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Design and Application of Magnetic-based Theranostic Nanoparticle Systems

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Abstract

Recently, magnetic-based theranostic nanoparticle (MBTN) systems have been studied, researched, and applied extensively to detect and treat various diseases including cancer. Theranostic nanoparticles are advantageous in that the diagnosis and treatment of a disease can be performed in a single setting using combinational strategies of targeting, imaging, and/or therapy. Of these theranostic strategies, magnetic-based systems containing magnetic nanoparticles (MNPs) have gained popularity because of their unique ability to be used in magnetic resonance imaging, magnetic targeting, hyperthermia, and controlled drug release. To increase their effectiveness, MNPs have been decorated with a wide variety of materials to improve their biocompatibility, carry therapeutic payloads, encapsulate/bind imaging agents, and provide functional groups for conjugation of biomolecules that provide receptor-mediated targeting of the disease. This review summarizes recent patents involving various polymer coatings, imaging agents, therapeutic agents, targeting mechanisms, and applications along with the major requirements and challenges faced in using MBTN for disease management.

Keywords

magnetic nanoparticles; polymeric shell; imaging agents; theranostics; therapeutic agents; hyperthermia

1. INTRODUCTION

Theranostic nanoparticles that simultaneously deliver both imaging and therapeutic agents have gained significant attention for disease management in recent years. Disease management not only includes the highly specific diagnosis and treatment of the diseased cells, but also the monitoring of the drug delivery process and therapeutic efficacy [1]. Conventional nanoparticle systems have been previously used to achieve each aspect of disease management separately; however, multiple administrations may be required to fulfill all the necessary functions, which bring concerns of patient compliance and safety [2]. To overcome these limitations, theranostic nanoparticle systems that can perform all the aspects

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of disease management in a single setting have been developed over the last decade. In particular, magnetic-based theranostic nanoparticles (MBTN) are of great interest in disease management due to the numerous advantages of these materials possess when in the presence of a magnetic field, and is summarized in Fig. (**1**). Magnetic nanoparticles (MNPs) are multifunctional agents that can be used: (a) for site-specific magnetic targeting [3], (b) as negative contrast agents in magnetic resonance imaging (MRI) [4], (c) for hyperthermia treatment under alternating magnetic fields [5], and (d) in magnetic field-dependent controlled drug delivery applications [3] collectively, rendering MNPs as ideal candidates in the development of advanced theranostic systems.

MNPs are composed of ferromagnetic elements such as iron, cobalt, nickel, or their oxides and alloys [6]. MNPs made of iron oxide (magnetite Fe_3O_4 or magnemite Fe_2O_3) and gadolinium (chelated organic gadolinium complexes) [7] have been widely used as contrast agents in MRI for biological applications due to their ability to dissociate into iron and oxygen inside the body, which can safely be eliminated and utilized in metabolic and oxygen transport systems [8, 9]. When fabricated into nanoparticles of approximately 10 nm in diameter, iron oxide nanoparticles begin to exhibit a superparamagnetic behavior (superparamagnetic iron oxide nanoparticles, SPIONs) leading to improved dispersive properties in the absence of a magnetic field, and later guided to accumulate to the site of interest in the presence of a magnetic field, which is of great importance in targeted drug delivery applications [4]. MNPs also possess low cytotoxicity and have been approved by the United States Food and Drug Administration (FDA) for clinical MRI applications [9, 10]. Numerous studies have explored the potential of MNPs as therapeutic and diagnostic agents for the management of diseases such as cancers and cardiovascular diseases. The following sections briefly describe the coating materials, targeting mechanisms, imaging agents, and therapeutic agents used in MBTN, along with applications and design considerations of MBTN.

2. POLYMER COATINGS

Recent research has been intensely focused on finding suitable biodegradable and biocompatible polymers that can efficiently incorporate drug molecules or imaging agents for delivery, and be decorated with ligands for active targeting of the diseased tissue [7, 11-13]. Hydrophilic natural and synthetic polymers have been used as coating materials due to their ability to prevent particle aggregation, increase solubilization, and improve the stability of the particles [1]. Natural polymers such as dextran are gaining prominence in the field since MNPs coated with these polymers have shown improved biocompatibility and tend to stay in circulation for relatively longer periods of time [5]. FDA approved dextran-coated MNPs have already been used to image spleen, liver, and lymph nodes [1]. For instance, dextran-coated MNPs prepared by Tassa et al. [14] imparted both stability and additional functional groups for bioconjugation on the nanoparticle surface. The dextran coating also supported diagnostic imaging of the nanoparticles by MR, optical, and positron emission tomography (PET) imaging. In addition to dextran, chitosan is another common natural material gaining importance as a suitable coating for MNPs due to material's biocompatibility and the added functional groups, which can be utilized for bioconjugation [11]. Microencapsulated MNPs coated with chitosan were injected into the blood vessel leading to the kidney of a New Zealand white rabbit via an angiographic catheter *in vivo*, and they appeared to be detected in MRI of the kidney [15, 16].

In addition to natural materials, MBTN have also been coated with synthetic biodegradable or non-degradable polymers including poly(lactic-co-glycolic acid) (PLGA) [17], poly(glyceryl monooleate) (PGMO) [18], and poly(*N*-isopropylacrylamide) (PNIPAAm) [12]. PLGA has been widely chosen to coat MNPs by many research groups due to its

biocompatible nature and ability to provide the sustained release of encapsulated drugs and/or contrast agents throughout the polymer degradation time to ensure prolong treatment. For example, PLGA-magnetite particles prepared by Chattopadhyay et al. [17] showed sustained drug release for a period of nine hours and could also be used for MRI. Coating of iron oxide nanoparticles using a long chained PGMO as patented by Sahoo et al. [18] improved the aqueous stability of the particles without the use of surfactants. These nanoparticles were loaded with rapamycin (7.3% loading) or paclitaxel (7.5% loading) drugs that showed sustained release kinetics (100% rapamycin and 80% paclitaxel was released) over three weeks period. The released of drugs were therapeutically active and showed anti-proliferative effects on breast cancer cells *in vitro*.

