8-2017

Magnetic Nanoformulations for Prostate Cancer

Pallabita Chowdhury
University of Tennessee Health Science Center

Allison M. Roberts

Sheema Khan
The University of Texas Rio Grande Valley

Bilal B. Hafeez
The University of Texas Rio Grande Valley, bilal.hafeez@utrgv.edu

Subhash C. Chauhan
The University of Texas Rio Grande Valley

See next page for additional authors

Recommended Citation

Chowdhury, P., Roberts, A. M., Khan, S., Hafeez, B. B., Chauhan, S. C., Jaggi, M., & Yallapu, M. M. (2017). Magnetic nanoformulations for prostate cancer. Drug discovery today, 22(8), 1233–1241. https://doi.org/10.1016/j.drudis.2017.04.018

HHS Public Access

Author manuscript

Drug Discov Today. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Drug Discov Today. 2017 August ; 22(8): 1233–1241. doi:10.1016/j.drudis.2017.04.018.

Magnetic Nanoformulations for Prostate Cancer

Pallabita Chowdhury, **Allison M. Roberts**, **Sheema Khan**, **Bilal B. Hafeez**, **Subhash C. Chauhan**, **Meena Jaggi**, and **Murali M. Yallapu***

Department of Pharmaceutical Sciences and Center for Cancer Research, College of Pharmacy, The University of Tennessee Health Science Center, Memphis, Tennessee 38163, USA

Abstract

Magnetic nanoparticles (MNPs) play a vital role for improved imaging applications. Recently, a number of studies demonstrate MNPs can be applied for targeted delivery, sustained release of therapeutics, and hyperthermia. Based on stable particle size and shape, biocompatibility, and inherent contrast enhancement characteristics, MNPs have been encouraged for pre-clinical studies and human use. As a theranostic platform development, MNPs need to balance both delivery and imaging aspects. Thus, this review provides significant insight and advances in the theranostic role of MNPs through the documentation of unique magnetic nanoparticles used in prostate cancer, their interaction with prostate cancer cells, *in vivo* fate, targeting, and biodistribution. Specific and custom-made applications of various novel nanoformulations in prostate cancer are discussed.

Keywords

Prostate cancer; Magnetic nanoparticle; Imaging; Drug delivery; Therapy

Introduction

Prostate cancer is the most frequently diagnosed malignancy in men [1]. According to the World Health Organization (GLOBOCAN 2012), 1.1 million cases of prostate cancer were recorded in 2012, accounting for 15% of all cancer cases in men [2,3]. France (~227 cases per 100,000) and Norway (~129 cases per 100,000) have the highest rates of prostate cancer, respectively, while the United States has the 14th highest prevalence rate with approximately 98 cases per 100,000. Although cancer death rates are declining, the management of the disease remains very expensive and painful. Therefore, it is highly crucial to ascertain the progress of the disease and identify better diagnosis, imaging and treatment modalities.

To whom correspondence should be addressed: Dr. Murali M. Yallapu Department of Pharmaceutical Sciences, 881 Madison Avenue, Suite 447, Memphis, Tennessee 38163, Phone: (901) 448-7313, Fax: (901) 448-3446.

Author Contributions Conceived idea and wrote the paper: MMY. Contributed writing parts of article: PC, AMR, BBH and SK. Participated in extensive editing and provided intellectual conceptual about magnetic nanoparticles: SCC, MJ and MMY.

Nanotechnology has demonstrated to be one of the most prominent developments in materials sciences, pharmaceutical, and medicine. This is supported by more than 65,000 reported studies that utilize/reference nanotechnology on PubMed [4]. Nanotechnology is generally referenced as a material science dedicated to the branches of science: engineering and medicine. The functional unit of nanotechnology, or nanoparticles, is frequently characterized by its size, measured on the nanometer scale. According to the National Institute of Health (Nanotechnology Safety and Health Program at the Division of Occupational Health and Safety), nanoparticles are defined as nanoscale materials whose dimensions are less than 100 nm. In fact, the smaller size and high surface to volume ratio are what provide nanoparticles with their unique physicochemical properties. Over the years, different versions of nanotechnology, from natural resources to various synthetic routes, have been generated based on the specific demand. Poly(lactic-*co*-glycolic acid) (PLGA) and poly(ε-caprolactone) (PCL) are the most commonly used biodegradable and biocompatible polymers in a number of medical applications.

Magnetic nanoparticles (MNPs) (Fig. 1) are a class of nanoparticles extensively used from basic biomaterial research to pre-clinical and clinical trials due to the ultra-small nanometer size, inherent magnetic resonance imaging (MRI) characteristics, superior biocompatibility, flexible surface chemistry, and lack of systemic toxicities. These unique properties are what gained the interest of scientists for evaluating the nanocarrier potential of MNPs in various therapeutic aspects for different types of cancers, including prostate cancer. In addition, magnetic nanoparticle degradation results in the production of iron ions, which exist abundantly in the human body, further indicating the safety perspective. As a result, among all types of magnetic nanoparticles, iron oxide based magnetic nanoparticles (Feridex I.V.®, Feraheme®, Endorem®, Lumiren®, and Gastromark®) have been approved for human clinical studies due to an extended safety profile and greater serum bioavailability (up to 30 hrs).

The main focus of our laboratory is dedicated to the fabrication and characterization of magnetic nanoparticles followed by testing their drug/biomacromolecular compositions in biologically and clinically relevant *in vitro* and *in vivo* cancer model systems [5–10]. As part of our continuous research efforts, we aim to focus on the role of magnetic nanoparticles in prostate cancer therapeutics. Therefore, this review is focused on demonstrating the application of magnetic nanoparticles in the treatment, diagnosis, and targeting of prostate cancer.

Magnetic Nanoparticles

Magnetic nanoparticles are a class of nanoparticles that can be applied to a wide number of biomedical applications, such as drug delivery, imaging, diagnosis, biosensing, bioseparation, targeting, and so on. A number of research/review articles have discussed the development of nanoparticles in biomedical applications [11–14]. Among these nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs) are not only approved by the Food and Drug Administration (FDA) but are also widely used as contrast agents for bowel, liver, and spleen imaging due to inherent biocompatibility and unique magnetic characteristics. These formulations are generally synthesized through the co-precipitation

approach in the presence of dextran polymer or a suitable stabilizing agent. However, this approach leads to broad particle size distribution and low crystallinity. Non-hydrolytic methods are used to produce high crystalline iron oxide nanoparticles with uniform size distribution. Since this review's focus is to delineate the application of magnetic nanoparticles in prostate cancer, we have not considered the extensive preparative synthetic procedures of magnetic nanoparticles, but this information can be found elsewhere [11–14]. Therefore, in this section, we will focus more on the creation of stable magnetic nanoparticle composition (regulating size and shape of magnetic nanoparticles) that is responsible for absorption, distribution, metabolism, and excretion (ADME). All these four criteria can influence the level of exposure of magnetic nanoparticles to the tissues and thus the overall activity of formulation.

Poly(ethylene glycol) or Pluronic® polymers are considered to be prime stabilizers for most magnetic nanoparticles, due to enhanced circulation, minimized RES recognition, and improved targeting of tumors by the enhanced permeation and retention (EPR) effect [11,15]. Additionally, polymers such as PVA [16,17], PVP [18], starch [19], and chitosan [20] have been successfully employed for this purpose. PLGA, PCL and their iron oxide nanoparticle-based combinations have been widely explored as cancer drug delivery systems [21–23]. Dextran is a universal stabilizer and approved FDA formulation of magnetic nanoparticle for imaging applications. Many dextran-based formulations are highly employed in proof-of-concept to clinic.

