Varallyay CG, Manninger S, et al. The potential of ferumoxytol nanoparticle magnetic resonance imaging, perfusion, and angiography in central nervous system malignancy: a pilot study. Neurosurgery 2007; 60: 601–11.

74. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J Magn Reson Imaging 2009; 30: 1259–67.

75. Abraham JL, Thakral C. Tissue distribution and kinetics of gadolinium and nephrogenic systemic fibrosis. Eur J Radiol 2008; 66: 200–7.

76. Faucher L, Guay-Begin AA, Lagueux J, et al. Ultra-small gadolinium oxide nanoparticles to image brain cancer cells in vivo with MRI. Contrast Media Mol Imaging 2011; 6: 209–18.

77. Mowat P, Mignot A, Rima W, et al. In vitro radiosensitizing effects of ultrasmall gadolinium based particles on tumour cells. J Nanosci Nanotechnol 2011; 11: 7833–9.

78. Bernd H, De Kerviler E, Gaillard S, et al. Safety and tolerability of ultrasmall superparamagnetic iron oxide contrast agent: comprehensive analysis of a clinical development program. Invest Radiol 2009; 44: 336–42.

79. Khurana A, Runge VM, Narayanan M, et al. Nephrogenic systemic fibrosis: a review of 6 cases temporally related to gadodiamide injection (omniscan). Invest Radiol 2007; 42: 139–45.

80. Neuwelt EA, Hamilton BE, Varallyay CG, et al. Ultrasmall superparamagnetic iron oxides (USPIOs): a future alternative magnetic resonance (MR) contrast agent for patients at risk for nephrogenic systemic fibrosis (NSF)? Kidney Int 2009; 75: 465–74.

81. Peng XH, Qian X, Mao H, et al. Targeted magnetic iron oxide nanoparticles for tumor imaging and therapy. Int J Nanomedicine 2008; 3: 311–21.

82. Wankhede M, Bouras A, Kaluzova M, et al. Magnetic nanoparticles: an emerging technology for malignant brain tumor imaging and therapy. Expert Rev Clin Pharmacol 2012; 5: 173–86.

83. Deshane J, Garner CC, Sontheimer H. Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2. J Biol Chem 2003; 278: 4135–44.

84. Lyons SA, O'Neal J, Sontheimer H. Chlorotoxin, a scorpion-derived peptide, specifically binds to gliomas and tumors of neuroectodermal origin. Glia 2002; 39: 162–73.

85. Soroceanu L, Gillespie Y, Khazaeli MB, et al. Use of chlorotoxin for targeting of primary brain tumors. Cancer Res 1998; 58: 4871–9.

86. Veiseh O, Gunn JW, Kievit FM, et al. Inhibition of tumor-cell invasion with chlorotoxin-bound superparamagnetic nanoparticles. Small 2009; 5: 256–64.

87. Kircher MF, Mahmood U, King RS, et al. A multimodal nanoparticle for preoperative magnetic resonance imaging and intraoperative optical brain tumor delineation. Cancer Res 2003; 63: 8122–5.

88. Christian S, Pilch J, Akerman ME, et al. Nucleolin expressed at the cell surface is a marker of endothelial cells in angiogenic blood vessels. J Cell Biol 2003; 163: 871–8.

89. Platt S, Nduom E, Kent M, et al. Canine model of convection-enhanced delivery of cetuximab-conjugated iron-oxide nanoparticles monitored with magnetic resonance imaging. Clin Neurosurg 2012; 59: 107–13.

90. Orringer DA, Koo YE, Chen T, et al. Small solutions for big problems: the application of nanoparticles to brain tumor diagnosis and therapy. Clin Pharmacol Ther 2009; 85: 531–4.

91. Tomanek B, Iqbal U, Blasiak B, et al. Evaluation of brain tumor vessels specific contrast agents for glioblastoma imaging. Neuro Oncol 2012; 14: 53–63.

92. Fillmore HL, Shultz MD, Henderson SC, et al. Conjugation of functionalized gadolinium metallofullerenes with IL-13 peptides for targeting and imaging glial tumors. Nanomedicine (Lond) 2011; 6: 449–58.

93. Aboody KS, Brown A, Rainov NG, et al. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. Proc Natl Acad Sci USA 2000; 97: 12846–51.

94. Benedetti S, Pirola B, Pollo B, et al. Gene therapy of experimental brain tumors using neural progenitor cells. Nat Med 2000; 6: 447–50.