Stimuli-responsive or 'smart' polymers, such as PNIPAAm, have also been used due to their thermo-responsive nature, which enables drug release when the temperature of solution is raised above the lower critical solution temperature (LCST) of the polymers. PNIPAAm copolymerized with acrylamide (AAm) and allylamine (AH) were developed in our laboratory and patented for their use to decorate MNPs [12, 19]. The PNIPAAm-AAm-AH decorated MNPs shrink and release the encapsulated drugs in response to increase in the surrounding temperature (~39 °C or above). Combinations of smart polymers, such as temperature-sensitive PNIPAAm and pH-sensitive chitosan, have also been used to formulate dual-responsive nanoparticles with combined properties of both the polymers [20]. As a result, these nanoparticles were shown to release the encapsulated drugs both at temperatures above the LCST and in an acidic environment, which are respectively beneficial attributes for cancer treatment since the tumor environment is characterized higher temperature and lower pH (< 7.2) when compared to healthy tissues [21]. While polymer coatings play an important role in drug delivery and release kinetics, they also provide valuable functional groups for bioconjugation, which can be utilized to provide targeting moieties for MBTN.

In order to treat multi-drug resistant tumors, multiple drug loading strategies have been developed using magnetic liposomes. The bilayered geometry of liposomes allows for the encapsulation of multiple therapeutic agents for multi-drug delivery [22]. For instance, hydrophilic drugs are incorporated in the hydrophilic core of the liposome, whereas hydrophobic drugs are loaded in the lipid bilayer of the liposome and amphiphilic molecules can be incorporated at the hydrophilic/hydrophobic interface of the liposome [23]. Amphiphilic poly(2,2,3,4,4,4-hexafluorobutyl methacrylate)-g-PEG monomethacrylate (PHFMA-*g*-PEGMA) has also been used to prepare magnetic micelles of ~100 nm diameter mainly for diagnosis of liver and spleen diseases. These nanoparticles showed high stability in water for up to 16 days and maintained sustained release of 5-fluorouracil for 40 hours. Further, these nanoparticles were successfully applied for *in vivo* MRI, which was evidenced by the dark contrast seen in the liver for up to 4 hours post-injection [24].

3. TARGETING STRATEGIES

A critical component in achieving an effective drug delivery and imaging tool is the ability to specifically target the diseased site and bypass healthy tissues. Targeting strategies for MBTN are met by various challenges such as selecting the appropriate target, methods to incorporate the correct targeting moieties, and strategies to avoid the rapid clearance of the delivery vehicles from the body [25]. The two basic mechanisms of targeting diseases are passive and active targeting, which is summarized in Fig. (**2**). Passive targeting is neither associated with the conjugation of antibodies nor influenced by any external forces. Instead, accumulation of the theranostic vehicle within the tumor site is accomplished by the enhanced permeability and retention (EPR effect) of tumor neovascularization [26]. The highly cluttered vasculature of the tumor tissue leads to a disorganized vasculature, and a

defective lymphatic system [27]. When this occurs, nanoparticles in the range of 10 to 500 nm in diameter with hydrophilic surfaces have shown enhanced accumulation within the interstitial space of the tumor [28]. Hydrophilicity is an important factor as it not only increases the circulation time of nanoparticle, but also prevents nanoparticle from being cleared by macrophages and plasma protein adsorption [25]. Passive targeting was employed by Yu et al. [29] using doxorubicin-loaded thermally crosslinked MNPs for cancer treatment and imaging. The stable and protein-resistant coating of PEG-based poly(TMSMA-*r*-PEGMA) helped in increased nanoparticle circulation time and preferential accumulation in tumor region by the EPR effect in an orthotopic mouse model of lung cancer. Passive targeting can also be achieved through utilization of tumor activated prodrug therapy [25] or a polymer directed enzyme prodrug therapy (PDEPT) [30]. In PDEPT, polymeric prodrug containing linkers for cleavage are first delivered, which are in an inactive state during systemic circulation. Next, a polymer enzyme conjugate is delivered that activates the prodrug at the cancer site. PDEPT was successfully utilized by Fainaro et al. [30], where they experimented with non-mammalian enzymes for passively targeting tumors. To achieve this end, a HPMA conjugate containing enzyme, β-lactamase, was used to activate the HPMA-copolymer-methacryloyl-glycine-glycine-cephalosporin-doxorubicin prodrug component at the tumor site. Preliminary *in vivo* studies showed good cytocompatibility of the PDEPT combination and a significant decrease in tumor growth following administration when compared to the control group. Although nanoparticles can be used for drug delivery via passive targeting, this process can be both time-consuming and less effective due to accumulation in other healthy organs as well [31]. Therefore, alternative, more specific routes of targeting to the sites of interest are greatly needed.