Albumin is another versatile coating for generating stable magnetic nanoparticle formulation as a delivery carrier [24]. Similarly, dendrimer [25,26], polymersomes [27,28] and Pluronic® polymers [5,7,27,29] are suitable for stabilization. Albumin is another commonly used and clinically relevant stabilizing agent seen in various drug nanoparticle or drug formulations. In a single step, magnetic nanoparticles decorated by albumin, which is cross-linked using glutaraldehyde, were suitable for providing a uniform nanoparticle system for prostate cancer [24,30]. Similarly, liposome [15,31,32], hybrid [33], and dual/multilayer can serve as layers for stable nanoformulations. Stimuli responsive polymer coating on magnetic nanoparticles can also induce controlled drug release characteristics [34,35]. In addition to the conventional coating approach, nanohybrid materials with a magnetic core and gold coating are very helpful in maintaining inherent characteristics of the iron core [36]. Table 1 demonstrates the critical role of nanoparticle surface coating in drug delivery application.

Delivery of therapeutics to prostate cancer

Upon diagnosis of prostate cancer, treatment options available are surgery, cryotherapy, radiation therapy, hormone therapy, vaccination and bone-directed treatment, depending on the stage of disease. These therapies are all moderately successful for the treatment of prostate cancer. Patients diagnosed with localized prostate cancer may not only experience therapy relapse, but also carry the major risk of developing advanced stage or androgen-independent prostate cancer. At this stage, chemotherapy is one of the most widely used treatment modalities. However, most often, therapeutic efficacy of drugs is limited due to lack of specificity, dose limiting systemic toxicity, and emergence of drug resistance in tumors. This suggests that there is an urgent need for developing novel strategies with

improved and selective targeting of agents, which can minimize systemic toxicity and maximize therapeutic benefit. Therefore, delivery of therapeutics (drugs, peptides, proteins or nucleic acids) with the construction of nanocarriers (magnetic nanoparticles) is a highly feasible approach for prostate cancer treatment. A number of magnetic nanocarriers for this application are presented **in** Table 1.

Paclitaxel is a commonly used chemotherapeutic agent for a wide variety of cancers. This drug can be immobilized in the shell of poly[aniline-*co*-sodium-*N*-(1-one-butyric acid) aniline] on MNP's core, which can promote cytotoxic potential in PC3 and CWR22R human prostate cancer cells over free paclitaxel drug [39]. Similarly, PEGylated magnetic nanoparticle micelles with paclitaxel were able to improve paclitaxel potency against C4-2 cells derived xenograft tumors in athymic nude mice [38].

Docetaxel (Dtxl, Taxotere®) is another FDA-approved chemotherapeutic agent for prostate cancer; however, its adverse toxic side effects significantly diminish its clinical use. A magnetic nanoparticle formulation can enhance the delivery and efficacy of docetaxel in prostate tumors [tested in prostate cancer cells (LNCaP, DU 145, and PC3)]. Such enhanced cytotoxic effects of docetaxel-magnetic nanoparticle formulation were obtained *via* suppression of nuclear transcription factor-κB (NF-κB) expression and increased apoptosis induction [44]. Our recent investigation further proved that docetaxel was effectively delivered to prostate cancer cells and tumor tissues with a specific construction of β-cyclodextrin and Pluronic® polymer layers [9]. Similarly, improved anticancer activity of docetaxel was achieved with a magnetic nanoparticle formulation decorated with polymer vesicle layers [23]. This formulation showed a diameter of about 147 nm and exhibited enhanced cellular uptake ability and antiproliferative activity in PC3 prostate cancer cells.

Mitoxantrone is another clinically approved drug for prostate cancer treatment. The cytotoxic potency of this agent can be increased by using mitoxantrone loaded in composite magnetic nanoparticles (an average size of 20 nm). This was confirmed by enhanced cleavage in Poly(ADP-ribose) polymerase (PARP) protein and activation of caspase 3 in DU 145 cells upon treatment with mitoxantrone-loaded magnetic nanoparticles [45]. Mitoxantrone-iron oxide nanoparticles aid in increasing mitoxantrone concentration in tumor tissue compared to mitoxantrone alone [46].

Moreover, magnetic nanoparticles often indicated increased efficacy of therapeutic agents due to improved cellular uptake and targeted delivery, thus exhibiting selective toxicity against prostate cancer cells. Therefore, magnetic nanoparticles represent a promising carrier for many other anticancer drug molecules such as 5-fluorouracil (5-FU) [22], doxorubicin (DOX) [37], flutamide (antagonist of the androgen receptor) [47], bicalutamide (antiandrogen) [42], and zoledronate (antiosteoclastic properties) [43]. In addition, lipid based magnetic nanoparticles are proposed extensively due to their drug depositing efficiency in hydrophobic layers and convenience to synthesize using seed-growth methods [15,48].

Stimuli-responsive polymer coatings can provide additional features to nanoparticle formulations. For example, magnetodendrimers containing hydroxyl- or amino-end surface

functional groups allow second generation nanocarriers to deliver drugs to prostate cancer cells [25]. The advantage of this system is due to higher release of loaded drug at pH 5.8 (mimicking tumor environment) than at pH 7.4 (normal physiological condition). For example, G1-NH_2: 69% vs. 39%; G2-NH_2: 49% vs. 33%; G1-OH: 92% vs. 46%; and G2-OH: 74% vs. 41%, at pH 5.8 and pH 7.4, respectively. Such pH sensitivity arose due to the presence of different amino groups in the inner layers of dendrimers. The higher drug release phenomenon at low pH could be attributed to electrostatic repulsion between the positive charges of ammonium ions. Due to hypoxia, pH of the tumors tends to be less than 7.4 at which stimuli-responsive magnetic nanoparticle can release high payload, thus helps for successful treatment. A thermosensitive poly(*N*-isopropylacrylamide-*co*-acrylamide-*co*-allylamine) coating on magnetic nanoparticles can release doxorubicin significantly at 41°C compared to 37°C [35]. Another dual responsive polymer, poly(*N*-isopropylacrylamide-*co*-acrylamide-*co*-chitosan) coating also offers an improved drug release characteristic (40°C: ~78%, 37°C:~33% and at pH 6: ~55%, pH 7.4: ~ 28%) [34].

Delivery of RNA therapeutics remains critical for many biomedical implications in medicine. Among many transfecting agents, magnetic nanovector-based transfection is under considerable attention. Magnetofection enhances cellular uptake of nanoparticles in prostate cancer cells or tumor models under a magnetic field [49]. Absorption of polyethyleneimine (PEI) on magnetic nanoparticles not only decreases PEI-associated toxicity, but also enhances nucleic acid uptake by PC3 and DU 145 cancer cells [50]. Superparamagnetic nanoparticles with cationic lipids exhibit superior transfection efficiency in PC3 prostate cancer cell lines [51]. Under gradient magnetic field, the transfection efficiency is further increased by ~21% and 42% compared to liposomal magnetofection and lipofection. More importantly, magnetic guided transfection is indeed less cytotoxic than that under a permanent magnetic field and lipofection. Redox-sensitive polymer (thiol-linked polyethyleneimine)-based iron oxide nanoparticle formulations are efficient magnetofection agents of plasmid DNA [52]. Similarly, poly-arginine/PEG layered iron oxide nanoparticle nanovector showed less toxicity and promoted SiRNA gene silencing in TC2/GFP(+) (mimicking human prostate cancer) cells over polylysine and polyethyleneimine-coated formulations [53]. Such an efficient transfection approach is feasible due to the cell transcytosis intracellular trafficking pathway. It is also possible to extend the use of magnetic nanoparticles for *in vivo* and *in vitro* transfection of antisense oligodeoxynucleotides, plasmids, siRNA and shRNA [54-56].

