12

# Multifunctional Magnetic Hybrid Nanoparticles as a Nanomedical Platform for Cancer-Targeted Imaging and Therapy

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## 1. Introduction

Nanotechnology offers tremendous potential for use in biomedical applications, including imaging, disease diagnosis, and drug delivery. The development of nanosystems has improved the molecular understanding of many diseases and permitted the controlled nanoscale manipulation of materials (Couvreur & Vauthier, 2006). Nanomedical platforms offer many advantages as delivery, sensing, and image-enhancing agents. In recent years, many studies have focused on multifunctional nanomedical platforms that incorporate therapeutic and diagnostic agents with molecular targeting capabilities. Gregoriadis et al. first proposed liposomes as drug carriers in cancer chemotherapy in 1974 (Gregoria et al., 1974). Today, drug delivery systems made of lipids or polymers frequently are exploited for the controlled delivery of therapeutic drugs in the body (Jain, 2005; Vasir et al., 2005).

Nanosized particles for biomedical platforms can be made from a variety of materials, including lipids (liposomes, nanoemulsions, and solid-lipid nanoparticles), self-assembling amphiphilic molecules, nondegradable and degradable polymers, dendrimers, metals, and inorganic semiconductor nanocrystals. The selection of the platform material is determined by the desired diagnostic or therapeutic goal, payload type, material safety profile, and administration route. Among the various types of functional nanostructures, nanomedical platforms based on magnetic nanoparticles (MNPs) are of particular interest in biomedical applications. Most frequently, MNPs are constructed of superparamagnetic iron oxides (SPIOs) (e.g., $Fe_3O_4$ or $\gamma$-$Fe_2O_3$), although metals such as cobalt and nickel are also employed. The characteristics of MNPs, including their composition, size, morphology, and surface chemistry, are tailored by various processes for their wide application in the detection, diagnosis, and treatment of illnesses. The most popular MNPs for biomedical applications are comprised of a magnetic inorganic nanoparticle core and a biocompatible surface coating that provides stabilization under physiological conditions. The additional application of a suitable surface chemistry allows the integration of functional ligands, such that MNPs can perform multiple functions. The modification and functionalization of MNPs improve their magnetic properties and affect their behavior in vivo (Tartaj et al., 2003; A.K. Gupta & M. Gupta, 2005).

Multifunctional MNPs (MFMNPs) are a major class of nanoscale materials with the potential to revolutionize clinical diagnostic and therapeutic techniques. Due to their unique magnetic properties and ability to function at the cellular and molecular levels of biological interactions, MFMNPs have been investigated as an attractive nanomedical platform. MFMNPs in the form of SPIOs have been actively investigated as contrast enhancement agents for magnetic resonance imaging (MRI) and hyperthermia in response to an external alternating magnetic field, due to their ability to enhance the proton relaxation of specific tissues. MFMNPs have been evaluated extensively as a nanomedical platform for the targeted delivery of pharmaceuticals through magnetic drug targeting (Neuberger et al., 2005) and through the attachment of high-affinity ligands (Zhang et al., 2002; Torchilin, 2006).

## 2. Surface coatings and functionalization of MNPs

### 2.1 Core–shell structure

Iron oxides with a core/shell structure are widely used as sources of MFMNP platforms. Iron oxides have several crystalline polymorphs, but only γ-$Fe_2O_3$ (maghemite) or $Fe_3O_4$ (magnetite) can be used for biomedical applications. These particles, which range in diameter from about 5–20 nm, have unique advantages, including (1) superparamagnetic behavior, with no magnetism after removal of the magnetic field; (2) high saturation magnetization values and high magnetic susceptibility, for effective magnetic enrichment; (3) biocompatibility and rapid removal through extravasation and renal clearance; and (4) easily tailored surface chemistry and functionalization.

Iron oxide nanoparticles have a significant tendency to agglomerate as a result of their high surface energy. Massart (1981) first prepared stable aqueous dispersions of $Fe_3O_4$ nanoparticles (ferrofluids) that were stabilized by electrical double layers. However, the colloidal electrostatic stabilization arising from surface charge repulsion on the nanoparticles typically is inadequate to prevent aggregation in biological solutions, due to the presence of salts or other electrolytes that can neutralize the charges. Furthermore, the iron oxide surfaces may be subjected to plasma protein adsorption or opsonization, leading to their rapid clearance by the reticuloendothelial system (RES) (Berry & Curtis, 2003).

To solve the above problems, proper surface coatings have been exploited as an integral component of the MFMNP platform for biomedical applications. The iron oxide core can be coated by organic materials [e.g., polymers such as dextrant (Thorek et al., 2006) and polyethylene glycol (PEG) (Gref et al., 1994)], inorganic metallic materials [e.g., gold (Ji et al., 2007)], or oxides [e.g., silica or alumina (Bumb et al., 2008)]. Polymer coatings will be introduced in detail in the next section. Silica shells are attractive as protective coatings on the iron oxide core, due to their stability under aqueous conditions and ease of synthesis. Recently, Ma et al. (2006) described one such core–shell MFMNP, composed of an iron oxide core (approximately 10 nm diameter) surrounded by a $SiO_2$ shell (10–15 nm thick). They doped an organic dye, tris(2,2′-bipyridine) ruthenium, inside a second silica shell to provide luminescence and prevent quenching by interaction with the magnetic core. As a core–shell structure exhibiting superparamagnetic and luminescent properties, this MFMNP platform can be used as a multifunctional imaging agent for biomedical applications.

Gold offers several advantages as a coating material for iron oxide cores, due to its low chemical reactivity and unique ability to form self-assembled monolayers on the core surface using alkanethiols (Prime & Whitesides, 1991). A variety of methods (reversed

microemulsion, combined wet chemical, and laser irradiation) can be used to synthesize gold-coated iron oxides (A. H. Lu et al., 2007).
The core/shell structure of MFMNPs offers several advantages, including good dispersibility and high stability against oxidation. In addition, an appreciable amount of therapeutic agent can be loaded on the MFMNP shell. Functionalization chemistries generally are better established when a coating material is used.

### 2.2 Polymer coatings

Polymers comprise some of the most important materials used as shells. Polymer coatings not only provide a steric barrier to prevent nanoparticle agglomeration, but also allow MNPs to evade uptake by the RES and thereby to maintain a long plasma half-life. Polymer coatings provide a means to tailor the surface properties of MNPs, such as the surface charge and chemical functionality. An ideal polymer coating will have a high affinity for the iron oxide core, as well as nonimmunogenic and nonantigenic properties. It also will prevent opsonization by plasma proteins. Polymer materials comprised of lipids, proteins, dendrimers, gelatin, dextran, chitosan, pullulan, PEG, poly(ethylene-co-vinyl acetate), poly(vinylpyrrolidone), poly(vinyl alcohol) (PVA), or poly(glycerol monoacrylate) (PGA) are often chosen as the surface coatings for MNPs.
PEG is the most widely used polymer for nanoparticle coating in biomedical applications. PEG provides a very attractive combination of properties: excellent solubility in aqueous solutions; high flexibility of its polymer chain; very low toxicity, immunogenicity, and antigenicity; lack of accumulation in the RES cells; and minimal influence on the specific biological properties of modified pharmaceuticals (Yamaoka et al., 1994). As a so-called "stealth" surface, PEG prevents the nanomedical platform from being recognized by RES, and thereby extends its blood circulation time in vivo. On the biological level, coating nanoparticles with PEG sterically hinders the interaction of blood components with the nanoparticle surface and reduces the binding of plasma proteins. Mechanisms of preventing opsonization by PEG include the shielding of the surface charges, increased surface hydrophilicity (Gabizon & Papahadjopoulos, 1992), and enhanced repulsive interaction between polymer-coated nanoparticles and blood components (Needham et al., 1992). Various methods have been utilized to attach PEG to the MNP surface, including silane grafting to the oxide surface (Butterworth et al., 2001), alkaline coprecipitation of ferric and ferrous ions in the presence of PEG-containing block copolymers (Wan et al., 2005), direct attachment of PEG-containing block copolymers (Guo et al., 2010), polymerization at the MNP surface (Flesch et al., 2005), and modification through sol-gel approaches (Y. Lu et al., 2002).
Polysaccharide dextran is another polymer coating that has been used widely and successfully in vivo. Dextran-coated iron oxide nanoparticles have become an important part of clinical cancer imaging, and have been shown to increase the accuracy of cancer nodal staging (Harisinghani & Weissleder, 2004; Ferrari, 2005). Because the dextran coating is not strongly associated with the iron oxide core, the polymer is susceptible to detachment. Accordingly, cross-linked iron oxide nanoparticles have been developed by cross-linking the dextran shell with epichlorohydrin (Josephson et al., 1999). The resulting particle offers superb stability under harsh conditions, without causing any change in size or blood half-life or loss of the dextran coat. Chemical functionality can be established by treating cross-linked iron oxide nanoparticles with ammonia to provide primary amino groups for the