Unlike passive targeting, active targeting involves with either the conjugation of targeting ligands to nanoparticles or the use of external forces to guide the therapeutic vehicle to the diseased tissue [26]. A wide range of targeting moieties such as hormones, growth factors, proteins, peptides, and/or monoclonal and polyclonal antibodies have been used to direct MNPs to tumors. The choice of the targeting moiety is of great importance as it should be specific to the receptors over-expressed on the target cells. Such ligand-conjugated nanoparticles are engulfed by the receptor-mediated endocytosis process and destroyed intracellularly to release their therapeutic payload [32]. The receptor-mediated targeting is also useful for finding and destroying circulating or metastatic cells that express the receptors of interest [33]. Yao et al. [34] successfully conjugated A10 aptamers to thermally crosslinked MNPs to target prostate specific membrane antigens (PSMA) over-expressed by the prostate cancer cells. They observed that in media containing physiologic levels of folate, PSMA expression increased folic acid uptake approximately 2-fold over non-expressing cells. Further, Wang et al. [35] have patented their theranostic nanoparticles for active targeting, diagnosis, and therapy of cancers. Poly(acrylic acid) (PAA) was coated on the MNP surface and conjugated with pluronic F127 bound to folic acid, which is a targeting molecule. These nanoparticles were later loaded with Nile red and tested for their feasibility *in vitro*. The MNPs showed ~ 80% cytocompatibility with KB oral epidermoid cells. Time-dependent uptake of the nanoparticles by folic acid receptor-expressing KB cells was seen by receptor-mediated endocytosis. Further, *in vitro* MRI studies showed greater negative contrast among KB cells incubated with folic acid-conjugated MNPs than with non-conjugated MNPs. Folic acid has also been used by Kaaki et al. [36] to conjugate with doxorubicin-loaded and PEG-coated MNPs for targeted breast cancer therapy via release of encapsulated doxorubicin. The folic acid-conjugated MNPs showed good stability and greater accumulation within MCF-7 breast cancer cells *in vitro,* when compared to non-conjugated MNPs. Moreover, Kievit et al. [37] have developed multifunctional MNPs tagged with HER2/neu antibody, which successfully bound to neu-expressing mammary carcinoma cells in mice. These MNPs could also specifically bind to metastatic cells in lung,

liver, and bone marrow, thus demonstrating their potential in diagnosis and treatment of metastasized cancer.

In addition to receptor-mediated targeting, active targeting by the use of external forces like magnetic fields has been investigated. Magnetic targeting involves the delivery of MNP locally, which can then be guided to the diseased site using an external magnetic field. MNPs become magnetized upon application of a magnetic field, and are quickly demagnetized when the magnetic field is removed due to superparamagnetic behavior [4]. Magnetic targeting is advantageous and more effective than passive targeting as rapid clearance of nanoparticles at specific disease sites by mononuclear macrophages can also be avoided [38]. Alexious et al. [39] recruited MNPs in the region of squamous cell carcinoma created in rabbits by using an external magnetic field of strength 1.7 T. Another study conducted by Chertok et al. [40] imaged brain tumors non-invasively with MRI by concentrating MNPs at the tumor site by locally applied external magnetic field of about 4 T. After effective targeting using MBTN, imaging of the delivery vehicles to highlight the diseased sites could be accomplished. The following section briefly describes the imaging agents used in the formulation of the MBTN.

4. IMAGING AGENTS

Imaging agents in theranostic nanomedicine play an important role in the diagnosis of a disease. Biodistribution, target accumulation, and pharmacokinetic activity of the nanomedicine for disease management can be visualized non-invasively and in real-time by the use of imaging agents [4]. The primary imaging agent used in the MBTN is SPION as it has been widely used as T2 negative contrast agents in MRI. Several SPION-based nanoparticles have been approved by the FDA for human use (Table 2) [41]. Examples include Feridex or ferumoxides as imaging agents for liver lesions; Combidex or ferumoxtran-10 for imaging of ‘hidden’ prostate cancer lymph node metastases; and Feraheme or ferumoxytol for treating iron deficiency anemia in chronic kidney diseases [10]. Further, manganese (Mn) and gadolinium (Gd)-based MRI contrast agents, such as multifunctional MnO and PEG functionalized Gd_2O_3 nanoparticles [42-44], have also been researched for *in vitro* and *in vivo* imaging applications, later was approved by FDA for human use. Gd-diethylenetriaminepentaacetic acid (Gd-DTPA) complexes with anti-fibrin antibodies have been utilized for MRI, which proved the capability of these nanoparticles to enhance the MRI signal contrast over the clot surface [45]. Moreover, Gd-DTPA-bisoleate and Gd-DTPA-phosphatidyethanolamine were synthesized and their relaxivities were studied, and showed improved ion and particle relaxivity [46].

Contrast agents for optical imaging, PET or computed tomography (CT), have also been incorporated in MBTN to provide multi-modality imaging capabilities for enhanced and more accurate imaging of diseases and is summarized in Fig. (**3**). A multi-modality imaging approach has several advantages over a single modality system [47]. MRI provides exceptional tissue contrast, penetration depth, and high spatial resolution, whereas fluorescence imaging provides extremely high sensitivity and can be used for molecular imaging [25]. The most popular example of fluorescent agents used in optical imaging is metal semiconductor quantum dots (QD). QDs have remarkable optical properties compared to other fluorescent dyes [48]. QDs can emit light in the spectrum ranging from visible to near-infrared region, depending on their size or material composition like CdSe, ZnS, and PbSe [25]. When QDs are used with MNPs, they are also called as magnetic QDs, which can be either heterodimers or homogeneous dispersion of QDs within MBTN [49]. Polyethyleneimine-capped QD were grafted on magnetite nanorings to develop magneto-fluorescent nanoprobes by Fan et al [50]. In addition, Koole et al. [51] synthesized Gd-based lipid-coated silica nanoparticles with QD core as a new contrast agent platform for

