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Nanoparticle-mediated thermal therapy: Evolving strategies for prostate cancer therapy

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Abstract

Purpose—Recent advances in nanotechnology have resulted in the manufacture of a plethora of nanoparticles with different sizes, shapes, core physicochemical properties and surface modifications that are being investigated for potential medical applications, particularly for the treatment of cancer. This review focuses on the therapeutic use of customized gold nanoparticles, magnetic nanoparticles and carbon nanotubes that efficiently generate heat upon electromagnetic (light and magnetic fields) stimulation after direct injection into tumors or preferential accumulation in tumors following systemic administration. This review will also focus on the evolving strategies to improve the therapeutic index of prostate cancer treatment using nanoparticle-mediated hyperthermia.

Conclusions—Nanoparticle-mediated thermal therapy is a new and minimally invasive tool in the armamentarium for the treatment of cancers. Unique challenges posed by this form of hyperthermia include the non-target biodistribution of nanoparticles in the reticuloendothelial system when administered systemically, the inability to visualize or quantify the global concentration and spatial distribution of these particles within tumors, the lack of standardized thermal modeling and dosimetry algorithms, and the concerns regarding their biocompatibility. Nevertheless, novel particle compositions, geometries, activation strategies, targeting techniques, payload delivery strategies, and radiation dose enhancement concepts are unique attributes of this form of hyperthermia that warrant further exploration. Capitalizing on these opportunities and overcoming these challenges offers the possibility of seamless and logical translation of this nanoparticle-mediated hyperthermia paradigm from the bench to the bedside.

Keywords

Nanoparticles; magnetic; optical; activatable; hyperthermia; prostate cancer

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Prostate cancer

Prostate cancer accounted for 25% of estimated newly diagnosed cases of non-skin cancer in men in the United States in 2009. It was predicted that 192,280 new cases of prostate cancer would be diagnosed in the US in 2009, with one in six men developing the disease during their lifetime. Nearly 90% of men with prostate cancer have clinically localized disease. The aggressiveness of prostate cancer is largely determined by the prostate specific antigen levels, clinical extent and volume of disease, and Gleason histologic score (a measure of glandular differentiation). By predicting the likelihood of adjacent organ invasion, nodal metastasis, distant metastasis, recurrence following treatment, and likelihood of progression without treatment, these factors help stratify tumors into low-, intermediate- and high-risk groups, and aid the choice of treatment options. For low-risk clinically localized disease, a potentially curable stage of disease, common treatments include watchful waiting, radical prostatectomy, external beam radiation therapy (RT) and interstitial RT (brachytherapy), freezing the prostate (cryotherapy), and androgen deprivation therapy (ADT). The choice of treatment is often governed by the patient's life expectancy, the likelihood of cancer progression without treatment, efficacy of treatment, convenience of treatment, treatment costs, and adverse effects (treatment-related urinary, bowel, and sexual dysfunction). For locally advanced cancers, the treatment options are based on the extent of disease but typically involve combinations of the treatments mentioned above with ADT usually being one of them. Less frequently, patients present with metastatic disease and treatment begins with ADT and palliative interventions but may proceed to involve chemotherapy when tumors become resistant to ADT. Locally recurrent prostate cancer is often treated with ADT, salvage radical prostatectomy, salvage brachytherapy, cryotherapy or thermal therapy. The focus of this article is on one form thermal therapy – hyperthermia.