attachment of biomolecules such as proteins or peptides (Wunderbaldinger et al., 2002; Schellenberger et al., 2002). These formulations of dextran-coated iron oxide nanoparticles have been evaluated extensively for a variety of MRI applications (Josephson et al., 1999).
In addition to the traditional polymer coatings, a new kind of biocompatible polymer material has been reported by Wan et al. (2005): namely, homopolymers of glycerol monoacrylate or glycerol monomethacrylate, or their block copolymers. Highly stable aqueous magnetic fluids were prepared by coating $Fe_3O_4$ nanoparticles with poly(glycerol monoacrylate) (PGA), poly(glycerol monomethacrylate) (PGMA), or diblock copolymers with PGA or PGMA segments. As shown in Fig. 1, the proposed mechanism of stabilization was the multidentate interactions of 1,2-diols on the polymer chain with iron atoms at the surface of the iron oxide nanoparticles (Wan et al., 2005). This process was a good choice for the preparation of stable magnetic fluids with tailored surfaces; PGA or PGMA binds very tightly to the iron oxide surface, is highly hydrophilic, and does not introduce charges on the surface. Moreover, various block copolymers containing PGA or PGMA can be used to modify the iron oxides and to introduce tailored functional groups for further functionalization.

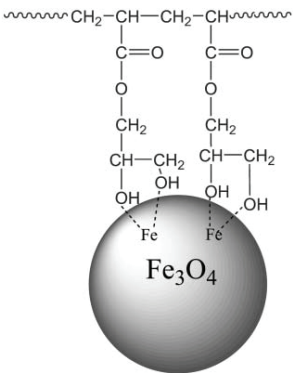


Fig. 1. Proposed structure in the interaction between the iron oxide surface and PGA (Wan et al., 2005).

### 2.3 Functional ligands

As discussed in the above sections, the core–shell structure of MFMNPs provides a means to tailor the nanoparticle surface properties, such as surface charge and chemical functionality. Various functional ligands, including targeting agents, permeation enhancers, optical dyes, and therapeutic agents, can be conjugated on the surface or incorporated within the nanostructure. The modification of the nanoparticle surface with targeting ligands was described recently as a promising biotargeting strategy. To generate target-specific nanoparticles, various biological molecules, such as antibodies, proteins, small molecular targeting agents, etc., can be bound to the coating surfaces of the MFMNPs by chemical coupling. Tumor cells are rapidly proliferating and overexpress certain receptors that lead to the enhanced uptake of nutrients, including folic acid, vitamins, sugars, and proteins. MFMNPs conjugated with these molecules can be targeted to tumor cells that overexpress the corresponding receptors. Table 1 summarizes a number of different ligands and their corresponding functions that have been investigated for the in vivo targeting of MFMNPs.

| Targeting ligand | Functional activity | References |
|---|---|---|
| Folic acid | Preferentially targets cancer cells that overexpress folate receptors and facilitates internalization | Zhang et al., 2002 |
| CREKA peptide or F3 peptide | Targets an antigen associated with colorectal carcinoma cells | Reddy et al., 2006; Simberg et al., 2007 |
| Pullulan | Increases receptor-mediated hepatic uptake | Kaneo et al., 2001 |
| Elastin | Cross-linked protein; Provides elasticity for many tissues | Debelle & Tamburro, 1999 |
| RGD peptide | Enhances cell spreading, differentiation, and DNA synthesis | Bhadriraju & Hansen, 2000 |
| Tat-peptide | Membrane-permeating peptide; Enhances intracellular delivery of nanoparticles | Josephson et al., 1999; Lewin et al., 2000 |
| Transferrin | Targets primary proliferating cells by transferrin receptors | Weissleder et al., 2000; Moore et al., 2001 |
| Insulin | Hormone; Regulates blood glucose levels | Gupta et al., 2003 |
| Monoclonal antibody A7 | Targets an antigen associated with colorectal carcinoma cells | Toma et al., 2005 |

Table 1. Selected functional ligands used for MFMNPs in biomedical applications

Organic dyes or fluorophores have been loaded on MNPs as optical imaging agents to allow detection by multiple imaging modalities. In addition to their use as contrast enhancement agents, FITC- (Zhang et al., 2002), rhodamine- (Bertorelle et al., 2006), or other fluorophore-labeled MNPs can be used for the in vitro fluorescent imaging of cells. Since both MRI and optical signals come from the same nanoparticles, the MR image can serve as a roadmap to the fluorescently labeled tumor cells. The conjugation of near-infrared fluorescent (NIRF) dyes to MNPs has received recent attention due to the deep penetration of NIRF light in the tissues (Weissleder & Ntziachristos, 2003). The integration of NIRF detectability allows for these nanoparticles to be used for presurgical planning by MRI and intraoperative resection of malignant tissues by optical imaging.

## 3. Biomedical applications of MFMNPs

### 3.1 Targeted drug delivery

One promising biomedical application of MFMNPs is as carriers for site-specific drug delivery. Many therapeutic agents, while pharmacologically effective, also exhibit side-effects because of their toxicities. For example, cytotoxic compounds used in cancer therapy kill not only target cells but also normal cells in the body, resulting in undesired side-effects. Meanwhile, many barriers to the delivery of therapeutic agents are presented, including renal clearance of small molecular therapeutic agents and overexpressed membrane-associated multi-drug resistance developed by tumor cells. Therefore, many therapeutic agents are limited in their clinical application. As widely used nanocarriers, MFMNPs have been considered as alternatives for the target-specific delivery of drugs to different sites in the body. These engineered nanoparticulate carriers offer some advantages, including passive targeting due to the enhanced permeability and retention (EPR) effect and functionalized surface features for target-specific localization. It also may be possible to develop nanocarriers that respond to physiological stimuli, or to combine drugs with energy (heat, light, and sound) delivery for synergistic therapeutic effects.

### 3.1.1 Passive targeting

Passive targeting relies on the properties of the delivery system and the disease pathology to accumulate the drug preferentially at the site of interest and avoid nonspecific distribution. Long-circulating nanoparticles of 20-200 nm in diameter containing surface PEG or poly(ethylene oxide) (PEO) blocks can accumulate at sites of disease such as tumors, infection, or inflammation through passive targeting via the EPR effect. Maeda and colleagues (2001) first described the EPR effect in their study of vascular abnormalities of solid tumors. Blood vessels in most solid tumors possess unique characteristics that are not usually observed in normal blood vessels, including: active angiogenesis and high vascular density; extensive production of vascular mediators that facilitate extravasation; defective vascular architecture (lack of smooth muscle layer cells, lack of receptors for angiotensin, large gap in endothelial cell-cell junctions, and anomalous conformations); and impaired lymphatic clearance of macromolecules and lipids from interstitial tissue.