multimodality imaging. Moreover, fluorophores such as Alexa Fluor 647 have also been used along with MNPs for the applications in MRI and fluorescent imaging. Zhang et al. [52] patented their multifunctional nanoparticles for labeling and imaging of T cells. Further, gold has also been used extensively along with MNPs for multifunctional imaging applications. They conjugated Alexa Fluor 647 and major histocompatibility complex (MHC) as a targeting molecule to the PEGylated iron oxide nanoparticles to specifically label T cells via MHC. Jiang et al. [53] developed bifunctional Fe_3O_4-Ag heterodimer nanoparticles of tunable sizes with high yield under mild conditions. The heterodimers also maintained high magnetic moments of Fe_3O_4. The macrophage cells labeled with these heterodimers were magnetically manipulated and imaged with two-photon fluorescence microscopy. Shi et al. [54] also anisotropically grew PbSe nanocrystals on Au-Fe_3O_4 hybrid nanoparticles that are useful for magnetic-based targeting, delivery, cell separation, MRI, and fluorescence-based labeling applications.

PET isotopes such as ^{18}F or ^{64}Cu and fluorescent dye VT680 have also been conjugated or encapsulated into the MBTN using azide-alkyne cycloaddition ‘click’ chemistry to enhance the sensitivity and reduce the dose required for clinical use [55]. Several other visible and near infrared fluorescent dyes, such as DiI/DiR, have been encapsulated in MBTN like poly(acrylic acid)-coated MNPs [56]. Moreover, bombesin was conjugated to dextran-coated MNPs and N-acetylhistidine-glycol chitosan nanoparticles for MRI application [57, 58]. Some other examples include rhodamine/FITC-labeled paramagnetic nanoparticles [59] and Cy5.5-labeled PEG/chitosan-coated MNPs [60]. However, currently used fluorescent tags are known to either be toxic or exhibit photobleaching. We have developed and patented a family of biodegradable photoluminescent polymers (BPLPs) that are inherently fluorescent without conjugating any organic dyes or QDs [61, 62]. BPLPs are completely degradable, biocompatible, and display superior photoluminescent properties such as high quantum yield, photobleaching resistance, and tunable emission up to near infrared region when compared to currently used fluorescent tags [63]. We are currently developing BPLP-conjugated MNPs (BPLP-MNPs) for prostate cancer management as shown in Fig. (**4**). Our BPLP-MNPs provide dual-imaging (optical imaging and MRI) and dual-targeting (biomaterial-mediated targeting and magnetic targeting) capabilities. BPLP coating enables prostate cancer cell-selective uptake depending on its hydrophilicity level. We observed that hydrophilic BPLP-MNPs were taken up more by metastatic $PSMA^-$ PC3 cells, whereas hydrophobic BPLP-MNPs were taken up more by non-metastatic $PSMA^+$ LNCaP cells. The development of BPLP-MNPs may address the specific targeting, toxicity, and photobleaching concerns when using organic dyes and cytotoxic QDs.

5. THERAPEUTIC AGENTS

Following disease diagnosis, a pivotal role of the MBTN is to treat the disease by either hyperthermia via alternating magnetic fields or releasing therapeutic agents as shown in Fig. (**5**). MBTN can be used without therapeutic agents to kill the heat-susceptible cancer cells by providing heat to the tumor region [5]. This is achieved by applying an external rotating or alternating magnetic field following the nanoparticle injection, which causes the MNPs to vibrate and generate heat to ultimately destroys the cancer cells [64]. In addition, MBTN have been used to deliver a wide variety of therapeutic agents ranging from chemotherapeutic drugs to peptides and genes [7, 8]. Chemotherapeutic agents are more frequently loaded into the MBTN for the treatment of various tumors. For example, anticancer drug doxorubicin was loaded in liposomal nanoparticles containing dextran-coated MNPs as magneto-fluorescent agents for cancer chemotherapy [65]. Moreover, doxorubicin-loaded, oleic acid-functionalized, and pluronic F-127-coated iron oxide nanoparticles were developed and patented by Labhasetwar et al. [66] for MRI and combinational anti-cancer therapies. These nanoparticles not only have a relatively higher

T2 relaxivity compared to Feridex IV, but also contain the capability of accommodating high payloads of multiple drugs (95% and 85% loading of paclitaxel and doxorubicin, respectively). The released drugs from these nanoparticles were effective in killing cancer cells and reducing tumor growth significantly. Further, novel biocompatible and biodegradable theranostic nanoparticles capable of targeted chemotherapeutic drug delivery, MRI, and optical imaging were also synthesized by Santa et al [56]. In this study, PAA-coated MNPs were encapsulated with a near infrared dye and a chemotherapeutic drug (taxol) to serve the dual functions of diagnosis and treatment. Similarly, poly(ε-caprolactone) (PCL)-coated MNPs encapsulating two anticancer drugs, Gemcitabine and Cisplatin, were prepared by Yang et al. [67], which could potentially be used for targeted drug delivery for cancer treatment. Other drugs used to date in the MBTN formulations include epirubicin [68] and mitoxantrone [69].