Hyperthermia for prostate cancer

Hyperthermia generally refers to temperatures between 40°C and 45°C whereas temperatures >45°C are considered thermoablative. Mild temperature hyperthermia mediates its antitumor effects via subtle influences on the tumor microenvironment (Horsman and Overgaard 1997), induction of apoptosis (Fuller et al. 1994; Harmon et al. 1991), activation of immunological processes (Servadio and Leib 1991; Stawarz et al. 1993; Zhang et al. 2008), and induction of gene and protein synthesis (Horsman and Overgaard 1997; Kampinga and Dikomey 2001; Roti Roti 2004). While these effects do not independently cause tumor cell cytotoxicity, they lead to greater effectiveness of other conventional treatment modalities such as RT, chemotherapy, and immunotherapy (van der Zee 2002) (Hildebrandt et al. 2002). In its role as an adjunct to RT, hyperthermia serves as a dose-modifying agent that increases the therapeutic ratio of RT (i.e., enhanced effectiveness of a given dose of RT without additional toxicity). Hyperthermia can be achieved a number of ways including local hyperthermia by external or internal energy sources, regional hyperthermia by irrigation of body cavities or perfusion of organs or limbs, and whole body hyperthermia. Regardless of the mechanism of heating, clinical trials of hyperthermia as stand-alone therapy or in combination with RT have demonstrated promising outcomes in the treatment of many cancers including prostate cancer (Anscher et al. 1997; Baronzio et al. 2009; Jones et al. 2005; Overgaard et al. 1995; Satoh et al. 1988; Sherar et al. 2004; Sherar et al. 2003; Shimm et al. 1988; Sneed et al. 1998; van der Zee et al. 2000; Vernon et al. 1996). Although an entirely non-invasive treatment approach is preferred, minimally invasive techniques such as intraluminal or intracavitary treatments are particularly appealing due to the flexibility of positioning endorectal applicators close to the posterior aspect of the prostate or transurethral catheters in the center of the prostate. This strategy has been employed successfully in the treatment of locally advanced prostate cancer using modalities such as ultrasound, radiofrequency and microwaves with appropriate applicators

positioned either externally, intraluminally or interstitially to generate heat. Multiple studies report gratifying outcomes with the use of endorectal microwave or ultrasound applicator mediated hyperthermia in conjunction with conventional RT (thermoradiotherapy) for the treatment of locally advanced prostate cancer (Algan et al. 2000; Fosmire et al. 1993; Hurwitz et al. 2002; Hurwitz et al. 2005; Hurwitz et al. 2001; Mendecki et al. 1980; Servadio and Leib 1991; Yerushalmi et al. 1982). Similarly, radiofrequency induced hyperthermia has been used in the treatment of prostate tumors through intracavitary applicators (Bhowmick et al. 2001; Dawkins et al. 1997; Sofras et al. 1996; Zargar Shoshtari et al. 2006). The main challenge with the intracavitary or intraluminal delivery of hyperthermia is the generation of adequate heat in the prostate without excessive temperature in critical adjacent structures such as the neurovascular bundle, urethra, bladder and rectum (Gillett et al. 2004; Marberger 2007). Alternatively, external regional hyperthermia can be used in combination with RT for the treatment of prostate cancer (Anscher et al. 1997). The lack of significant temperature conformality at the interface between the prostate and the rectum remains a major challenge with this technique. Interstitial hyperthermia offers the possibility of generating uniform temperatures within the prostate without any significant temperature rise in surrounding normal structures, but is an invasive procedure (Emami et al. 1996; Lancaster et al. 1999; Prionas et al. 1994; Sherar et al. 2004; Sherar et al. 2003).