Magnetic nanoparticles for targeted delivery

Clinical management of prostate cancer is often difficult due to the lack of specific and targeted therapeutic intervention. Earlier approaches involved the use of anionic glycosaminoglycan (dermatan sulfate) coated magnetic nanoparticles (enriched oligosaccharide sequences that confers high heparin cofactor II binding), which target the upregulated transport activities of neovascular endothelium [37]. This correlates with higher cellular and tumor uptake in prostate R3327 AT1 rat tumors. Another magnetic nanoparticle formulation with chlorotoxin peptide exhibits substantial targeting and accumulation in cancer cells and inhibits invasiveness of cells (98%) [57]. The intercalation of doxorubicin in the CG-rich duplex of prostate specific membrane antigen (PSMA) aptamer and in polymer

layer exhibited a selective delivery and efficacy in the LNCaP xenograft mouse model [58]. Administration of this targeted drug nanoformulation was able to reduce tumor volume by approximately 54% compared to the control group. A liposomal formulation consisting of CdSe quantum dot decorated with phospholipid bilayer and iron oxide core particles, PEG derivative and cRGDyk peptide showed good specificity against bone metastasized prostate tumors [59].

Many other magnetic nanoparticle formulations are able to target prostate cancer cells and tumors by targeting folate receptors [60], Mucin 1 [61,62]; urokinase plasminogen activator (uPAR) [63]; gastric-releasing peptide receptors (GRPR) [64]; secreted protein, acidic and rich in cysteine (SPARC) [65]; luteinizing hormone–releasing hormone (LHRH) [66]; heat shock protein (HSP) [67]; prostate stem cell antigen (PSCA) [41]; and prostate cancer-specific R11 peptides [34]. The PLGA magnetic NPs formulation with cell penetrating peptide-R11 and radio-sensitizer 8-dibenzothiophen-4-yl-2-morpholin-4-yl-chromen-4-one (NU7441) allows prostate cancer-specific targeting and sustained delivery over 3 weeks in PC3 cells [40]. However, PSMA targeting using magnetic nanoparticles [38,58,68] is a widely used approach for prostate cancer since almost all prostate tumors express PSMA. Table 2 delineates important targeted delivery approaches that can be used for delivery, imaging or diagnosis of prostate cancer.

Magnetic nanoparticle based imaging, and detection

Early detection is the most vital module for the timely diagnosis of almost all human cancers, including prostate cancer. This allows uro-oncologists to develop a successful treatment modality for each individual prostate cancer patient. Detection of cancer cells is most feasible by choosing exogenous contrast agents. Magnetic resonance imaging (MRI) is a widely employed imaging tool in medicine that provides a high degree of resolution and soft tissue contrast without the use of harmful radioisotopes. Typically, SPIONs act as negative contrast agents (T_2 contrast agents or susceptibility agents), because they can produce hypointense signals of the sample region in T_2 and T_2^*-weighted images, thus appearing darker. Such a phenomenon is referred to as susceptibility-induced relaxation, which results from the diffusion of water molecules surrounding the SPIONs through the large heterogeneity of the magnetic field, leading to relaxation of the protons. This process provides efficient spin dephasing and transverse relaxation, resulting in decrease in signal intensity. Gadolinium chelates are FDA-approved MRI T_1 contrast agents [69]. However, their frequent use may lead to toxicity and even tumor formation in patients. Considering this perspective, recent studies aimed at tailoring SPIONs to offer positive contrast indicated that increased T_1 contrast signals could be achieved [14,70].

Various studies have shown a high degree of sensitivity and specificity in identifying benign and malignant lymph nodes (abdominal and pelvic malignancies) using SPIONs through MR imaging [71–73]. In addition, SPIONs have been successfully implemented in imaging bladder cancer [74], ovarian cancer [75], gynecologic malignancy [76], genitourinary tumors [77], cervical lymph nodes [78], and sentinel lymph nodes for breast cancer [79], etc. In fact, SPION based formulations that have a marketed status with prescription for various indications are being used as active ingredients for MRI modality [80]. Molecular Imaging

and Contrast Agent Database (MICAD) Book [81] recorded at the National Center for Biotechnology Information (Bethesda, MD, USA) demonstrates that magnetic nanoparticles as agents were used in animals or human studies. This content exhibits iron oxide nanoparticles with various single or multi-model dye/radio nucleotides/imaging molecules including GFP, Cy 5.5, Cy 5.5/FITC, Cy 7, RITC, VT680/64 Cu, and 11ln. These efforts minimize photobleaching (optical instability) of dyes in physiologically relevant conditions while reducing the dose and repeated use of imaging agents.

Assembly of probes with desirable properties that combine MRI contrast characteristics with optical imaging, biological separations, magnetic manipulation, and capture biologically active molecules has received much attention in the recent past. Magneto-fluorescent nanoprobes can be achieved by a combination of magnetic nanoparticles and quantum dots [49]. In this perspective, a combination of two distinct imaging characteristics of iron oxide nanoparticles and quantum dots can be achieved in a single nanoscale platform for multimodal imaging [49]. The reason to choose SiQDs over Cd based quantum dots is due to the fact that it is 10 times safer in biological systems *in vitro*. This study demonstrated an improved stability of MSiQD-Mag nanoparticles in the prostate cancer tumor microenvironment, which can be seen as pseudo-color luminescence signals at the tumor site spectrally unmixed from autofluorescence in mice even after 24 h post injection. Its quantitative measurements for stability using emission spectral readings indicate MSiQD-Mag nanoparticles show superiority both in water and plasma. FITC labeled bombesin receptor-targeted peptide (FITC-BCDDDGQRLGNQWAVGHLM) conjugated with Cy5.5-linked superparamagnetic iron oxide nanoparticle (Cy5.5.-CLIO), which establishes both MRI contrast and near infrared (NIR) fluorescein imaging modalities [82]. Due to bombesin peptide, it binds to BN binding receptor on the cells that internalizes ligands and instantaneously accumulates nanoparticles for sensitive detection.

Previous reports demonstrated that a number of factors play a key role in improving specificity and sensitivity of MRI contrast properties of magnetic nanoparticles. However, magnetic nanoparticles enhanced MRI detection of lymph node metastases. It is possible that, in conventional MR imaging, metastases have been missed. A comparative study indicates that the higher accumulation of intracellular iron in human prostate carcinoma DU 145 cells is indeed reflective in shortening T_2 weighed MRI signals in 9.4 T magnet [83]. In detail, internalized concentration of starch-coated bionized nanoferrite (BNF) (80 pg/cell) > dextran-coated Johns Hopkins University (JHU) (~45 pg/cell) > Feridex™ (15 pg/cell) > iron oxide (Nanomag® D-SPIO) (~10 pg/cell), by cancer cells, correlates closely with the signal intensity of T_2-weighted images. A recent study was developed using the one-pot synthesis approach, which involved iron oxide core and direct encapsulation of amphiphiles of PEG, DOTA and the PSMA-targeting ligand (glutamate-urea-lysine (GUL) termed as DOTA-IO-GUL [84]). It demonstrated that there was a dose-dependent binding efficiency in LNCaP (PSMA+) cells. Both PET and MR imaging results demonstrated selective targeting and uptake in 22Rv1 (PSMA+), but not PC3 (PSMA−) in tumor xenograft mouse. Aptamers are a novel class of targeting ligands that can be applied as biological drugs for various diseases. Bagalkot et al. [85] produced a prostate-specific membrane antigen-specific aptamer (A10 RNA aptamer) formed by 1:1 physical complex conjugated with doxorubicin (Dox) through the intercalation approach. This aptamer-Dox conjugate specifically binds to

PSMA-expressing cells, internalized, and intracellularly delivers doxorubicin in prostate cancer cells. Additionally, these PSMA aptamer-Dox conjugates are tri-functional, such as escort molecule (targeting), Dox delivery, and imaging [86]. This behavior was confirmed by superior targeting using Prussian blue staining, proliferation assay, and MR imaging.