Besides chemotherapeutic reagents, MBTN have also been used to deliver bioactive molecules including double-stranded DNA (dsDNA), small interfering RNA (siRNA), and proteins. For instance, the MBTN containing both dsDNA and covalently bonded doxorubicin molecules have been prepared for cancer treatment [70]. Recent research has also been focused on the development of polymer-coated iron oxide nanoparticles as agents for transfection and as DNA vaccine carriers [71]. Such nanoparticles can be used as effective DNA carriers for the transfection of cells and also as agents for vaccination. MNPs coated with polymers or proteins have shown success as transfection agents. Further, surface modified silica-iron oxide composite nanoparticles have also been used for delivering DNA to the targeted cells [71]. For gene delivery, stable lentiviral complexes were developed by Mykhaylyk et al. [72] using polyethylenimine-capped silica-iron oxide nanoparticles. Moreover, the MBTN have also been synthesized for small interfering RNA (siRNA) delivery. To achieve this end, Lee et al. [73] conjugated the siRNA onto the surface of the iron oxide nanoparticles along with the targeting moieties and fluorescent dyes for targeted siRNA delivery and fluorescence imaging. Another innovative example of siRNA delivery is the hollow manganese oxide nanoparticles prepared by Bae et al. [42] which was surface functionalized using 3,4-dihydroxy-L-phenylalanine and incorporated therapeutic siRNA for simultaneous cancer diagnosis and treatment. In addition, protein delivery has also been implemented using MBTN. For example, Chertok et al. [74] synthesized β-Galactosidase-loaded heparin-coated MNPs for MRI and protein delivery to diagnose and treat brain tumor lesions. The permeability to biological membranes imparted by the polyethylenimine-modified protein, together with magnetic targeting will help in selective accumulation of the nanoparticles at the tumor site.

6. APPLICATIONS OF MBTN

MNPs have been used in numerous applications, which can be categorized in three major application fields: (a) imaging (contrast agents for MRI), (b) therapy (chemotherapy via controlled drug release and hyperthermia via heat generation in alternating magnetic fields), and (c) cell separation (cell labeling/tracking and isolation using magnetic force). These are the mostly reported applications of MNPs, which have been covered in following sections.

6.1. Imaging

Nanotechnology has opened doors to new imaging agents that help not only in detection but also aid in management of diseases like cancer and cardiovascular diseases throughout the treatment. With imaging results, it is possible to determine if the treatment should be altered or terminated depending on the treatment efficacy or response of the disease [25]. Contrast agents serve as a powerful tool for characterization at the cellular and sub-cellular level. Due to the presence of MNPs, the MBTN are used as negative contrast agents in MRI. MNPs such as Fe_3O_4, Gd, and Mn have high molar T2 relaxavities [75]. High spatial resolution

provided by MRI and enhanced negative contrast provided by MNPs, when used with T2 weighted pulse sequences, make MRI attractive imaging modality for disease detection [28]. High spatial resolution of MRI and target specificity of MBTN allows the imaging of tumors as small as 2-3 mm in clinical applications [22]. Reddy et al. [76] tracked the migration of human bone derived mesenchymal stem cells in rabbit ischemic brain using chitosan-coated MNPs with MRI, which was also confirmed from several histological studies. In addition, Branca et al. [77] detected pulmonary micro-metastases with the help of luteinizing hormone-releasing, hormone-conjugated MNPs and MRI in mice bearing breast adenocarcinoma cells. Further, MBTN that have gained significant clinical attention, are iron oxide nanoparticles coated with either dextran or liposomes. Recent clinical trials have tried to image MNPs after administration *in vivo*. Clinical studies on prostate cancer patients by Harisinghani et al. [78] using lymphotropic MNPs, showed that the lymph node metastases could be accurately identified by high-resolution MR imaging of the MNPs. Phase I clinical trials on cancer patients using magnetic fluids bound to anticancer drugs such as epirubicin have shown that iron oxide could be guided to the region of interest using an external magnetic field and these fluids showed minimal toxicity *in vivo* [79].

MBTN have many times been used as dual-modality imaging agents. Optical imaging is often coupled with MRI, because optical imaging provides extremely high sensitivity and can be used for molecular imaging, thereby is widely used for *in vivo* applications [49]. A combination of MRI and fluorescence imaging was successfully achieved by Lee et al. [1] for the diagnosis of prostate cancer. Use of QDs and other fluorescent tags along with iron oxide has become a common multi-modal technique. Franck et al. [80] demonstrated the use of covalently attached fluorescent dye and MNPs in a nanoparticle formulation as a dual-imaging modality. Further, in another study, Li et al. [81] concluded that use of QDs was advantageous, as they exhibited bright fluorescence and did not undergo photobleaching as did the organic dyes.

6.2. Chemotherapy

With increasing prevalence rates of cancer, the management of cancer has become one of the leading research areas to find more effective imaging and therapeutic modalities. Traditional chemotherapies involve delivery of antineoplastic drugs to the cancer patients. Due to the non-specificity of these drugs, they manifest various side effects as a result of systemic toxicity [25]. The development of MBTN can also play a significant role in cancer management, due to their multi-functional capabilities. Using MBTN, systemic toxicity can be avoided by delivering the drugs only to the cancer cells via active/magnetic targeting while sparring healthy tissue and/or cells [25]. The dual-targeting mechanism (combination of receptor-mediated and magnetic targeting) may greatly reduce the toxicity of chemotherapeutic reagents by targeting cancer cells only and localizing of these drugs at the tumor site. Further, the chemotherapeutic drugs can be either loaded into the polymer shell or directly coated on the MNPs surface of MBTN. For example, Sun et al. [82] demonstrated extended particle retention and decreased survival rate in tumor cells when treated with methotrexate- and chlorotoxin-conjugated MNPs. Moreover, Yu et al. [29] developed doxorubicin-loaded thermally crosslinked MNPs that were administered intravenously into the tumor bearing mice to study the multi-functionality of the particles. The nanoparticles preferentially accumulated in the tumor region within 4.5 hours of the administration and were removed from the body within 24 hours. The nanoparticles showed their therapeutic effect within 12 hours of injection and a significant decrease in tumor size was noticed within 19 days of the treatment. Further, the MR imaging showed a strong negative contrast with the darkening of tumor region in the T2-weighted images, indicating accumulation of the nanoparticles. The results showed the potential of these theranostic MNPs for use in diagnosis (MRI) and treatment (drug release) of cancers.