Clinical hyperthermia experience has led to the recognition that high minimum temperatures achieved in most parts of the target volume correlate better with clinical outcome than maximum temperatures attained in small parts of the target volume (Dewhirst et al. 1984). A standardized nomenclature has been proposed and validated for the representation of variable time-temperature data as an Arrhenius isoeffect relationship where the total thermal dose is expressed as the cumulative equivalent minutes at 43°C achieved or exceeded in 90% of the prostate (CEM 43°C T₉₀) (Jones et al. 2005; Sapareto and Dewey 1984; Thrall et al. 2005). The targeted clinical thermal dose for hyperthermia when combined with RT is a CEM 43°C T₉₀ of 5–10 minutes (Hurwitz et al. 2005; Jones et al. 2005; Oleson et al. 1993; Tilly et al. 2005). Despite the increasingly convincing evidence for clinical hyperthermic radiosensitization and the evolving consensus in reporting these data, it is underutilized in routine clinical practice due to: (a) the invasive means of achieving and maintaining hyperthermia, (b) the lack of good thermal dosimetry, and (c) the inability to achieve localized hyperthermic temperatures (Moros et al. 2007). Hence, a relatively non-invasive approach with externally regulatable and quantifiable prostate-specific hyperthermia could provide renewed enthusiasm for this treatment paradigm. The above mentioned hyperthermia strategies solely rely on the ability of the cancer tissues to convert the imparted electromagnetic energy into heat. In contrast to methods relying on modifying the energy source to generate heat, there is evolving interest in methods to preferentially enhance the heat generating capacity of the cancer tissues by introducing exogenous materials in to them. Along these lines, ferromagnetic seeds have been used in conjunction with a magnetic field to induce hyperthermia in prostate cancer (Brezovich and Meredith 1989; Meredith et al. 1989; Partington et al. 1989). Ferromagnetic seeds or thermoseeds are needle-shaped devices that are interstitially placed into the tumor, similar to brachytherapy implants, and the heating is accomplished by an externally applied magnetic field. The uniqueness of thermoseed hyperthermia are (i) the lack of requirement for external power connections and (ii) the automatic regulation of temperature of the implanted thermoseeds depending on the compositional characteristics of the implants (Meredith et al. 1989; Partington et al. 1989). Being an interstitial modality, thermoseed mediated hyperthermia has limitations similar to other interstitial hyperthermia techniques. Further, due to the heating equipment size and the requirement to limit electromagnetic radiation to meet federal (FCC) regulations, thermoseed implant hyperthermia treatments are performed in special electromagnetic shielded rooms located in dedicated hyperthermia suites.

Alternatively, nanoscale materials, particularly metal nanoparticles that are activatable by externally applied electromagnetic fields, can be used to induce cancer-specific hyperthermia.

Nanoparticles

In the broadest sense, nanotechnology involves utilizing the unique properties and behaviors of materials made at the nanoscale, a scale that ranges from 1 to 100 nm. At the simplest level, what drives these unique behaviors and properties is the significantly larger surface area per unit volume of nanoscale materials than the same material in the bulk scale – the greater surface area affords greater opportunities for interactions with adjacent materials. Capitalizing on these observations, recent advances in nanotechnology have resulted in the manufacture of a plethora of nanoparticles with different sizes, shapes, core physicochemical properties and surface modifications that are being investigated for potential medical applications. From a biological perspective, the size of such particles tends to be similar to that of a DNA doublestrand (2 nm thick), a ribosome (20 nm), or the smallest bacteria (200 nm Mycoplasma) and considerably smaller than the typical eukaryotic cell (7 micron diameter of a small red blood cell). Therefore, systemically administered nanoparticles readily extravasate out of blood vessels and can interact with biomolecules at the cellular and molecular level. The most common nanoparticles studied for biomedical applications are liposomes and uni- or multi-lamellar vesicles (organic biolipid layers encapsulating imaging and therapeutic payloads), dendrimers (repeatedly branched polymers), quantum dots (metallic core-shell nanoparticles that are intensely fluorescent at specific wavelengths), gold nanoparticles (ranging in shape from spheres and shells to rods and cages), paramagnetic nanoparticles (iron oxide laden particles), and carbon nanotubes. In the arena of cancer research, there has been an explosion of knowledge and research regarding oncologic uses of such nanoparticles. In addition to several diagnostic applications of nanoparticles using optical, magnetic resonance, positron emission tomography, computed tomography and x-ray techniques, the therapeutic application of nanoparticles via tumor heating is emerging as a novel form of “nanothermal therapy” of tumors (Sharma and Chen 2009). Although several potential hyperthermic particles such as silver, lanthanum and zinc nanoparticles are available (Naruse et al. 1986), the thermal activation properties of gold nanoparticles, magnetic nanoparticles and carbon nanotubes have been extensively characterized preclinically and they are furthest along in potential translation to clinical biomedical applications. In addition, these particles serve as platforms for development of additional novel nanoparticle ensembles comprised of alloys, dopants and hybrid particles. Hence, this review will focus on the potential application of gold nanoparticles, magnetic nanoparticles and carbon nanotubes (see Figure 1) in the thermal therapy of prostate cancer.