PLGA-iron oxide hybrid nanoparticles [23,41] and GoldMag particles (Au/Fe_3O_4) [87,88] that have been immobilized or covalently linked with prostate stem cell antigen (PSCA) antibody exhibit probing capacity of tumors through MR imaging. Magnetic-gold hybrid nanoparticles carrying fluorescence molecules conjugated with PSMA have shown specific binding to human prostate cancer cell lines PC3 (PSMA−) and LNCaP (PSMA+) [36]. All of these findings demonstrate PSMA conjugation benefits both tissue-specific detection/imaging and therapeutic outcomes [90]. A proof-of-concept study evaluating clinically relevant detection limits of PSMA (0.05 to 2 pg/mL) can be achieved through magnetic nanoparticle decorated with anti-PSMA in high-throughput electrochemical microfluidic immunoarray [89]. According to Table 2 and other related studies, it is important to note that PSMA ligand tagged formulation can be successfully employed as a multi-/dual-modality probe for prostate cancer imaging.

Magnetic drug targeting and hyperthermia

Magnetic nanoparticle mediated drug targeting is a novel treatment modality to treat prostate cancer. There is significant evidence that magnetic guided concentration of nanoparticles to a specified or designated area is feasible under an applied magnetic field. Such an approach can enhance the local concentration of drug effect. For example, magnetic nanoparticles with a polyaniline derivative shell exhibited dose dependent cell cytotoxicity in PC3 or CWR22R cells in a confocal microscopy and proliferation assay [39]. Under a magnetic field, the increased number of dead cells due to bound PTX was concentrated in a specific area. This is further reflected in a reduced IC_{50} (50% cellular growth inhibitions) value MNPs-PTX applied magnetic field < MNPs-PTX < PTX (4.6 < 9.7 < 11.1 μg/mL in PC3 cells and 1.7 < 4.2 < 7.1 μg/mL in CWR22R cells). Krukemeyer *et al.* [46] successfully applied the magnetic targeting principle using extracorporeal 0.6 tesla magnets in adult Wag/Rij mice, in which higher concentrations of ferromagnetic nanoparticles in tumor tissues achieved lower systemic concentration, indicating minimal damage of healthy organs. Tumors treated using this method exhibited fresh necrosis, while the liver and spleen showed no necrosis. More importantly, no allergies or toxicity concerns were noticed.

Magnetic hyperthermia, an upcoming technology of hyperthermia based on applied current magnetic field (AMF), induced excitation of iron oxide nanoparticles, which produce localized heat. A PubMed survey (accessed on Decenter 10, 2016) suggests about 150 peer-reviewed magnetic hyperthermia articles suggests its possible role of hyperthermia in cancer therapeutics (https://www.ncbi.nlm.nih.gov/pubmed/?term=magnetic+nanoparticles+and+hyperthermia). The absolute iron concentration of magnetic nanoparticles correlates with the hyperthermia potential [83]. Magnetic nanoparticles can be efficiently internalized intracellularly *via* differential endocytosis pathways, offering the perspective hyperthermia potential. The absolute iron concentration of magnetic nanoparticles correlates with the hyperthermia potential [83]. Various rat models of prostate cancer indicated not only

feasibility and good tolerability of magnetic hyperthermia, but also significant local hyperthermic effects in reducing tumor burden. Physicochemical properties of the iron oxide nanoformulation play a critical role in the ability to generate heat. For example, although the surfactants used to stabilize the iron oxide nanoparticles do alter in their overall size of nanoformulation, the amount of surfactant drastically decreases heating capacity (Sodium citrate 0–30 mM changes SAR from ~ 100 to 20 W/g; oleic acid 0–30 mM changes SAR from ~ 100 to 38 W/g) [92].

Magnetic nanoparticle mediated delivery of 5-FU is much more prominent with 2 Gy X-ray treatment in DU 145 prostate cancer cells [22]. A recent study demonstrates that upon treatment with 5.5 mgFe/cm^3 tumor in LAPC4 and PC3, xenograft nude mice tumors yield statistically significant tumor growth delay when applied to variable AMF peak amplitude with 5 Gy radiation compared with a fixed thermal dose or radiation. [93]. Similarly, magnetic hyperthermia helps to sensitize PC3/LAPC4 tumors in athymic BALB/c nu/nu mice for radiation treatment [86]. In an Orthotopic Dunning R3327 Rat Model [94] study, magnetic hyperthermia could reduce tumor burden while only 5.3, 1.0, and 0.5% of the injected magnetic nanoparticle dose was found in the liver, lung, and spleen, respectively. All of these investigations indicate positive therapeutic outcomes of magnetic hyperthermia for prostate cancer. Magnetic cationic liposomes show excellent therapeutic outcomes in conjunction with AMF heat therapy in calvaria F344 male rats [31]. This combination therapy suppressed tumor growth in the bone microenvironment, which may be useful for bone metastatic prostate tumors.

NanoTherm™ therapy was developed by MagForce AG (a Germany based company, http://www.magforce.de/en/produkte/nanothermr-therapie.html), which is an advanced treatment modality of magnetic hyperthermia for the local treatment of solid tumors. This therapy uses ~15 nm in diameter aminosilane-coated iron oxide nanoparticles (Nanotherm®) and a magnetic field activator (NanoActivator®) that changes its polarity up to 100,000 times per second, generating heat. Such therapy outcomes are positive in glioblastoma multiforme, prostate, esophageal, and pancreatic cancers. MagForce has taken an initial step, has some early, yet encouraging, research results in glioblastoma trials, and intends to examine some studies in the USA. However, magnetic hyperthermia technology is still undergoing investigational studies and is not readily available for clinical use.

Concluding remarks and future perspective

This review article summarizes magnetic nanoparticles, which can be modified and established for superior biocompatibility, magnetic resonance imaging characteristic and targeted delivery of payloads. Such modified magnetic nanoparticles are attractive and potentially well suitable for theranostic applications in prostate cancer. More importantly, these theranostic nanoformulations would enable monitoring of disease progression while undergoing treatment, implied as see-and-treat technology. However, the scope of magnetic nanoparticles is still mainly limited to imaging purposes and has not yet been implemented as a therapeutic module, which needs to occur.

In this regard, magnetic nanocarriers need to be modified with targeting ligands that can specifically bind to prostate cancer-specific antigens. Moreover, there are several specific enzymes in the tumor microenvironment of prostate cancer that can be exploited for stimulus-responsive therapeutic system(s). These systems can specifically release the active drug in the tumor microenvironment of prostate cancer, leading to enhanced tumor penetration efficiency. Moreover, developing a magnetic nanoparticle formulation with a chemosensitizer along with a main clinical drug would improve chances of applicability in clinical settings. Magnetic hyperthermia would also be beneficial to improve both chemo and radiation therapies. However, it shows some regional toxicity.