6.3. Hyperthermia

Hyperthermia is a treatment in which high temperatures (> 41°C) are applied to kill cancer cells, as they are more sensitive to high temperatures than healthy cells [5]. The metallic and magnetic properties of MNPs make them suitable for hyperthermia treatment [83]. Upon administration and targeting of MBTN to cancer site, an alternating magnetic field can be applied, in which MNPs vibrate and generate thermal energy as a result of absorption of large amounts of magnetic energy by hysteresis loss [5]. Heat generated from the MNPs is affected by several factors, such as magnetic properties, particle size, amplitude and frequency of applied magnetic field, and cooling rate of blood [84]. Thus, by regulating these factors, the heat generation from MNPs can be controlled. However, an optimal hyperthermia effect can be achieved with 10 kA/m amplitude and 400 kHz frequency [84]. The following is an example of the MBTN used for hyperthermia: Poloxamer, chitosan, alginate, and polyvinyl alcohol hydrogels loaded with MNPs were formulated by Renard et al. [85] and implanted in human cancer tumors xenografted in mice for hyperthermia treatment. In another study, Tseng et al. [86] proved that the viability of cancer cells significantly reduced when hyperthermia treatment was conducted using MNPs.

Hyperthermia has been used with other forms of therapy including chemotherapy to provide more effective treatment. At high temperatures, cancer cells become more vulnerable and respond to chemotherapeutic drugs or radiation effectively in an accelerated fashion [5]. Therefore, the combination of two therapies such as hyperthermia and chemotherapy or hyperthermia and radiation therapy would result in better treatment efficacies. For example, Wang et al. [87] synthesized MNPs encapsulated As_2O_3 nanoparticles for treating nude mice bearing xenograft human hepatocarcinoma with both thermal and chemo therapy. The application of two therapies in unison showed significant inhibitory effect over tumors in comparison to controls.

6.4. Cell separation/isolation

Applications of magnetism in cell separation have emerged in the last decade as an important driving force to separate magnetic from non-magnetic complexes in the cell mixtures. Magnetic cell separation permits isolation of specific cell types from crude samples such as blood, bone marrow, and cultivation media. The cell separation and purification process primarily consists of three steps: (a) incubating MBTN/MNPs coated with antibodies against interested cells with mixed cell suspension; (b) separating magnetic complex containing cells attached to MBTN/MNPs using an external magnetic force and washing it several times to remove contaminants; finally (c) either use the complexes directly or separate the cells from magnetic label, depending on the final application [88]. Various magnetic particles have been developed for use in separation processes including purification and immunoassays [75]. Cell separation with magnetic colloidal labels [89] and carbohydrate-coated (e.g., cellulose, sucrose) magnetic beads [90] have also been studied. In all cell isolation applications, MNPs are used to target and isolate a particular cell type using a ligand-receptor based mechanism leading to more specific cell isolation. For example, Xu et al. [91] isolated cancer cells from fresh whole blood using anti-HER2-conjugated amphiphilic polymer-coated iron oxide nanoparticles. However, conventional MNPs do not support cell adhesion and cell growth on their surface. Another problem with the conventional MNP-based cell isolation system is that they are not loaded with proteins or growth factors for cell enrichment and differentiation.

7. CURRENT & FUTURE DEVELOPMENTS

The primary goal in designing a MBTN is to create an advanced medical tool, which can detect and treat diseases in a single setting. Current developments of the MBTN are mainly

focused on combining a therapeutic agent and an imaging agent to achieve dual-functionality. MBTN can be made more effective by incorporating additional functionalities to achieve multiple actions required for a disease management in a single setting. Future developments of the MBTN will consist of active targeting capabilities and/or multi-modal imaging or therapeutic capabilities in conjunction with the current functionalities. The incorporation of multiple functionalities in a single system may raise several design consideration issues. There are several factors related to nanoparticles, which limit the development of an effective MBTN. Nanoparticle properties such as size, shape, surface charge, and surface modification are important factors to consider while designing MBTN with maximum effect at the target tissues while minimizing its clearance and toxicity to healthy tissues. Nanoparticle size plays a critical role in maintaining the magnetic properties and the rate of internalization by the target cells [92]. An optimum nanoparticle size between 10 to 100 nm prevents the removal of nanoparticles from circulation and enables them to pass through small capillaries. The size and shape of the particles can be manipulated by surfactant concentrations and types [93], while uniform sizes can be maintained by stirring the ferrofluid during preparation under constant temperature [94]. Further, a surface charge (zeta potential) of 10 to 30 mV or −10 to −30 mV is optimum to achieve a stable nanoparticle suspension with minimal aggregation [95]. Polymer coatings and surface modifications can also affect the surface charge of the MBTN. For example, MNPs charged neutrally, positively and negatively were achieved by Villanueva et al. [96] using dextran, aminodextran, and heparin, respectively. The authors concluded that surface charge of the nanoparticles can play a major role in cellular uptake. The aminodextran-coated MNPs will be useful for hyperthermia due to their rapid accumulation within desired cells. The cationic charge on dextran-coated MNPs assists in uptake by HeLa cells following which live tracking of the cells can be carried out, whereas heparin-coated MNPs proved to be toxic to the tested cells. Hydrophobic MNP surfaces can also be converted into hydrophilic by surface modification to prevent rapid clearance of particles from circulation. For instance, pullulan modified MNPs synthesized by Gupta et al. [92] resulted in increased hydrophilicity, reduced cytotoxicity, and better cellular uptake of particles.