95. Yang SY, Liu H, Zhang JN. Gene therapy of rat malignant gliomas using neural stem cells expressing IL-12. DNA Cell Biol 2004; 23: 381–9.

96. Wu X, Hu J, Zhou L, et al. In vivo tracking of superparamagnetic iron oxide nanoparti-

cle-labeled mesenchymal stem cell tropism to malignant gliomas using magnetic resonance imaging. Laboratory investigation. J Neurosurg 2008; 108: 320–9.

97. Tang C, Russell PJ, Martiniello-Wilks R, et al. Concise review: Nanoparticles and cellular carriers – allies in cancer imaging and cellular gene therapy? Stem Cells 2010; 28: 1686–702.

98. Chertok B, Moffat BA, David AE, et al. Iron oxide nanoparticles as a drug delivery vehicle for MRI monitored magnetic targeting of brain tumors. Biomaterials 2008; 29: 487–96.

99. Chertok B, David AE, Huang Y, et al. Glioma selectivity of magnetically targeted nanoparticles: a role of abnormal tumor hydrodynamics. J Control Release 2007; 122: 315–23.

100. Pulfer SK, Ciccotto SL, Gallo JM. Distribution of small magnetic particles in brain tumor-bearing rats. J Neurooncol 1999; 41: 99–105.

101. Hynynen K, McDannold N, Vykhodtseva N, et al. Focal disruption of the blood-brain barrier due to 260-kHz ultrasound bursts: a method for molecular imaging and targeted drug delivery. J Neurosurg 2006; 105: 445–54.

102. Pardridge WM. Drug and gene delivery to the brain: the vascular route. Neuron 2002; 36: 555–8.

103. Muldoon LL, Soussain C, Jahnke K, et al. Chemotherapy delivery issues in central nervous system malignancy: a reality check. J Clin Oncol 2007; 25: 2295–305.

104. Maier-Hauff K, Rothe R, Scholz R, et al. Intracranial thermotherapy using magnetic nanoparticles combined with external beam radiotherapy: results of a feasibility study on patients with glioblastoma multiforme. J Neurooncol 2007; 81: 53–60.

105. Maier-Hauff K, Ulrich F, Nestler D, et al. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. J Neurooncol 2011; 103: 317–24.

106. Goldstein LS, Dewhirst MW, Repacholi M, et al. Summary, conclusions and recommendations: adverse temperature levels in the human body. Int J Hyperthermia 2003; 19: 373–84.

107. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. Crit Rev Oncol Hematol 2002; 43: 33–56.

108. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. Lancet Oncol 2002; 3: 487–97.

109. Hadjipanayis CG, Bonder MJ, Balakrishnan S, et al. Metallic iron nanoparticles for MRI contrast enhancement and local hyperthermia. Small 2008; 4: 1925–9.

110. Dennis CL, Jackson AJ, Borchers JA, et al. Nearly complete regression of tumors via collective behavior of magnetic nanoparticles in hyperthermia. Nanotechnology 2009; 20: 395103.

111. Lee JH, Jang JT, Choi JS, et al. Exchange-coupled magnetic nanoparticles for efficient heat induction. Nat Nanotechnol 2011; 6: 418–22.

112. Pradhan P, Giri J, Samanta G, et al. Comparative evaluation of heating ability and biocompatibility of different ferrite-based magnetic fluids for hyperthermia application. J Biomed Mater Res B Appl Biomater 2007; 81: 12–22.

113. Kaman O, Pollert E, Veverka P, et al. Silica encapsulated manganese perovskite nanoparticles for magnetically induced hyperthermia without the risk of overheating. Nanotechnology 2009; 20: 275610.

114. Atsarkin VA, Levkin LV, Posvyanskiy VS, et al. Solution to the bioheat equation for hyperthermia with La(1-x)Ag(y)MnO(3-delta) nanoparticles: the effect of temperature autostabilization. Int J Hyperthermia 2009; 25: 240–7.

115. Huber DL. Synthesis, properties, and applications of iron nanoparticles. Small 2005; 1: 482–501.

116. Corchero JL, Villaverde A. Biomedical applications of distally controlled magnetic nanoparticles. Trends Biotechnol 2009; 27: 468–76.

117. Jordan A, Scholz R, Maier-Hauff K, et al. The effect of thermotherapy using magnetic nanoparticles on rat malignant glioma. J Neurooncol 2006; 78: 7–14.