Due to the EPR effect, nanopharmaceuticals (macromolecular drugs and drug-loaded nanoparticles) accumulate in tumor tissues with remarkable selectivity as schematically illustrated in Fig. 2. For example, the administration of polymer-drug conjugates results in 10-100 fold higher drug concentrations in the tumor compared to the administration of free drug (van Vlerken et al., 2007). This selective drug targeting to solid tumors results in substantial therapeutic benefits due to the higher drug accumulation in the tumor tissue, as well as fewer side effects. The EPR effect also has been observed in inflammatory and infectious tissues. Thus, the application of nanocarriers is expected to have therapeutic benefits for treating these diseases as well (Allen & Cullis, 2004).

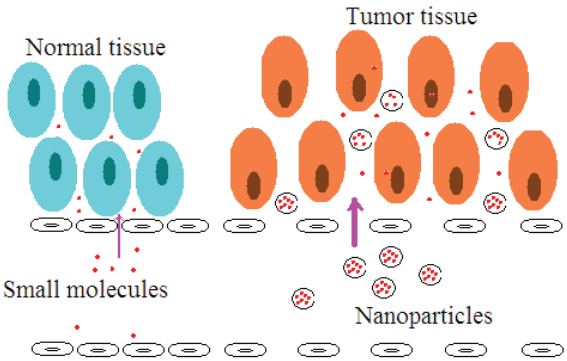


Fig. 2. Schematic illustration for passive targeting using the EPR effect.

Another approach for passive targeting involves the tendency of nanoparticles to localize in the RES. This phenomenon provides an opportunity for nanoparticles to accumulate at high concentrations in the liver or spleen, where many macrophages are present. Overall, the passive targeting strategy provides a means of delivering MFMNPs (as contrast agents or drug carriers) or other nanoparticles to the targeted organs or tissues.

### 3.1.2 Active targeting

Another promising approach towards increasing the local accumulation of nanoparticles in diseased tissue is known as active (or specific) targeting. Active targeting involves the

conjugation of targeting molecules that possess high affinity toward unique molecular signatures found on malignant cells. Targeting ligands, such as proteins, peptides, aptamers and small molecules, have been investigated to increase the site-specific accumulation of MFMNPs. For example, there are certain receptors that are overexpressed on the surface of solid tumor cells, such as antigens, integrin receptors, and folate receptors (Table 1). By bonding with these targeting molecules, MFMNPs can be targeted to the corresponding tumor cells and internalized by receptor- or antigen-mediated endocytosis.

Monoclonal antibodies (mAbs) were the first targeting agents to exploit molecular recognition to deliver MNPs; mAbs continue to be used widely, due to their high specificity. For instance, Herceptin®, an FDA-approved mAb to the HER2/neu (erbB2) receptor, has been used to modify DMSA-coated magnetite nanoparticles. When these MFMNPs were used as contrast enhancement agents, the MR imaging of mice bearing xenograft tumors showed a T2 decrease of ~20% due to the specific accumulation of the nanoprobe in the tumor (Huh et al., 2005). Nanoparticles modified with an HER2-specific antibody (Trastuzumab® or Herceptin®) also are able to localize and deliver the therapeutic payload specifically in HER2-expressing tumor cells (Kirpotin et al., 2006). Certain tumor cells express specific integrin receptors, such as $\alpha_v\beta_5$ or $\alpha_v\beta_3$ that can bind to the arginine-glycine-aspartic acid (RGD) peptide sequence. The RGD peptide has been utilized for the delivery of MNPs to a variety of neoplastic tissues, including breast tumors, malignant melanomas, and squamous cell carcinomas (Montet et al., 2006).

Among the small targeting molecules, folate has been used to modify nanoparticles for targeted delivery to tumor cells that overexpress folate receptors. Recently, our group reported multilayer MFMNPs with a folate-modified surface and doxorubicin (an anticancer chemotherapeutic agent) loaded in the inner shell (Fig. 3) (Guo et al., 2011). The folate-conjugated MFMNPs displayed a much greater cellular uptake than nonfolate-conjugated MFMNPs by a folate receptor–mediated endocytosis process (Fig. 4). Folate conjugation significantly increased nanoparticle cytotoxicity against human cervical carcinoma HeLa cells (Guo et al., 2011).

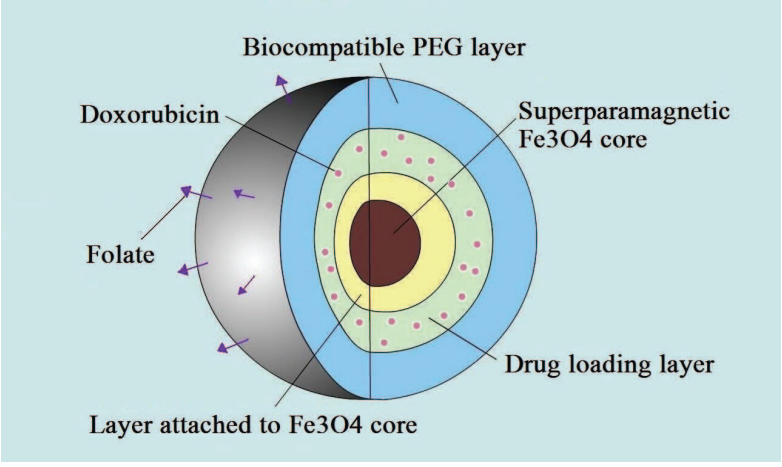


Fig. 3. Schematic illustration of multilayer MFMNPs with folate as the targeting ligand and loaded doxorubicin as the anticancer chemotherapeutic agent in the inner shell.

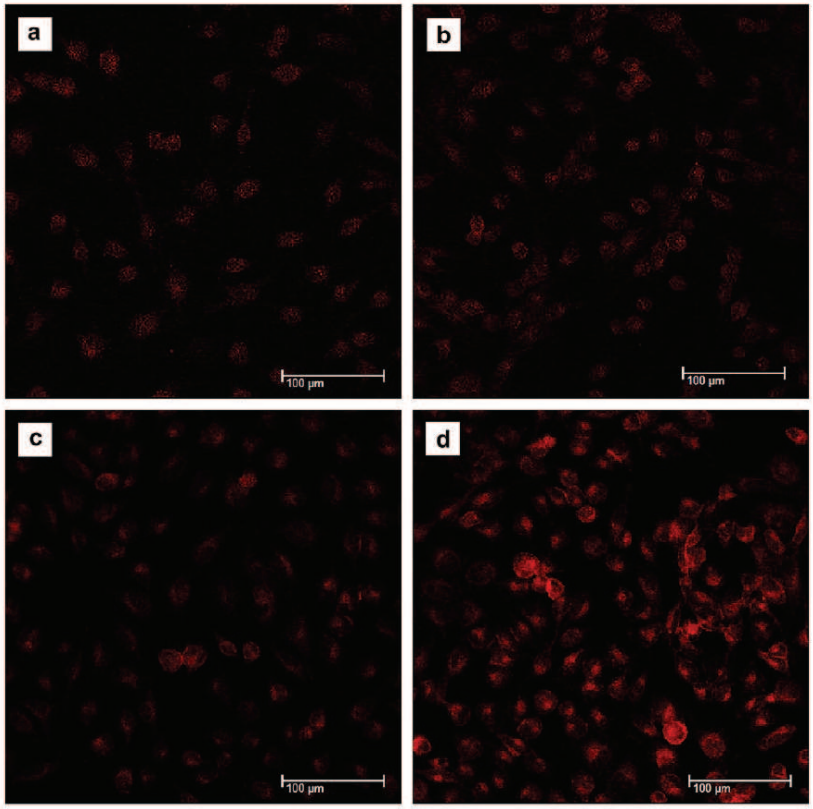


Fig. 4. Confocal microscopic images of HeLa cells incubated with (a, b) doxorubicin-loaded MFMNPs without folate conjugation or (c, d) folate–conjugated and doxorubicin-loaded MFMNPs in (a, c) folate-containing or (b, d) folate-free media (Guo et al., 2011).