A number of investigations dealing with the monoclonal antibody conjugated to the surface of magnetic nanoparticles have been tested in both *in vitro* and *in vivo* milieus. Most of these formulations exhibited substantial targeting in *in vitro* prostate cancer cell line models. However, from the accumulated data it appeared that due to the formation of additional coating development on magnetic nanoparticles by the protein corona in *in vivo* conditions, they were unable to detect the targeting site efficiently, resulting in poor *in vivo* targeting profile. Such formulations may end up residing in the liver and spleen due to extensive absorption of the opsonin proteins on the surface of particles. These drawbacks compromise not only the imaging agent potential for detecting, but also the monitoring of prostate cancer response during treatment regimens. Therefore, there is a strong possibility that generation of stable and targeted magnetic nanoparticle formulations may resolve these issues. In order to use magnetic nanoparticle formulations as a clinical therapeutic weapon to fight against prostate cancer, there must be a facile preparative approach, high reproducibility and stability, and greater accumulation at the tumor site.

Acknowledgments

This research was funded by National Institute of Health/National Cancer Center's Career Development Award K22 CA174841 to MMY. This work was supported by the National Institutes of Health Research Project Grant Program (R01 CA210192, R01 CA206069, and CA204552) and UTHSC-College of Pharmacy-Dean's Seed Grant to YMM, MJ and SCC.

References

1. Siegel RL, et al. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66(1):7–30. [PubMed: 26742998]
2. http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/prostate-cancer-statistics.
3. Ferlay, J., SI, Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, DM., Forman, D., Bray, F. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2014. GLOBOCAN 2012 v1.1.
4. https://www.ncbi.nlm.nih.gov/pubmed/?term=nanotechnology, A.o.N., 2016.
5. Yallapu MM, et al. Multi-functional magnetic nanoparticles for magnetic resonance imaging and cancer therapy. Biomaterials. 2011; 32(7):1890–1905. [PubMed: 21167595]
6. Yallapu MM, et al. Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications. Int J Nanomedicine. 2012; 7:1761–1779. [PubMed: 22619526]
7. Yallapu MM, et al. PEG-functionalized magnetic nanoparticles for drug delivery and magnetic resonance imaging applications. Pharm Res. 2010; 27(11):2283–2295. [PubMed: 20845067]
8. Yallapu MM, et al. Novel curcumin-loaded magnetic nanoparticles for pancreatic cancer treatment. Mol Cancer Ther. 2013; 12(8):1471–1480. [PubMed: 23704793]

9. Nagesh PK, et al. PSMA targeted docetaxel-loaded superparamagnetic iron oxide nanoparticles for prostate cancer. Colloids Surf B Biointerfaces. 2016; 144:8–20. [PubMed: 27058278]
10. Boya VN, et al. Probing mucin interaction behavior of magnetic nanoparticles. J Colloid Interface Sci. 2016; 488:258–268. [PubMed: 27837716]
11. Lu AH, et al. Magnetic nanoparticles: synthesis, protection, functionalization, and application. Angew Chem Int Ed Engl. 2007; 46(8):1222–1244. [PubMed: 17278160]
12. Siddiqi KS, et al. Biogenic Fabrication of Iron/Iron Oxide Nanoparticles and Their Application. Nanoscale Res Lett. 2016; 11(1):498. [PubMed: 27837567]
13. Wu W, et al. Designed synthesis and surface engineering strategies of magnetic iron oxide nanoparticles for biomedical applications. Nanoscale. 2016
14. Shen Z, et al. Iron Oxide Nanoparticle Based Contrast Agents for Magnetic Resonance Imaging. Mol Pharm. 2016
15. Martina MS, et al. Magnetic targeting of rhodamine-labeled superparamagnetic liposomes to solid tumors: in vivo tracking by fibered confocal fluorescence microscopy. Mol Imaging. 2007; 6(2): 140–146. [PubMed: 17445508]
16. Petri-Fink A, et al. Development of functionalized superparamagnetic iron oxide nanoparticles for interaction with human cancer cells. Biomaterials. 2005; 26(15):2685–2694. [PubMed: 15585272]
17. Chiang CS, et al. Synergistic Combination of Multistage Magnetic Guidance and Optimized Ligand Density in Targeting a Nanoplatform for Enhanced Cancer Therapy. Adv Healthc Mater. 2016; 5(16):2131–2141. [PubMed: 27337051]
18. Rose PA, et al. Drug embedded PVP coated magnetic nanoparticles for targeted killing of breast cancer cells. Technol Cancer Res Treat. 2013; 12(5):463–472. [PubMed: 23547975]
19. Hedayati M, et al. The effect of cell cluster size on intracellular nanoparticle-mediated hyperthermia: is it possible to treat microscopic tumors? Nanomedicine (Lond). 2013; 8(1):29–41. [PubMed: 23173694]
20. Parsian M, et al. Loading of Gemcitabine on chitosan magnetic nanoparticles increases the anti-cancer efficacy of the drug. Eur J Pharmacol. 2016; 784:121–128. [PubMed: 27181067]
21. Sadat Tabatabaei Mirakabad F, et al. PLGA-based nanoparticles as cancer drug delivery systems. Asian Pac J Cancer Prev. 2014; 15(2):517–535. [PubMed: 24568455]
22. Hajikarimi Z, et al. Evaluation of the cytotoxic effects of PLGA coated iron oxide nanoparticles as a carrier of 5- fluorouracil and mega-voltage X-ray radiation in DU145 prostate cancer cell line. IEEE Trans Nanobioscience. 2014; 13(4):403–408. [PubMed: 25051558]
23. Ling Y, et al. Dual docetaxel/superparamagnetic iron oxide loaded nanoparticles for both targeting magnetic resonance imaging and cancer therapy. Biomaterials. 2011; 32(29):7139–7150. [PubMed: 21726899]
24. Zeybek A, et al. In vitro evaluation of doxorubicin-incorporated magnetic albumin nanospheres. Chem Biol Drug Des. 2014; 84(1):108–115. [PubMed: 24524300]
25. Dayyani N, et al. Design and synthesis of pH-sensitive polyamino-ester magneto-dendrimers: Surface functional groups effect on viability of human prostate carcinoma cell lines DU145. Eur J Med Chem. 2015; 98:190–202. [PubMed: 26021708]
26. Sun W, et al. Dendrimer-based magnetic iron oxide nanoparticles: their synthesis and biomedical applications. Drug Discov Today. 2016
27. Bleul R, et al. Continuously manufactured magnetic polymersomes--a versatile tool (not only) for targeted cancer therapy. Nanoscale. 2013; 5(23):11385–11393. [PubMed: 23820598]
28. Hickey RJ, et al. Size-controlled self-assembly of superparamagnetic polymersomes. ACS Nano. 2014; 8(1):495–502. [PubMed: 24369711]
29. Jain TK, et al. Iron oxide nanoparticles for sustained delivery of anticancer agents. Mol Pharm. 2005; 2(3):194–205. [PubMed: 15934780]
30. Ak G, et al. Preparation of magnetically responsive albumin nanospheres and in vitro drug release studies. Artif Cells Nanomed Biotechnol. 2014; 42(1):18–26. [PubMed: 23419121]
31. Kawai N, et al. Effect of heat therapy using magnetic nanoparticles conjugated with cationic liposomes on prostate tumor in bone. Prostate. 2008; 68(7):784–792. [PubMed: 18302228]