Although MBTN have gained increased attention for biological and biomedical applications, it is critical to obtain more understanding on particle size control, *in vivo* particle degradation, distribution, and intracellular trafficking before it can move to clinical applications. Magnetic properties of MBTN are associated with the chemical composition, size, and morphology of the particles. For the efficient use of MBTN in targeting, imaging, and therapy, the particle size should be appropriate to allow attraction by magnetic field; the strength of magnetic field should be considerably strong in order to localize particles in the desired area; and finally particles may be injected in area accessible to tumor vasculature that would avoid reticulo-endothelial system. *In vivo* degradation of MBTN is mainly dependent on the dissociation of MNPs and the degradation of polymer coatings. Therefore, the polymer of choice should be highly biocompatible and biodegradable to avoid toxic effects to the other healthy organs. The chosen polymer should also provide functional groups for bioconjugation of targeting ligands to make MBTN site-specific. Further, understanding of the relaxivity of MBTN is highly essential for MRI and hyperthermia applications. Relaxivity is dependent not only on magnetic properties but also on the applied magnetic field strength, temperature, and the medium in which the measurements are carried out. Equally as important, advances in imaging and diagnostic tools are also critical to realize the full potential of MBTN for disease management. Impressive developments in the nanotechnology and biomaterials fields have provided numerous tools and techniques to manipulate the nanoparticle properties. With the increasing rate of advances in nano-/bio-materials and the success of MNP-based nanoparticles in biomedical field, the clinical use of MBTN can be foreseen.

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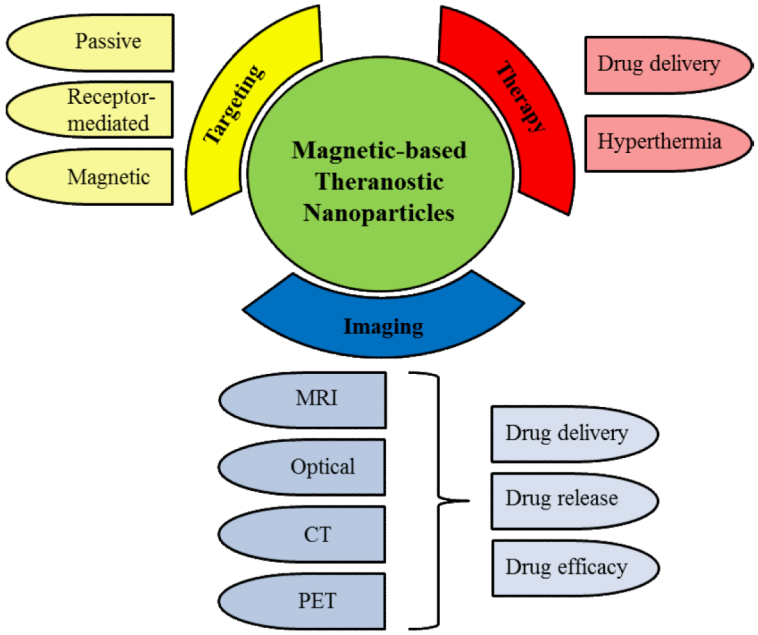

Figure 1.
Attributes and applications of MBTN.

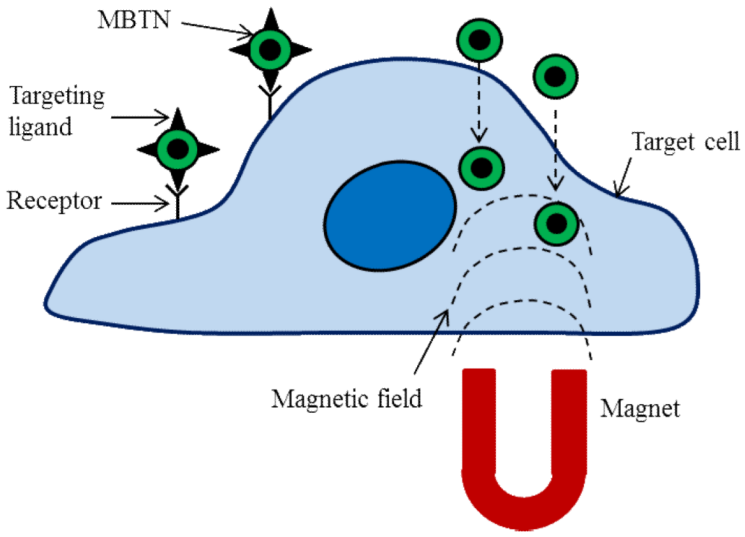

Figure 2.
Targeting mechanisms of MBTN emphasizing on receptor-mediated and magnetic targeting.

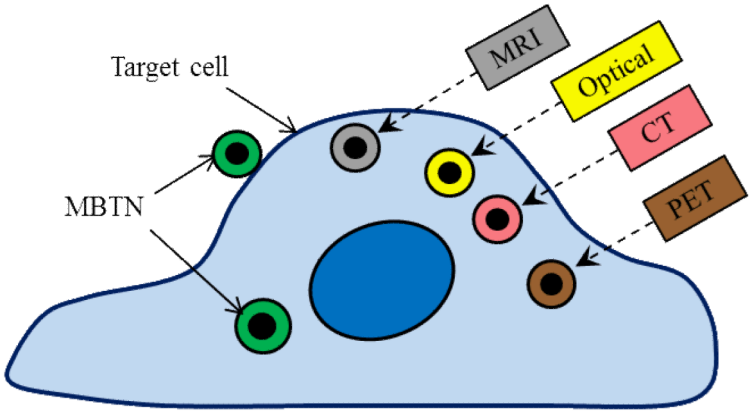

Figure 3.
Imaging modalities used for MBTN.