118. Jiang X, Xin H, Sha X, et al. PEGylated poly(trimethylene carbonate) nanoparticles loaded with paclitaxel for the treatment of advanced glioma: in vitro and in vivo evaluation. Int J Pharm 2011; 420: 385–94.

119. Costantino L, Boraschi D. Is there a clinical future for polymeric nanoparticles as brain-targeting drug delivery agents? Drug Discov Today 2012; 17: 367–78.

120. Zhan C, Meng Q, Li Q, et al. Cyclic RGD-polyethylene glycol-polyethylenimine for intracranial glioblastoma-targeted gene delivery. Chem Asian J 2012; 7: 91–6.

121. Sousa F, Mandal S, Garrovo C, et al. Functionalized gold nanoparticles: a detailed in vivo multimodal microscopic brain distribution study. Nanoscale 2010; 2: 2826–34.

122. Cheng Y, Meyers JD, Broome AM, et al. Deep penetration of a PDT drug into tumors by noncovalent drug-gold nanoparticle conjugates. J Am Chem Soc 2011; 133: 2583–91.

123. Sonavane G, Tomoda K, Makino K. Biodistribution of colloidal gold nanoparticles after intravenous administration: effect of particle size. Colloids Surf B Biointerfaces 2008; 66: 274–80.

124. Lasagna-Reeves C, Gonzalez-Romero D, Barria MA, et al. Bioaccumulation and toxicity of gold nanoparticles after repeated administration in mice. Biochem Biophys Res Commun 2010; 393: 649–55.

125. Khlebtsov N, Dykman L. Biodistribution and toxicity of engineered gold nanoparticles: a review of in vitro and in vivo studies. Chem Soc Rev 2011; 40: 1647–71.

126. De Jong WH, Hagens WI, Krystek P, et al. Particle size-dependent organ distribution of gold nanoparticles after intravenous administration. Biomaterials 2008; 29: 1912–9.

127. Kircher MF, de la Zerda A, Jokerst JV, et al. A brain tumor molecular imaging strategy using a new triple-modality MRI-photoacoustic-Raman nanoparticle. Nat Med 2012; 18: 829–34.

128. Bernardi RJ, Lowery AR, Thompson PA, et al. Immunonanoshells for targeted photothermal ablation in medulloblastoma and glioma: an in vitro evaluation using human cell lines. J Neurooncol 2008; 86: 165–72.

129. Baek SK, Makkouk AR, Krasieva T, et al. Photothermal treatment of glioma; an in vitro study of macrophage-mediated delivery of gold nanoshells. J Neurooncol 2011; 104: 439–48.

130. Smith AM, Duan H, Mohs AM, et al. Bioconjugated quantum dots for in vivo molecular and cellular imaging. Adv Drug Deliv Rev 2008; 60: 1226–40.

131. Gao X, Yang L, Petros JA, et al. In vivo molecular and cellular imaging with quantum dots. Curr Opin Biotechnol 2005; 16: 63–72.

132. Oostendorp M, Douma K, Hackeng TM, et al. Gadolinium-labeled quantum dots for molecular magnetic resonance imaging: R1 versus R2 mapping. Magn Reson Med 2010; 64: 291–8.

133. Arndt-Jovin DJ, Kantelhardt SR, Caarls W, et al. Tumor-targeted quantum dots can help surgeons find tumor boundaries. IEEE Trans Nanobioscience 2009; 8: 65–71.

134. Schneider T, Becker A, Ringe K, et al. Brain tumor therapy by combined vaccination and antisense oligonucleotide delivery with nanoparticles. J Neuroimmunol 2008; 195: 21–7.

135. Caruso G, Caffo M, Alafaci C, et al. Could nanoparticle systems have a role in the treatment of cerebral gliomas? Nanomedicine 2011; 7: 744–52.

136. Zhang Z, Yang X, Zhang Y, et al. Delivery of telomerase reverse transcriptase small interfering RNA in complex with positively charged single-walled carbon nanotubes suppresses tumor growth. Clin Cancer Res 2006; 12: 4933–9.

137. Hunt MA, Bago AG, Neuwelt EA. Single-dose contrast agent for intraoperative MR imaging of intrinsic brain tumors by using ferumoxtran-10. AJNR Am J Neuroradiol 2005; 26: 1084–8.