### 3.1.3 Drug loading and controlled release

An essential step in the use of MFMNPs for drug delivery is the controlled release of the therapeutic payload in the desired tumor cells or tissues. The drug-loading capacity and release rate are correlated with the binding affinity of the drug. Strong carrier–drug interactions may enhance the loading capacity and decrease the release rate of the drug from the carrier; therefore, the choice of proper carrier–drug interactions is critical in the design and preparation of nanocarriers for drug delivery.

Successful MNP delivery devices with a prolonged circulation time can carry a chemotherapeutic payload and can be engineered to release its drugs after cell internalization. To successfully integrate a drug into a NP system, several design strategies can be explored, including physical complexation with hydrophobic drugs, or covalent bonding with cleavable linkages for intracellular release. Currently, several chemical drug formulations have been combined with MNPs, including paclitaxel, doxorubicin, and methotrexate, all specifically developed for cancer therapy. For example, methotrexate, an anticancer drug, has an affinity to the target cells, and after grafting the drug to the surface,

MNPs can be internalized more rapidly. Kohler et al. (2006) first demonstrated this utility in a study where methotrexate was covalently attached to the surface of PEG-coated MNPs via a cleavable amide linkage. Recently, Sun et al. (2008b) further modified the same MFMNP system with chlorotoxin to enhance the NP's targeting abilities against brain tumor cells.

Ideal drug delivery systems should be stable with a long circulation time, and should keep the loaded drugs unreleased during circulation in the bloodstream or in normal tissues. Upon reaching the tumor tissues and being taken up by cancer cells, the systems should release the drugs rapidly to kill cancer cells.

To achieve this purpose, stimuli-triggered drug delivery systems have been used that respond to characteristics of the local microenvironment, such as pH, temperature, redox potential, etc. [reviewed by Danhier et al. (2010) and Muthu et al. (2009)]. In particular, pH gradients have been used widely to design responsive nanoparticle delivery systems. Various nanocarriers with pH-responsive delivery behaviors have been developed on the basis of the differential pH values of blood plasma (pH 7.4), extracellular tumor matrix (pH 5.8–7.2), and endocytic compartments such as endosomes (pH 5–6) and lysosomes (pH 4–5). Drugs have been loaded into polymeric nanocarriers by acidic pH-induced cleavable covalent bonds, creating smart drug delivery systems that respond to the endosomal/lysosomal pH (Yoo et al., 2002; Bae et al., 2003; Gillies et al., 2004; Hruby et al., 2005). The pH-induced cleavage of such bonds can accelerate drug release from the nanocarriers.

Drugs are otherwise loaded into the core of polymeric micelles by noncovalent (e.g., hydrophobic) interactions. Compared to chemical attachment, noncovalent entrapment is convenient and easy to achieve. Nasongkla et al. (2006) described the preparation of micelles of PEG-b-poly(D, L-lactide) that encapsulated doxorubicin and a cluster of SPIO nanoparticles by noncovalent hydrophobic interactions. The protonation of doxorubicin under acidic conditions increased its water-solubility and induced its release.

Recently, our group reported a MFMNP platform that can load drugs with ionizable groups and hydrophobic moieties by the combined action of ionic bonding and hydrophobic interactions (Guo et al., 2008, 2010) (Fig. 5). The use of double noncovalent interactions resulted in a high loading affinity at a neutral pH (7.4), preventing premature release into the bloodstream. At an endosomal/lysosomal pH (<5.5), protonation of polycarboxylate anions in the polymer chains led to ionic bond breakage and drug release. The release process was controlled, responded well to pH, and displayed good kinetics.

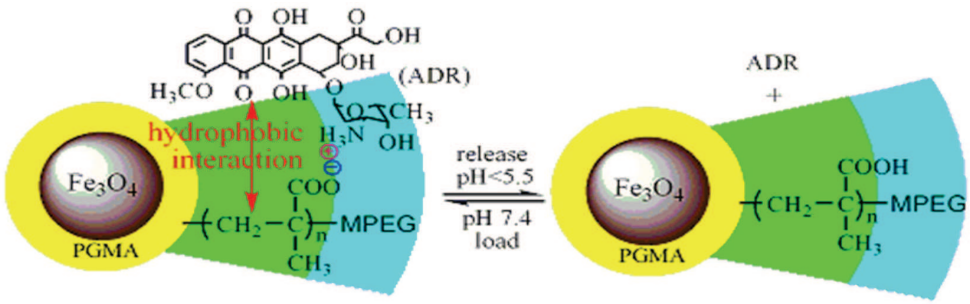


Fig. 5. Schematic illustration of the MFMNP structure, and the load and release of model drug adriamycin (ADR) (Guo et al., 2008).

### 3.2 MRI

MRI is a powerful noninvasive imaging modality that is utilized widely in clinical medicine. MRI is based on the property that hydrogen protons will align and process around an external alternating magnetic field. The subsequent process through which these protons return to their original state is referred to as the relaxation phenomenon. Two independent processes, longitudinal relaxation (T1-recovery) and transverse relaxation (T2-decay), are monitored to generate the MR image. Local variations in relaxation, corresponding to image contrast, arise from the proton density and the chemical and physical natures of the different tissues. Due to their ability to enhance proton relaxation and accumulation in specific tissues, MFMNPs have been actively investigated as contrast enhancement agents for MRI.

#### 3.2.1 Magnetic properties of iron oxide nanoparticles

Particles whose unpaired electron spins align themselves spontaneously so that the material can exhibit magnetization without being in a magnetic field are called ferromagnetic particles. Materials such as iron oxide nanoparticles that exhibit ferromagnetism can be permanently magnetized. The magnetic properties of iron oxide nanoparticles can be described by the dependence of the magnetic induction $B$ on the magnetic field $H$. For most materials, the relationship between $B$ and $H$ is linear: $B = \mu H$, where $\mu$ is the magnetic permeability of the particles. Iron oxide particles exhibit paramagnetism if $\mu > 1$, and diamagnetism if $\mu < 1$.

Usually, ferromagnetic properties arise only when a certain number of atoms are bound together in solid form; single atoms cannot exhibit ferromagnetism. When the size of particles is smaller than the ferromagnetic domain, they are no longer ferromagnetic but exhibit superparamagnetism (Bansil et al., 1998). Magnetic nanoparticles smaller than ~ 30 nm show superparamagnetic behavior without any magnetic remanence (i.e., restoration of the induced magnetization to zero upon removal of the external magnetic field), but the particles still exhibit very strong paramagnetic properties with a very large susceptibility. This is one important advantage for magnetic nanoparticles: it enables their stability and dispersion upon removal of the magnetic field, as no residual magnetic force exists between the particles.

In MRI, superparamagnetic nanoparticles made of iron oxide act as contrast enhancement agents by shortening both the T1 and T2 relaxations of the surrounding protons. The influence on the T1 relaxation depends strongly on the local MNP concentration, and the shortening processes can be hindered by the coating thickness. The effect of MNPs on T2 shortening is caused by the large susceptibility difference between the particles and surrounding medium, which results in microscopic magnetic field gradients. At low concentrations, a T1-positive contrast can be observed; at high concentrations, the susceptibility effects cause irreversible destruction of the MR signal around the particles.

NMP agglomeration tends to slightly decrease the T1 relaxation times but markedly decrease the T2 times. Therefore, superparamagnetic nanoparticles typically are used to provide negative contrast enhancement using T2-weighted pulse sequences. The effectiveness of a contrast agent can be described by its relaxivity, which is the proportionality constant of the measured rate of relaxation, or R1 (1/T1) and R2 (1/T2). The relaxivity depends on not only the composition, size, and magnetic properties of the MNP, but also depends on experimental variables such as the field strength, temperature, and medium in which the measurements are made.

### 3.2.2 Molecular imaging in cancer

The generation of new molecular targets that are closely related to pathophysiology will open the way for the development of new treatment paradigms for currently untreatable diseases. In recent years, many new diagnostic technologies have been developed, including molecular diagnostic compounds and new imaging technologies such as MR molecular imaging. Molecular imaging is the noninvasive imaging of targeted macromolecules, cells, and biological or cellular processes in living organisms. Due to their ability to act as molecularly targeted imaging agents, MNPs play an integral role in the applications of early disease detection, individualized treatment, and drug development. In the clinical imaging of tumors, MNPs can be used as contrast enhancement agents to improve the detection, diagnosis, and therapeutic management of solid tumors by exploiting the unique molecular signatures of the diseases. MNPs also have been investigated to improve the delineation of the tumor position, boundaries, and volume.