32. Hodenius M, et al. Fluorescent magnetoliposomes as a platform technology for functional and molecular MR and optical imaging. Contrast Media Mol Imaging. 2012; 7(1):59–67. [PubMed: 22344881]
33. Pablico-Lansigan MH, et al. Magnetic nanobeads as potential contrast agents for magnetic resonance imaging. ACS Nano. 2013; 7(10):9040–9048. [PubMed: 24047405]
34. Sundaresan V, et al. Dual-responsive polymer-coated iron oxide nanoparticles for drug delivery and imaging applications. Int J Pharm. 2014; 466(1–2):1–7. [PubMed: 24607216]
35. Rahimi M, et al. In vitro evaluation of novel polymer-coated magnetic nanoparticles for controlled drug delivery. Nanomedicine. 2010; 6(5):672–680. [PubMed: 20172050]
36. Machulkin AE, et al. Nanohybride Materials Based on Magnetite-Gold Nanoparticles for Diagnostics of Prostate Cancer: Synthesis and In Vitro Testing. Bull Exp Biol Med. 2016; 161(5): 706–710. [PubMed: 27704352]
37. Ranney D, et al. Dermatan carriers for neovascular transport targeting, deep tumor penetration and improved therapy. J Control Release. 2005; 109(1–3):222–235. [PubMed: 16290245]
38. Taylor RM, Sillerud LO. Paclitaxel-loaded iron platinum stealth immunomicelles are potent MRI imaging agents that prevent prostate cancer growth in a PSMA-dependent manner. Int J Nanomedicine. 2012; 7:4341–4352. [PubMed: 22915856]
39. Hua MY, et al. Magnetic-nanoparticle-modified paclitaxel for targeted therapy for prostate cancer. Biomaterials. 2010; 31(28):7355–7363. [PubMed: 20609471]
40. Menon JU, et al. Polymeric nanoparticles for targeted radiosensitization of prostate cancer cells. J Biomed Mater Res A. 2015; 103(5):1632–1639. [PubMed: 25088162]
41. Gao X, et al. Prostate stem cell antigen-targeted nanoparticles with dual functional properties: in vivo imaging and cancer chemotherapy. Int J Nanomedicine. 2012; 7:4037–4051. [PubMed: 22888241]
42. Lee KJ, et al. Synthesis and characterization of bicalutamide-loaded magnetic nanoparticles as anti-tumor drug carriers. J Nanosci Nanotechnol. 2012; 12(2):1611–1615. [PubMed: 22630012]
43. Benyettou F, et al. Superparamagnetic nanovector with anti-cancer properties: gamma Fe2O3@Zoledronate. Int J Pharm. 2009; 379(2):324–327. [PubMed: 19457625]
44. Sato A, et al. Magnetic nanoparticles of Fe3O4 enhance docetaxel-induced prostate cancer cell death. Int J Nanomedicine. 2013; 8:3151–3160. [PubMed: 23990723]
45. Lee KJ, et al. In vitro analysis of the anti-cancer activity of mitoxantrone loaded on magnetic nanoparticles. J Biomed Nanotechnol. 2013; 9(6):1071–1075. [PubMed: 23858972]
46. Krukemeyer MG, et al. Mitoxantrone-iron oxide biodistribution in blood, tumor, spleen, and liver--magnetic nanoparticles in cancer treatment. J Surg Res. 2012; 175(1):35–43. [PubMed: 21470623]
47. Licciardi M, et al. Polymeric nanocarriers for magnetic targeted drug delivery: preparation, characterization, and in vitro and in vivo evaluation. Mol Pharm. 2013; 10(12):4397–4407. [PubMed: 24168360]
48. Huang HC, et al. Formulation of novel lipid-coated magnetic nanoparticles as the probe for in vivo imaging. J Biomed Sci. 2009; 16:86. [PubMed: 19772552]
49. Erogbogbo F, et al. Biocompatible magnetofluorescent probes: luminescent silicon quantum dots coupled with superparamagnetic iron(III) oxide. ACS Nano. 2010; 4(9):5131–5138. [PubMed: 20738120]
50. Oral O, et al. Effect of Varying Magnetic Fields on Targeted Gene Delivery of Nucleic Acid-Based Molecules. Ann Biomed Eng. 2015; 43(11):2816–2826. [PubMed: 25963582]
51. Vainauska D, et al. A novel approach for nucleic acid delivery into cancer cells. Medicina (Kaunas). 2012; 48(6):324–329. [PubMed: 22885367]
52. Huang RY, et al. Redox-Sensitive Polymer/SPIO Nanocomplexes for Efficient Magnetofection and MR Imaging of Human Cancer Cells. Langmuir. 2015; 31(23):6523–6531. [PubMed: 25989343]
53. Veiseh O, et al. Cell transcytosing poly-arginine coated magnetic nanovector for safe and effective siRNA delivery. Biomaterials. 2011; 32(24):5717–5725. [PubMed: 21570721]
54. Jiang S, et al. Lipidoid-Coated Iron Oxide Nanoparticles for Efficient DNA and siRNA delivery. Nano Letters. 2013; 13(3):1059–1064. [PubMed: 23394319]

55. Wang C, et al. Tumor-targeting magnetic lipoplex delivery of short hairpin RNA suppresses IGF-1R overexpression of lung adenocarcinoma A549 cells in vitro and in vivo. Biochemical and Biophysical Research Communications. 2011; 410(3):537–542. [PubMed: 21683689]
56. Wen M, et al. Preparation and Quality Test of Superparamagnetic Iron Oxide Labeled Antisense Oligodeoxynucleotide Probe: A Preliminary Study. Annals of Biomedical Engineering. 2009; 37(6):1240–1250. [PubMed: 19337837]
57. Veiseh O, et al. Inhibition of tumor-cell invasion with chlorotoxin-bound superparamagnetic nanoparticles. Small. 2009; 5(2):256–264. [PubMed: 19089837]
58. Yu MK, et al. Image-guided prostate cancer therapy using aptamer-functionalized thermally cross-linked superparamagnetic iron oxide nanoparticles. Small. 2011; 7(15):2241–2249. [PubMed: 21648076]
59. Wang F, et al. cRGD-conjugated magnetic-fluorescent liposomes for targeted dual-modality imaging of bone metastasis from prostate cancer. J Liposome Res. 2015; 25(2):89–100. [PubMed: 24960451]
60. An Q, et al. Peroxidase-like activity of Fe3O4@carbon nanoparticles enhances ascorbic acid-induced oxidative stress and selective damage to PC-3 prostate cancer cells. ACS Appl Mater Interfaces. 2013; 5(24):13248–13257. [PubMed: 24199694]
61. Shahbazi-Gahrouei D, Abdolahi M. Detection of MUC1-expressing ovarian cancer by C595 monoclonal antibody-conjugated SPIONs using MR imaging. ScientificWorldJournal. 2013; 2013:609151. [PubMed: 24194685]
62. Guo F, et al. Enhancement of Thermal Damage to Adenocarcinoma Cells by Iron Nanoparticles Modified with MUC1 Aptamer. J Nanosci Nanotechnol. 2016; 16(3):2246–2253. [PubMed: 27455625]
63. Abdalla MO, et al. Enhanced noscapine delivery using uPAR-targeted optical-MR imaging trackable nanoparticles for prostate cancer therapy. J Control Release. 2011; 149(3):314–322. [PubMed: 21047537]
64. Lee CM, et al. Prostate cancer-targeted imaging using magnetofluorescent polymeric nanoparticles functionalized with bombesin. Pharm Res. 2010; 27(4):712–721. [PubMed: 20182773]
65. Ghosh D, et al. M13-templated magnetic nanoparticles for targeted in vivo imaging of prostate cancer. Nat Nanotechnol. 2012; 7(10):677–682. [PubMed: 22983492]
66. Branca RT, et al. iDQC anisotropy map imaging for tumor tissue characterization in vivo. Magn Reson Med. 2009; 61(4):937–943. [PubMed: 19215050]
67. Rylander MN, et al. Heat shock protein expression and temperature distribution in prostate tumours treated with laser irradiation and nanoshells. Int J Hyperthermia. 2011; 27(8):791–801. [PubMed: 22098363]
68. Taylor RM, et al. Multifunctional iron platinum stealth immunomicelles: targeted detection of human prostate cancer cells using both fluorescence and magnetic resonance imaging. J Nanopart Res. 2011; 13(10):4717–4729. [PubMed: 22121333]
69. Caravan P, et al. Gadolinium(III) chelates as MRI contrast agents: Structure, dynamics, and applications. Chemical Reviews. 1999; 99(9):2293–2352. [PubMed: 11749483]
70. Tromsdorf UI, et al. A highly effective, nontoxic T1 MR contrast agent based on ultrasmall PEGylated iron oxide nanoparticles. Nano Lett. 2009; 9(12):4434–4440. [PubMed: 19799448]
71. Barentsz JO, et al. Use of ultrasmall superparamagnetic iron oxide in lymph node MR imaging in prostate cancer patients. Eur J Radiol. 2007; 63(3):369–372. [PubMed: 17689215]
72. Anzai Y. Superparamagnetic iron oxide nanoparticles: nodal metastases and beyond. Top Magn Reson Imaging. 2004; 15(2):103–111. [PubMed: 15269613]
73. Fortuin AS, et al. Lymphotropic nanoparticle-enhanced MRI in prostate cancer: value and therapeutic potential. Curr Urol Rep. 2014; 15(3):389. [PubMed: 24430170]
74. Green DA, et al. Role of magnetic resonance imaging in bladder cancer: current status and emerging techniques. BJU Int. 2012; 110(10):1463–1470. [PubMed: 22500557]
75. Leung K. Ovarian cancer antigen 183B2 monoclonal antibody conjugated to ultrasmall superparamagnetic iron oxide nanoparticles. Molecular Imaging and Contrast Agent Database (MICAD). 2004