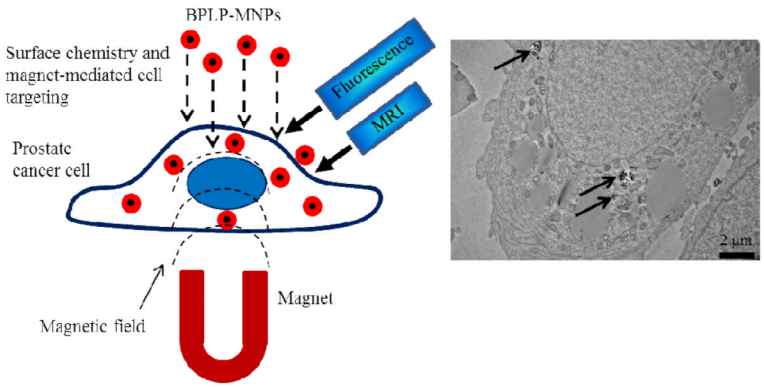

Figure 4.

Prostate cancer cell-specific dual-imaging enabled targeted BPLP-MNPs. Schematic representation of proposed working of system (left); and transmission electron microscopy image of cellular uptake of BPLP-MNPs (indicated by arrows) by prostate cancer cells (right).

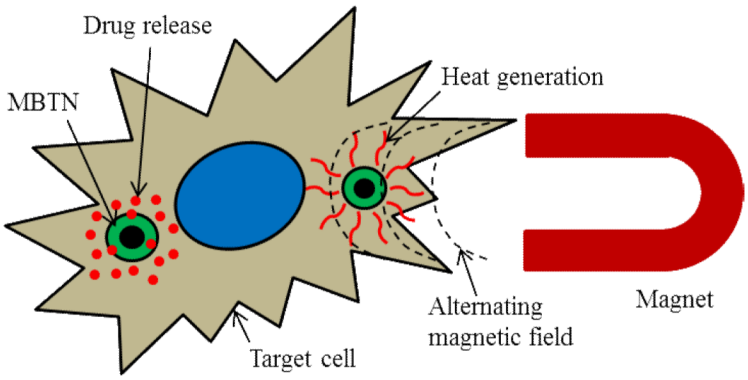

Figure 5.
Therapeutic action of MBTN showing drug release and hyperthermia treatment.

Table 1

Core, shell, imaging, therapeutic, and targeting materials used in MBTN along with application of MBTN.

Core	Shell	Imaging agent	Therapeutic agent	Targeting	Applications	Ref
SPION	PNIPAAm-AAm-AH	SPION	BSA	Magnetic	Temperature-dependent drug release	12
SPION	Chitosan-PNIPAAm-*N,N*-DMAAm	SPION	Doxorubicin	Magnetic	Temperature-dependent drug release	20
SPION	PEG	SPION	Doxorubicin	Active (folic acid)	Anti-cancer drug delivery, hyperthermia, MRI	36
Ferro fluid	-	SPION	Mitoxanthrone	Magnetic	Locoregional cancer treatment	39
Manganese oxide	PEI	Manganese oxide	siRNA	Active (Herceptin)	MRI, siRNA delivery	42
Gadolinium oxide	PEG	Gadolinium oxide	Rhodamine	Passive	MRI	43
SPION	PEI-QDs	SPION/QDs		Magnetic	Dual-modality imaging	48
SPION	PAA	SPION/Di-alkylcarbocyanine fluorescent dyes	Taxol	Active (folic acid)	MRI and optical imaging	54
SPION	Glycol chitosan	SPION/Cy5.5	-	Active (Bombesin)	Prostate cancer-specific delivery, imaging	56
SPION	PEGylated chitosan	SPION	-	Active (Chlorotoxin)	Imaging, brain tumor targeting	58
SPION	PCL	SPION	Gemcitabine	Magnetic	Anti-cancer drug delivery	67

Table 2

FDA approved MRI contrast agents.

Material	Commercial name	Application	Status	Ref
SPION	Feridex IV/Ferumoxides	Liver MRI	Withdraw in 2008	41
SPION	Resovist/Cliavist	Liver MRI	Withdraw in 2009	41
SPION	Combidex/Ferumoxtran-10	Prostate cancer lymph node metastases MRI	Withdraw in 2007	41
SPION	Feraheme/Ferumoxytol	Iron deficiency anemia treatment	Pending	41
SPION	Lumirem/Gastromark	MRI of Gastrointestinal lumen	Approved in 1996	41
SPION	Clariscan/Feruglose	MR angiography, tumor microvasculature MRI	Development discontinued	41
Gadolinium	Gadodiamide/Omniscan	Cranial and spinal MRI	Approved	44
Gadolinium	Gadobenic acid/Multihance	MRI contrast agent	Approved	44
Gadolinium	Gadopentetic acid/Magnevist	MRI of blood vessels and intracranial lesions	Approved	44
Gadolinium	Gadoteridol/Prohance	MRI of central nervous system	Approved	44
Gadolinium	Gadofosveset/Vasovist	MR angiography agent	Approved	44
Gadolinium	Gadoversetamide/OptiMARK	Brain, spine, liver MRI	Approved	44
Gadolinium	Gadoxetic acid/Eovist	Liver MRI	Approved	44