The first clinical indication for iron oxide nanoparticles was the imaging of liver tumors and metastases. After intravenous injection, MNPs are taken up rapidly by hepatic specialized macrophages. This process causes a drop in MR signal intensity and generates hypointense images, mostly because of a susceptibility effect. However, tumors lack a permanent decrease in signal intensity after MNP administration; tumors are almost devoid of macrophages, which are located exclusively in the healthy hepatic parenchyma. Therefore, MNPs can markedly increase the contrast between healthy and diseased tissue. The clinical imaging of liver tumors and metastases through RES-mediated uptake of MNPs has allowed the detection of lesions as small as 2–3 mm (Semelka & Helmberger, 2001). In combination with MRI, MNPs also have been shown to be effective in the identification of lymph node metastases of 5–10 mm in diameter (Harisinghani et al., 2003). The use of MFMNPs as contrast enhancement agents provides increased lesion conspicuousness and lesion detection compared to nonenhanced imaging.

MFMNPs are currently under evaluation for use in improving the delineation of brain tumor boundaries and quantifying tumor volumes (Enochs et al., 1999; Neuwelt et al., 2004). Some recent approaches have explored utilizing iron oxide nanoparticles as drug delivery vehicles for the MRI-monitored magnetic targeting of brain tumors (Chertok et al., 2008). The accumulation of iron oxide nanoparticles in gliosarcomas is enhanced by magnetic targeting and successfully quantified by MRI (Chertok et al., 2008) (Fig. 6). Such noninvasive approaches for cancer diagnosis and therapy also have been adopted in the treatment of prostate, breast, and colon cancers.

As both drug delivery devices and MRI contrast enhancement agents, MNPs retain the ability to track the movement of drug through the body. This is significant because it allow clinicians to monitor the effectivity of injected therapeutics to reach their target sites. There remains significant flexibility in the contrast agents implemented in these constructs and the manner in which drugs are delivered. Medarova et al. (2007) recently developed cross-linked iron oxide nanoparticles modified with a NIR fluorophore, therapeutic siRNA sequences, and a cell penetrating peptide. The MNPs used passive targeting by the EPR effect to direct tumor localization. In vivo, these MNPs demonstrated therapeutic efficacy against target tissue, as determined by real time PCR and histological evaluation, while simultaneously demonstrating image contrast in both MR and optical imaging. In a study by Sun et al. (2008a) active cell targeting was shown by PEG-coated MNPs to which the chemotherapeutic, methotrexate, and targeting molecule, chlorotoxin, were attached. The selective contrast enhancement of the 9L brain tumor by these MNPs indicates preferential accumulation compared with the same MNP construct without the chlorotoxin peptide in a 3-day study.

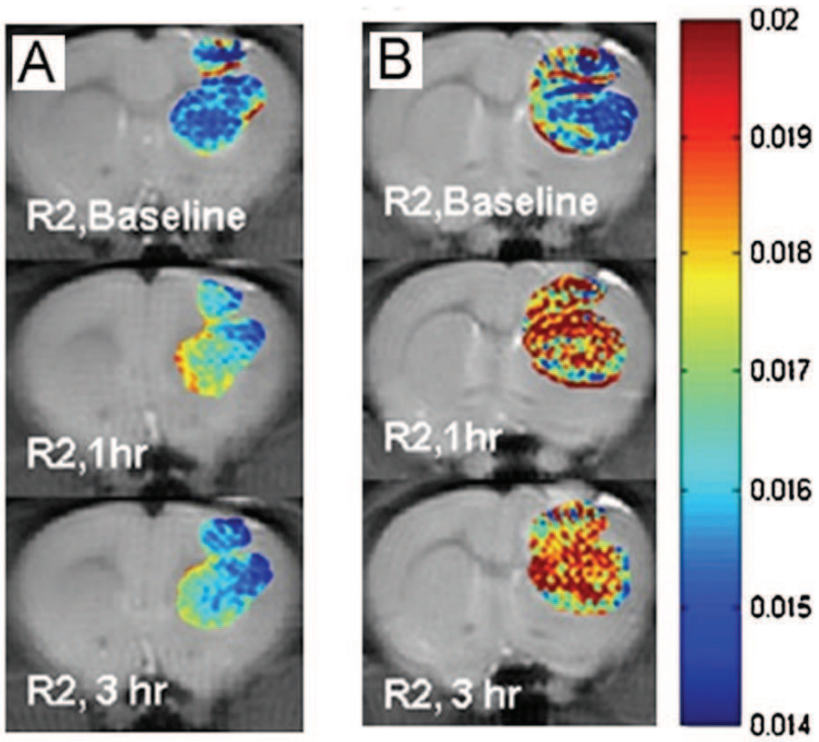


Fig. 6. MR images of brain tumor. Change in the R2 relaxation for the tumor regions before (baseline) and 1–3 h after MNPs administration in (A) control and (B) targeted rats (Chertok et al., 2008).

In another recent study by Yang et al. (2007) simultaneous targeted drug delivery and MR imaging of breast cancer tumors were demonstrated through the use multifunctional magneto-polymeric nanohybrids composed of magnetic nanocrystals and doxorubicin which were simultaneously encapsulated within an amphiphilic block copolymer shell. The surfaces of these micelles were additionally functionalized with the breast cancer targeting/therapeutic ligand, anti-Herceptin antibody. In vivo evaluations of this nanoparticle system were performed in nude mice bearing NIH3T6.7 breast cancer tumors. The quantitative evaluation of MR images revealed preferential accumulation of the targeted MNPs compared to the control MNPs. The therapeutic functionality of the MNPs developed in this study were additionally evaluated and it was determined that the HER-MMPNs which were decorated with targeting ligands and loaded with doxorubicin were most effective in inhibiting tumor growth. Combined, these findings illustrate the functionality and efficacy of targeted multifunctional MNPs for simultaneous MR imaging and drug delivery.

### 3.3 Hyperthermia

Hyperthermia is the method of using heat as a treatment for malignant tumors. It is based on the observation that tumor cells are more susceptible to heat than normal cells, due to the

higher rates of metabolism of cancer cells. Cancer cells typically show signs of apoptosis and necrosis when heated to 41-47 °C, whereas normal cells can survive at higher temperatures (Milleron & Bratton, 2007). Hyperthermia with targeted nanoscale heaters is recognized as a useful therapeutic modality to kill cancer by essentially "cooking" malignant cells from the inside out.

Magnetic nanoparticle hyperthermia is actualized by the exposure of cancer tissues to an alternating magnetic field. The magnetic field cannot be absorbed by the living tissues and can be applied to deep regions in the living body. When MNPs are injected into an organ with a tumor, they tend to accumulate in the tumor due to passive and active targeting strategies (as described above). Subsequent exposure to an alternating magnetic field causes heat to be generated in the tumor tissue due to magnetic hysteresis loss. This process effectively destroys the tumor but not the surrounding healthy tissue. The amount of heat generated depends on the nature of the MNPs and magnetic field parameters used.

The use of MFMNPs for targeted hyperthermia has shown a therapeutic effect in several types of tumors. Using dextran-coated MNPs conjugated to breast cancer–targeting chimeric L6 mAb, DeNardo et al. (2005) demonstrated the feasibility of this method for treating breast cancer cells. Kobayashi et al. constructed a novel therapeutic tool of magnetite nanoparticle-loaded anti-HER2 immunoliposomes that was applicable to the treatment of HER2-overexpressing cancer (Ito et al., 2004).