76. Lai G, Rockall AG. Lymph node imaging in gynecologic malignancy. Semin Ultrasound CT MR. 2010; 31(5):363–376. [PubMed: 20974356]
77. Mouli SK, et al. Lymphotropic nanoparticle enhanced MRI for the staging of genitourinary tumors. Nat Rev Urol. 2010; 7(2):84–93. [PubMed: 20084078]
78. Mack MG, et al. Cervical lymph nodes. Eur J Radiol. 2008; 66(3):493–500. [PubMed: 18337039]
79. Nohara T, et al. Identification of sentinel lymph nodes and mapping procedure of sentinel lymph nodes for breast cancer. Nihon Rinsho. 2007; 65(Suppl 6):193–197.
80. [Accessed on November 27, 2016] https://www.ncbi.nlm.nih.gov/books/NBK5330/ fdaApprovedContrastAgents (Excel file)
81. [Accessed on November 27, 2016] https://www.ncbi.nlm.nih.gov/pubmed/?term=%22Molecular+Imaging+and+Contrast+Agent+Database+(MICAD)%22%5Bbook%5D
82. Team, TMR. Molecular Imaging and Contrast Agent Database (MICAD). 2004. Bombesin peptide conjugated-cross-linked iron oxide-Cy5.5.
83. Wabler M, et al. Magnetic resonance imaging contrast of iron oxide nanoparticles developed for hyperthermia is dominated by iron content. Int J Hyperthermia. 2014; 30(3):192–200. [PubMed: 24773041]
84. Moon SH, et al. Development of a complementary PET/MR dual-modal imaging probe for targeting prostate-specific membrane antigen (PSMA). Nanomedicine. 2016; 12(4):871–879. [PubMed: 26739097]
85. Bagalkot V, et al. An aptamer-doxorubicin physical conjugate as a novel targeted drug-delivery platform. Angew Chem Int Ed Engl. 2006; 45(48):8149–8152. [PubMed: 17099918]
86. Wang AZ, et al. Superparamagnetic iron oxide nanoparticle-aptamer bioconjugates for combined prostate cancer imaging and therapy. ChemMedChem. 2008; 3(9):1311–1315. [PubMed: 18613203]
87. Ren J, et al. MRl of prostate cancer antigen expression for diagnosis and immunotherapy. PLoS One. 2012; 7(6):e38350. [PubMed: 22761679]
88. Ren J, et al. MRI of prostate stem cell antigen expression in prostate tumors. Nanomedicine (Lond). 2012; 7(5):691–703. [PubMed: 22630152]
89. Tang CK, et al. High-Throughput Electrochemical Microfluidic Immunoarray for Multiplexed Detection of Cancer Biomarker Proteins. ACS Sens. 2016; 1(8):1036–1043. [PubMed: 27747294]
90. Tse BW, et al. PSMA-targeting iron oxide magnetic nanoparticles enhance MRI of preclinical prostate cancer. Nanomedicine (Lond). 2015; 10(3):375–386. [PubMed: 25407827]
91. Harisinghani MG, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med. 2003; 348(25):2491–2499. [PubMed: 12815134]
92. PIPS, et al. Thermal and magnetic properties of iron oxide colloids: influence of surfactants. Nanotechnology. 2015; 26(42):425704. [PubMed: 26421876]
93. Attaluri A, et al. Magnetic nanoparticle hyperthermia enhances radiation therapy: A study in mouse models of human prostate cancer. Int J Hyperthermia. 2015; 31(4):359–374. [PubMed: 25811736]
94. Johannsen M, et al. Magnetic fluid hyperthermia (MFH)reduces prostate cancer growth in the orthotopic Dunning R3327 rat model. Prostate. 2005; 64(3):283–292. [PubMed: 15726645]

Highlights

- Magnetic nanoparticles with multi-functionality can used for theranostic applications
- Various magnetic nanoparticle mediated therapeutic strategies are summarized.
- Magnetic hyperthermia and targeting is an alternative strategy to treat prostate cancer
- Targeted magnetic nanoparticles delivery of therapeutics is still warranted

Teaser

This review article highlights the current state of the magnetic nanoparticle technologies for prostate cancer. A detailed recent advances in research and development of magnetic nanoparticles for theranostic application.

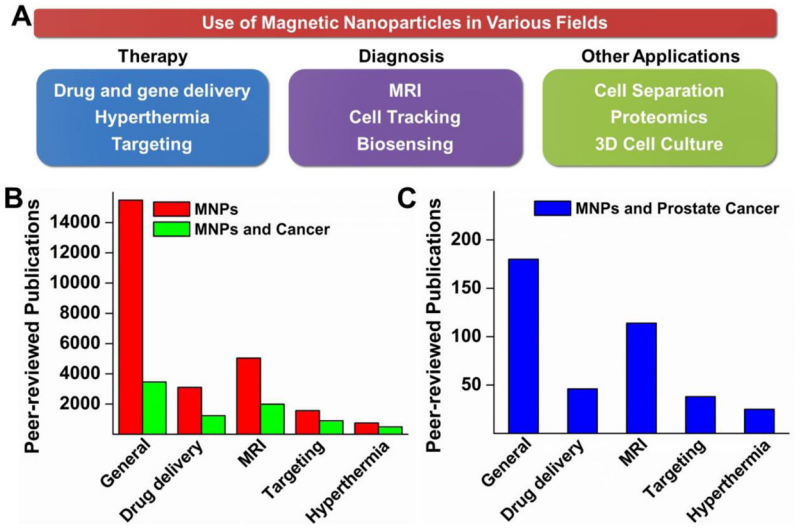

Figure 1.