A clinical breakthrough in MNP use was made in 2007, when Maier-Hauff et al. (2007) reported the results of using heated implanted MNPs for therapeutic hyperthermia in humans. In that study, 14 patients with recurrent glioblastoma multiforme, a type of severe brain cancer, received an intratumoral injection of aminosilane-coated MNPs. The tumor sites were located by several comprehensive MRI scans, and the patients were exposed to an alternating magnetic field to induce particle heating. The nanoparticle deposits were stable for several weeks, and all patients tolerated the nanoparticles without any complications. These findings indicate that MNP hyperthermia may be an effective therapeutic method to cure human brain cancer.

As a potential approach for the treatment of malignant tumors, MNP hyperthermia has the following advantages: it provides a noninvasive way to raise cell temperatures to a therapeutic level; MNPs can be visualized using MRI, thus combining diagnostic and therapeutic approaches in one type of particle; and the particles can be functionalized and combined with other types of treatment, such as chemotherapy or radiotherapy.

## 4. Conclusions

Multifunctional nanomaterials have been widely used as nanoplatforms for multimodal imaging or simultaneous imaging and therapy. As a multifunctional nanoplatform with many biomedical applications, MFMNPs of various formulations have been developed to diagnose and treat diseases for which conventional therapy has shown limited efficacy, such as cancer. The use of MFMNPs as MRI contrast enhancement agents and anticancer drug carriers has drawn enormous attention, and may provide new opportunities for early cancer detection and targeted therapies. This technology not only will minimize the need for invasive procedures, but also will reduce the side effects to healthy tissues, which are primary concerns in conventional cancer therapies.

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## 6. References

Allen, T. M. & Cullis, P. R. (2004). Drug Delivery Systems: Entering the Mainstream. *Science,* Vol. 303, No. 5665, pp. 1818-1822.

Bae, Y.; Fukushima, S.; Harada, A. & Kataoka, K. (2003). Design of Environment-Sensitive Supramolecular Assemblies for Intracellular Drug Delivery: Polymeric Micelles that Are Responsive to Intracellular pH Change. *Angewandte Chemie International Edition,* Vol. 42, No. 38, pp. 4640-4643.

Bansil, A.; Sawatzky, G.; Fujii, Y.; Shelton, R. & Prosser, D. (1998). Journal of Physics and Chemistry of Solids 40th Anniversary – Preface. *Journal of Physics and Chemistry of Solids,* Vol. 59, No. 4, pp. III-IIV.

Berry, C. C. & Curtis, A. S. G. (2003). Functionalisation of Magnetic Nanoparticles for Applications in Biomedicine. *Journal of Physics D-Applied Physics,* Vol. 36, No. 13, pp. R198-R206.

Bertorelle, F.; Wilhelm, C.; Roger, J.; Gazeau, F.; Menager, C. & Cabuil, V. (2006). Fluorescence-Modified Superparamagnetic Nanoparticles: Intracellular Uptake and Use in Cellular Imaging. *Langmuir,* Vol. 22, No. 12, pp. 5385-5391.

Bhadriraju, K. & Hansen, L. K. (2000). Hepatocyte Adhesion, Growth and Differentiated Function on RGD-Containing Proteins. *Biomaterials,* Vol. 21, No. 3, pp. 267-272.

Bumb, A.; Brechbiel, M. W.; Choyke, P. L.; Fugger, L.; Eggeman, A.; Prabhakaran, D.; Hutchinson, J. & Dobson, P. J. (2008). Synthesis and Characterization of Ultra-Small Superparamagnetic Iron Oxide Nanoparticles Thinly Coated with Silica. *Nanotechnology,* Vol. 19, No. 33, pp. 335601-335606.

Butterworth, M. D.; Illum, L. & Davis, S. S. (2001). Preparation of Ultrafine Silica- and PEG-Coated Magnetite Particles. *Colloids and Surfaces A-Physicochemical and Engineering Aspects,* Vol. 179, No. 1, pp. 93-102.

Chertok, B.; Moffat, B. A.; David, A. E.; Yu, F. Q.; Bergemann, C.; Ross, B. D. & Yang, V. C. (2008). Iron Oxide Nanoparticles as a Drug Delivery Vehicle for MRI Monitored Magnetic Targeting of Brain Tumors. *Biomaterials,* Vol. 29, No. 4, pp. 487-496.

Couvreur, P. & Vauthier, C. (2006). Nanotechnology: Intelligent Design to Treat Complex Disease. *Pharmaceutical Research,* Vol. 23, No. 7, pp. 1417-1450.

Danhier, F.; Feron, O. & Preat V. (2010). To Exploit the Tumor Microenvironment: Passive and Active Tumor Targeting of Nanocarriers for Anti-Cancer Drug Delivery. *Journal of Controlled Release*, Vol. 148, No. 2, pp. 135–146.

Debelle, L. & Tamburro, A. M. (1999). Elastin: Molecular Description and Function. *International Journal of Biochemistry & Cell Biology,* Vol. 31, No. 2, pp. 261-272.

DeNardo, S. J.; DeNardo, G. L.; Miers, L. A.; Natarajan, A.; Foreman, A. R.; Gruettner, C.; Adamson, G. N. & Ivkov, R. (2005). Development of Tumor Targeting Bioprobes (In-111-Chimeric L6 Monoclonal Antibody Nanoparticles) for Alternating Magnetic Field Cancer Therapy. *Clinical Cancer Research,* Vol. 11, No. 19, pp. 7087S-7092S.

Enochs, W. S.; Harsh, G.; Hochberg, F. & Weissleder, R. (1999). Improved Delineation of Human Brain Tumors on MR Images Using a Long-Circulating,

Superparamagnetic Iron Oxide Agent. *Journal of Magnetic Resonance Imaging,* Vol. 9, No. 2, pp. 228-232.

Ferrari, M. (2005). Cancer Nanotechnology: Opportunities and Challenges. *Nature Reviews Cancer,* Vol. 5, No. 3, pp. 161-171.

Flesch, C.; Unterfinger, Y.; Bourgeat-Lami, E.; Duguet, E.; Delaite, C. & Dumas, P. (2005). Poly(ethylene glycol) Surface Coated Magnetic Particles. *Macromolecular Rapid Communications,* Vol. 26, No. 18, pp. 1494-1498.

Gabizon, A. & Papahadjopoulos, D. (1992). The Role of Surface-Charge and Hydrophilic Groups on Liposome Clearance In Vivo. *Biochimica et Biophysica Acta,* Vol. 1103, No. 1, pp. 94-100.

Gillies, E. R.; Goodwin, A. P. & Frechet, J. M. J. (2004). Acetals as pH-Sensitive Linkages for Drug Delivery. *Bioconjugate Chemistry,* Vol. 15, No. 6, pp. 1254-1263.

Gref, R.; Minamitake, Y.; Peracchia, M. T.; Trubetskoy, V.; Torchilin, V. & Langer, R. (1994). Biodegradable Long-Circulating Polymeric Nanospheres. *Science,* Vol. 263, No. 5153, pp. 1600-1603.

Gregoria, G.; Wills, E. J.; Swain, C. P. & Tavill, A. S. (1974). Drug-Carrier Potential of Liposomes in Cancer Chemotherapy. *Lancet,* Vol. 1, No. 7870, pp. 1313-1316.

Guo, M.; Que, C. L.; Wang, C. H.; Liu, X. Z.; Yan, H. S. & Liu, K. L. (2011). Multifunctional Superparamagnetic Nanocarriers with Folate-Mediated and pH-Responsive Targeting Properties for Anticancer Drug Delivery. *Biomaterials,* Vol. 32, No. 1, pp. 185-194.

Guo, M.; Yan, Y.; Liu, X. Z.; Yan, H. S.; Liu, K. L.; Zhang, H. K.; & Cao, Y. J. (2010). Multilayer Nanoparticles with a Magnetite Core and a Polycation Inner Shell as pH-Responsive Carriers for Drug Delivery. *Nanoscale,* Vol. 2, No. 3, pp. 434-441.

Guo, M.; Yan, Y.; Zhang, H. K.; Yan, H. S.; Cao, Y. J.; Liu, K. L.; Wan, S. R.; Huang, J. S. & Yue, W. (2008). Magnetic and pH-responsive Nanocarriers with Multilayer Core-Shell Architecture for Anticancer Drug Delivery. *Journal of Materials Chemistry,* Vol. 18, No. 42, pp. 5104-5112.

Gupta, A. K.; Berry, C.; Gupta, M. & Curtis, A. S. G. (2003). Receptor-Mediated Targeting of Magnetic Nanoparticles Using Insulin as a Surface Ligand to Prevent Endocytosis. *IEEE Transactions on Nanobioscience,* Vol. 2, No. 4, pp. 255-261.

Gupta, A. K. & Gupta, M. (2005). Synthesis and Surface Engineering of Iron Oxide Nanoparticles for Biomedical Applications. *Biomaterials,* Vol. 26, No. 18, pp. 3995-4021.

Harisinghani, M. G. & Weissleder, R. (2004). Sensitive, Noninvasive Detection of Lymph Node Metastases. *Plos Medicine,* Vol. 1, No. 3, pp. 202-209.

Hruby, M.; Konak, C. & Ulbrich, K. (2005). Polymeric Micellar pH-Sensitive Drug Delivery System for Doxorubicin. *Journal of Controlled Release,* Vol. 103, No. 1, pp. 137-148.

Huh, Y. M.; Jun, Y. W.; Song, H. T.; Kim, S.; Choi, J. S.; Lee, J. H.; Yoon, S.; Kim, K. S.; Shin, J. S.; Suh, J. S. & Cheon, J. (2005). In Vivo Magnetic Resonance Detection of Cancer by Using Multifunctional Magnetic Nanocrystals, *Journal of the American Chemical Society,* Vol. 127, No. 35, pp. 12387-12391.

Ito, A.; Kuga, Y.; Honda, H.; Kikkawa, H.; Horiuchi, A.; Watanabe, Y. & Kobayashi, T. (2004). Magnetite Nanoparticle-Loaded Anti-Her2 Immunoliposomes for Combination of Antibody Therapy with Hyperthermia. *Cancer Letters,* Vol. 212, No. 2, pp. 167-175.

Jain, K. K. (2005). The Role of Nanobiotechnology in Drug Discovery. *Drug Discovery Today,* Vol. 10, No. 21-24, pp. 1435-1442.

Ji, X. J.; Shao, R. P.; Elliott, A. M.; Stafford, R. J.; Esparza-Coss, E.; Bankson, J. A.; Liang, G.; Luo, Z. P.; Park, K.; Markert, J. T. & Li, C. (2007). Bifunctional Gold Nanoshells with a Superparamagnetic Iron Oxide-Silica Core Suitable for both MR Imaging and Photothermal Therapy. *Journal of Physical Chemistry*, Vol. 111, No. 17, pp. 6245-6251.

Josephson, L.; Tung, C. H.; Moore, A. & Weissleder, R. (1999). High-Efficiency Intracellular Magnetic Labeling with Novel Superparamagnetic-Tat Peptide Conjugates. *Bioconjugate Chemistry,* Vol. 10, No. 2, pp. 186-191.

Kaneo, Y.; Tanaka, T.; Nakano, T. & Yamaguchi, Y. (2001). Evidence for Receptor-Mediated Hepatic Uptake of Pullulan in Rats. *Journal of Controlled Release,* Vol. 70, No. 3, pp. 365-373.

Kirpotin, D. B.; Drummond, D. C.; Shao, Y.; Shalaby, M. R.; Hong, K. L.; Nielsen, U. B.; Marks, J. D.; Benz, C. C. & Park, J. W. (2006). Antibody Targeting of Long-Circulating Lipidic Nanoparticles does not Increase Tumor Localization but does Increase Internalization in Animal Models. *Cancer Research*, Vol. 66, No. 13, pp. 6732-6740.

Kohler, N.; Sun, C.; Fichtenholtz, A.; Gunn, J.; Fang, C. & Zhang, M. Q. (2006). Methotrexateimmobilized poly(ethylene glycol) magnetic nanoparticles for MR imaging and drug delivery. *Small,* Vol. 2, No. 6, pp. 785-792.

Lewin, M.; Carlesso, N.; Tung, C. H.; Tang, X. W.; Cory, D.; Scadden, D. T. & Weissleder, R. (2000). Tat Peptide-Derivatized Magnetic Nanoparticles Allow In Vivo Tracking and Recovery of Progenitor Cells. *Nature Biotechnology,* Vol. 18, No. 4, pp. 410-414.

Lu, A. H.; Salabas, E. L. & Schuth, F. (2007). Magnetic Nanoparticles: Synthesis, Protection, Functionalization, and Application. *Angewandte Chemie International Edition,* Vol. 46, No. 8, pp. 1222-1244.

Lu, Y.; Yin, Y. D.; Mayers, B. T. & Xia, Y. N. (2002). Modifying the Surface Properties of Superparamagnetic Iron Oxide Nanoparticles through a Sol-Gel Approach. *Nano Letters,* Vol. 2, No. 3, pp. 183-186.

Ma, D. L.; Guan, J. W.; Normandin, F.; Denommee, S.; Enright, G.; Veres, T. & Simard, B. (2006). Multifunctional Nano-Architecture for Biomedical Applications. *Chemistry of Materials,* Vol. 18, No. 7, pp. 1920-1927.

Maeda, H. (2001). The Enhanced Permeability and Retention (EPR) Effect in Tumor Vasculature: The Key Role of Tumor-Selective Macromolecular Drug Targeting. *Advances in Enzyme Regulation,* Vol 41, v. 41, pp. 189-207.

Maier-Hauff, K.; Rothe, R.; Scholz, R.; Gneveckow, U.; Wust, P.; Thiesen, B.; Feussner, A.; von Deimling, A.; Waldoefner, N.; Felix, R. & Jordan, A. (2007). Intracranial Thermotherapy Using Magnetic Nanoparticles Combined with External Beam Radiotherapy: Results of a Feasibility Study on Patients with Glioblastoma Multiforme. *Journal of Neuro-Oncology,* Vol. 81, No. 1, pp. 53-60.

Massart, R. (1981). Preparation of Aqueous Magnetic Liquids in Alkaline and Acidic Media. *IEEE Transactions on Magnetics*, Vol. 17, No. 2, pp. 1247-1248.

Medarova, Z.; Pham, W.; Farrar, C.; Petkova, V. & Moore, A. (2007). In Vivo Imaging of siRNA Delivery and Silencing in Tumors. *Nature Medicine,* Vol. 13, No. 3, pp. 372-377.

Milleron, R. S. & Bratton, S. B. (2007). 'Heated' Debates in Apoptosis. *Cellular and Molecular Life Sciences,* Vol. 64, pp. 2329-2333.

Montet, X.; Montet-Abou, K.; Reynolds, F.; Weissleder, R. & Josephson, L. (2006). Nanoparticle Imaging of Integrins on Tumor Cells. *Neoplasia,* Vol. 8, No. 3, pp. 214-222.

Moore, A.; Josephson, L.; Bhorade, R. M.; Basilion, J. P. & Weissleder, R. (2001). Human Transferrin Receptor Gene as a Marker Gene for MR Imaging. *Radiology,* Vol. 221, No. 1, pp. 244-250.

Muthu, M. S.; Rajesh, C. V.; Mishra A. & Singh S. (2009). Stimulus-Responsive Targeted Nanomicelles for Effective Cancer Therapy. Nanomedicine, Vol. 4, No. 6, 657-667.

Nasongkla, N.; Bey, E.; Ren, J. M.; Ai, H.; Khemtong, C.; Guthi, J. S.; Chin, S. F.; Sherry, A. D.; Boothman, D. A. & Gao, J. M. (2006). Multifunctional Polymeric Micelles as Cancer-Targeted, MRI-Ultrasensitive Drug Delivery Systems. *Nano Letters,* Vol. 6, No. 11, pp. 2427-2430.