Use of magnetic nanoparticles in various materials science and biomedical research applications. ***A)*** Use of magnetic nanoparticles in therapy, diagnosis (*in vitro*, *in vivo, and* pre-clinical) and other nanotechnology research areas. ***B-C)*** Peer-reviewed articles published in PubMed until December 15, 2016.

Table 1

Role of surface coating and therapeutic effects of chemotherapeutic agents with magnetic nanoparticle mediated delivery

Coating	Drug	Physicochemical characterization	Utilization
Anionic glycosaminoglycan [37]	Doxorubicin	11 nm particle size -39 mV zeta potential	Enhanced tumor-cell internalization and tumor uptake in R3327 AT1 rat tumors.
Serum albumin [24]	Doxorubicin	210 nm particle size 2.5 emu/g magnetic saturation (M_s)	Doxorubicin pharmacodynamic property retained upon loading in BSA coated MNPs. DOX-BSA-NPs exhibits superior inhibition effect against PC3 and A549 cells over DOX. IC_{50} values of DOX and DOX-BSA-NPs were 0.14 and 0.51 μM (PC3 cells), and 3.24 and 9.13 μM (A549 cells).
PNIPAAm-AAm-AH thermosensitive polymer coated nanoparticles [35]	Doxorubicin	~100 nm particle size ~2% DOX loading	6-fold increase of doxorubicin release at 41°C over 37°C and 4°C.
Oleic acid – Pluronic® F127 [29]	Doxorubicin	193 nm particle size with a polydispersity index of 0.262 (TEM size data was 11 ± 2 nm) 88.8 ± 0.5 emu/g M_S	DOX-loaded MNPs exhibited a dose-dependent cytotoxicity on MCF-7 and PC3 cells. Due to slow release DOX-loaded MNPs demonstrated slightly lower effects than DOX in solution
1-octadecylamine and DSPE-PEG [38]	Paclitaxel	29 ± 2 nm particle size 247 ± 33 μg/mL of platinum loading Transverse relaxivities of r_2 = 300 ± 12 and 389 ± 16 Hz/mM iron	PSMA-targeted J591-SPMs bound specifically to C4-2 cells. The data show that only the J591-SPMs and paclitaxel were able to prevent growth of tumors in the mice significantly.
polyaniline derivative doped nanoparticles [39]	Paclitaxel	73.7 nm particle size −30.5 ± 0.45 mV zeta potential 53.2 emu/g M_S	Bound-PTX MNPs were more toxic to PC3 and CWR22R cells. The IC_{50} value of bound-PTX MNPs was 9.7 μg/mL (free PTX, 11.1 μg/mL) and 4.2 μg/mL (free-PTX, 7.1 μg/mL) in PC3 and CWR22R cells, respectively. (specify R as resistance cells)
PLGA-iron oxide [40]	Radio-sensitizer 8-dibenzothiophen-4-yl-2-morpholin-4-yl-chromen-4-one (NU7441)	260 nm particle size 48.64 emu/g M_S Bi-phasic release of NU7441: 41% (a day) and 90.48% (for 3 weeks)	NU7441 PLGA-MNPs were more effective in H460 and PC3 cells.
PLGA Poly(allylamine hydrochloride) PEG [41]	Docetaxel	187.4 ± 32.7 nm particle size Cumulative release 75.9% for scAb-PLGA-SPIO/ docetaxel	The IC_{50} of scAb-PLGA-SPIO/ docetaxel formulation was demonstrated to be 1.38, 1.68, and 1.95-fold lower than those for unconjugated docetaxel nanoformulation at 24, 48, and 72 hrs in PC3M cells.
Carboxy-terminated PLGA [23]	Docetaxel	124.5 ± 10.2 nm and 146.9 ± 8.6 nm particle size 60.5 emu/g and 23.3 emu/g M_S before and after modification	Improved cellular internalization ability and thus induces superior anti-proliferative activity in PC3 cells, confirmed by confocal laser scanning microscopy and proliferation assays.
Ethylene glycol composite [42]	Bicalutamide	20 nm particle size	A basic study indicating bicalutamide loaded composite

Coating	Drug	Physicochemical characterization	Utilization
			MNPs were cytotoxic to DU145 cells.
Pluronic® L-121 [27]	Camptothecin	Polymersomes were coated on to 10 nm MNP core nanoparticles	This formulation demonstrated higher signal amplitudes with respective to iron content in magnetic particle spectroscopy compared to Endorem® and Feraheme®.
Citrate-octanoic acid coated nanoparticles [43]	Zoledronate	10 nm particle size with polydispersity of 20%	The γFe_2O_3@Zoledronate formulation promotes inhibitory effect due to nanocrystal cell internalization.

Table 2

Role of magnetic nanoparticles in specific targeting, imaging and detection of prostate cancer

Formulation/Composition	Linker /conjugation process	Targeting ligand	Outcome	Imaging modality
Oleic acid-coated IO NPs DOTA Polysorbate 60	Physical absorption on the surface of NPs	GUL	Cellular uptake in LNCaP cells a specific targeting in 22Rv1 mouse xenografts.	MRI and PET [84]
Iron oxide core nanoparticles with CdSe QDs, PEG derivatives	Conjugation at the distal ends of lipid-PEG derivative	cRGDyk peptide	Stable and effective detection signals with low systemic toxicity and mainly accumulates in tumors and liver.	MRI and fluorescence [59]
Silicon quantum dots and SPIONs with phospholipid-PEG micelles			Significant cellular uptake stable luminescence in prostate cancer tumor model.	Luminescence [49]
SPION with PEG	Biotinylated phospholipids	PSMA	SPIONs with PSMA MAb targets efficiently C4-2 xenograft tumors in mice and specifically directs the drug to the tumors, thus prevents tumor growth. Further, it showed good transverse relaxivities of 389 ± 15.5 Hz/mM (MRI contrast enhancement *in vivo*) with this formulation	MRI [38]
oleic acid-capped nanoparticles	N-hydroxysuccinimide/N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride near-infrared fluorescence probe 1,1′-dioctadecyl-3,3,3′,3′-tetramethyl indotricarbocyanine iodide (DIR)	PSMA	A proof-of-concept study demonstrates conjugation with PSMA-targeting antibody, J591, and demonstrated enhanced MRI potential in a preclinical model of orthotopic prostate cancer xenografts in mice.	MRI and Fluorescence [90]
PLGA composite iron oxide nanoparticles	α-maleinimido-omega-carboxy PEG	PSCA	Due to PSCA conjugation significant cellular uptake of formulation was found which is evident from their T2- weighted images (comparable or slightly better than of the Endorem® at the same concentration of Fe concentration) in PC3 cells.	MRI and fluorescence [23]

Formulation/Composition	Linker /conjugation process	Targeting ligand	Outcome	Imaging modality
SPIONs	Direct attachment/binding	Chlorotoxin tumor cell-specific peptide	A proof-of-concept nanoparticle probe with magnetic nanoparticles with chlorotoxin peptide exhibits substantial targetability and accumulation in cancer cells and thus inhibits invasiveness of cells (98%).	[57].
SPIONs	No agent	EPR effect	This is an early attempted study demonstrating ability to detect nodal metastases, and a node-by-node analysis with significantly higher sensitivity than conventional MRI.	MRI [91]