Needham, D.; Mcintosh, T. J. & Lasic, D. D. (1992). Repulsive Interactions and Mechanical Stability of Polymer-Grafted Lipid-Membranes. *Biochimica et Biophysica Acta,* Vol. 1108, No. 1, pp. 40-48.

Neuberger, T.; Schopf, B.; Hofmann, H.; Hofmann, M. & von Rechenberg, B. (2005). Superparamagnetic Nanoparticles for Biomedical Applications: Possibilities and Limitations of a New Drug Delivery System. *Journal of Magnetism and Magnetic Materials,* Vol. 293, No. 1, pp. 483-496.

Neuwelt, E. A.; Varallyay, P.; Bago, A. G.; Muldoon, L. L.; Nesbit, G. & Nixon, R. (2004). Imaging of Iron Oxide Nanoparticles by MR and Light Microscopy in Patients with Malignant Brain Tumours. *Neuropathology and Applied Neurobiology,* Vol. 30, No. 5, pp. 456-471.

Prime, K. L. & Whitesides, G. M. (1991). Self-Assembled Organic Monolayers - Model Systems for Studying Adsorption of Proteins at Surfaces. *Science,* Vol. 252, No. 5009, pp. 1164-1167.

Reddy, G. R.; Bhojani, M. S.; McConville, P.; Moody, J.; Moffat, B. A.; Hall, D. E.; Kim, G.; Koo, Y. E. L.; Woolliscroft, M. J.; Sugai, J. V.; Johnson, T. D.; Philbert, M. A.; Kopelman, R.; Rehemtulla, A. & Ross, B. D. (2006). Vascular Targeted Nanoparticles for Imaging and Treatment of Brain Tumors. *Clinical Cancer Research,* Vol. 12, No. 22, pp. 6677-6686.

Schellenberger, E. A.; Bogdanov, A.; Hogemann, D.; Tait, J.; Weissleder, R. & Josephson, L. (2002). Annexin V-CLIO: a Nanoparticle for Detecting Apoptosis by MRI. *Molecular Imaging,* Vol. 1, No. 2, pp. 102-107.

Semelka, R. C. & Helmberger, T. K. G. (2001). Contrast Agents for MR Imaging of the Liver. *Radiology,* Vol. 218, No. 1, pp. 27-38.

Simberg, D.; Duza, T.; Park, J. H.; Essler, M.; Pilch, J.; Zhang, L.; Derfus, A. M.; Yang, M.; Hoffman, R. M.; Bhatia, S.; Sailor, M. J. & Ruoslahti, E. (2007). Biomimetic Amplification of Nanoparticle Homing to Tumors. *Proceedings of the National Academy of Sciences of the United States of America,* Vol. 104, No. 3, pp. 932-936.

Sun, C.; Fang, C.; Stephen, Z.; Veiseh, O.; Hansen, S.; Lee, D.; Ellenbogen, R. G.; Olson, J. & Zhang, M. Q. (2008a). Tumor-Targeted Drug Delivery and MRI Contrast Enhancement by Chlorotoxin-Conjugated Iron Oxide Nanoparticles. *Nanomedicine*, Vol. 3, No. 4, pp. 495-505.

Sun, C.; Veiseh, O.; Gunn, J.; Fang, C.; Hansen, S.; Lee, D.; Sze, R.; Ellenbogen, R. G.; Olson, J. & Zhang, M. (2008b). In Vivo MRI Detection of Gliomas by Chlorotoxin-Conjugated Superparamagnetic Nanoprobes. *Small,* Vol. 4, No. 3, pp. 372-379.

Tartaj, P.; Morales, M. D.; Veintemillas-Verdaguer, S.; Gonzalez-Carreno, T. & Serna, C. J. (2003). The Preparation of Magnetic Nanoparticles for Applications in Biomedicine. *Journal of Physics D-Applied Physics,* Vol. 36, No. 13, pp. R182-R197.

Thorek, D. L. J.; Chen, A.; Czupryna, J. & Tsourkas, A. (2006). Superparamagnetic Iron Oxide Nanoparticle Probes for Molecular Imaging. *Annals of Biomedical Engineering,* Vol. 34, No. 1, p. 23-38.

Toma, A.; Otsuji, E.; Kuriu, Y.; Okamoto, K.; Ichikawa, D.; Hagiwara, A.; Ito, H.; Nishimura, T. & Yamagishi, H. (2005). Monoclonal Antibody A7-Superparamagnetic Iron Oxide as Contrast Agent of MR Imaging of Rectal Carcinoma. *British Journal of Cancer,* Vol. 93, No. 1, pp. 131-136.

Torchilin, V. P. (2006). Multifunctional nanocarriers. *Advanced Drug Delivery Reviews,* Vol. 58, No. 14, pp. 1532-1555.

van Vlerken, L. E.; Duan, Z. F.; Seiden, M. V. & Amiji, M. M. (2007). Modulation of Intracellular Ceramide Using Polymeric Nanoparticles to Overcome Multidrug Resistance in Cancer. *Cancer Research,* Vol. 67, No. 10, pp. 4843-4850.

Vasir, J. K.; Reddy, M. K. & Labhasetwar, V. D. (2005). Nanosystems in Drug Targeting: Opportunities and Challenges. *Current Nanoscience,* Vol. 1, No. 1, pp. 47-64.

Wan, S. R.; Zheng, Y.; Liu, Y. Q.; Yan, H. S. & Liu, K. L. (2005). $Fe_3O_4$ Nanoparticles Coated with Homopolymers Of Glycerol Mono(meth)acrylate and Their Block Copolymers. *Journal of Materials Chemistry,* Vol. 15, No. 33, pp. 3424-3430.

Weissleder, R.; Moore, A.; Mahmood, U.; Bhorade, R.; Benveniste, H.; Chiocca, E. A. & Basilion, J. P. (2000). In Vivo Magnetic Resonance Imaging of Transgene Expression. *Nature Medicine,* Vol. 6, No. 3, pp. 351-354.

Weissleder, R. & Ntziachristos, V. (2003). Shedding Light onto Live Molecular Targets. *Nature Medicine,* Vol. 9, No. 1, pp. 123-128.

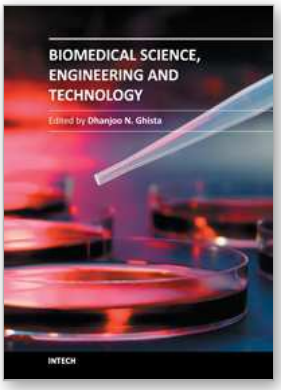
Wunderbaldinger, P.; Josephson, L. & Weissleder, R. (2002). Tat Peptide Directs Enhanced Clearance and Hepatic Permeability of Magnetic Nanoparticles. *Bioconjugate Chemistry,* Vol. 13, No. 2, pp. 264-268.

Yamaoka, T.; Tabata, Y. & Ikada, Y. (1994). Distribution and Tissue Uptake of Poly(ethylene glycol) with Different Molecular-Weights after Intravenous Administration to Mice. *Journal of Pharmaceutical Sciences,* Vol. 83, No. 4, pp. 601-606.

Yang, J.; Lee, C. H.; Ko, H. J.; Suh, J. S.; Yoon, H. G.; Lee, K.; Huh, Y. M. & Haam, S. (2007). Multifunctional Magneto-Polymeric Nanohybrids for Targeted Detection and Synergistic Therapeutic Effects on Breast Cancer. *Angewandte Chemie International Edition,* Vol. 46, No. 46, pp. 8836-8839.

Yoo, H. S.; Lee, E. A. & Park, T. G. (2002). Doxorubicin-Conjugated Biodegradable Polymeric Micelles Having Acid-Cleavable Linkages. *Journal of Controlled Release*, Vol. 82, No. 1, pp. 17-27.

Zhang, Y.; Kohler, N. & Zhang, M. Q. (2002). Surface Modification of Superparamagnetic Magnetite Nanoparticles and Their Intracellular Uptake. *Biomaterials,* Vol. 23, No. 7, pp. 1553-1561.

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