Gold nanoparticle induced hyperthermia

A number of features of gold nanoparticles have rendered them particularly attractive to biomedical researchers and account for their popularity in preclinical research leading up to potential clinical translation. The most striking feature is the familiarity of the medical community with gold as a clinically useful therapeutic agent for various ailments such as melancholy, fainting, fevers, syphilis and arthritis (Higby 1982; Parish 1999). The most prominent use of gold has been for the treatment of rheumatic arthritis. Treatment of rheumatoid arthritis with a cumulative dose of a little less than 2gm/yr for 10 years without any appreciable toxicity speaks to the good overall tolerance of gold in humans (Abrams and Murrer 1993). Due to its physical inertness, gold is unlikely to interact chemically with biomolecules in humans. In addition to its apparent clinical safety and tolerability, gold can be used to synthesize nanoparticles with very precise sizes, shapes and surface chemistries at the nanoscale using simple techniques and relatively inexpensive reagents (Daniel and Astruc 2004). The most unique property that lends itself to hyperthermia applications is the

photothermal activation of gold nanoparticles. However, there are concerns regarding the biocompatibility of these gold nanoparticles for clinical applications. For instance, a recent study noted activation of the immune complement system by gold (Hulander et al. 2009). While this raises concerns about its clinical safety, the study also reports that when coated on Bactriguard commercial surfaces the gold nanoparticles are less effective in activating the immune complement system, a feature attributed to the altered nanostructure and chemistry of gold nanoparticles and nanogalvanic effects. Furthermore, similar biocompatible coatings such as polyethylene glycol or dextran provide “stealth” characteristics to these particles for evasion of capture by and accumulation within the reticuloendothelial system, further enhancing their biocompatibility.

It is known that, at the nanoscale, bulk metals exhibit optical resonances of their surface plasmons. In colloidal form, these metals typically absorb and scatter light strongly at a characteristic wavelength (plasmon resonance) in the visible region of the spectrum. Working with wavelengths in the near infrared (NIR) region of the spectrum is clinically meaningful because light penetrates deep within tissue (up to several centimeters) at these wavelengths. Indeed, certain geometries (spheres, rods and shells) of metal nanoparticles have optical plasmon resonances that can be tuned to the NIR region (Oldenburg et al. 1999). While gold nanospheres and nanorods are made of solid gold, nanoshells consist of a dielectric core (e.g. silica) surrounded by a thin gold shell. Nanospheres exhibit resonances around 540 nm without much tunability of this peak whereas nanoshells and nanorods have peak resonances that can be tuned throughout the NIR spectrum (Jain et al. 2006; Oldenburg et al. 1998). Nanoshells are tuned via their core-to-shell ratio while nanorods are tunable through their aspect ratio (i.e. ratio of the length to diameter). For instance, gold nanoshells comprised of an aminated colloidal silica (120 nm diameter) core with a 14-nm-thick shell of gold colloid adsorbed onto it as sequential nucleating sites result in an absorption peak between 780 and 800nm. Furthermore, due to their metal structure, gold nanoparticles are extremely efficient photothermal coupling devices. Their large absorption cross sections convert light to heat, and their high thermal conductivity couples this heat to the surrounding tissue. Lastly, the handling of gold nanoparticles as devices rather than drugs could reduce time and expense incurred in translating their use from the bench to the bedside.

For clinically pertinent oncologic applications, interstitial injection of these particles within tumors is a readily available option but a more exciting and possibly elegant option is to deliver these nanoparticles systemically and have them accumulate within tumors either passively or via active targeting of tumor-specific molecules. Passive yet selective sequestration of nanoparticles within tumors capitalizes on a phenomenon termed enhanced permeability and retention (EPR) effect (Baluk et al. 2003; McDonald and Choyke 2003) where macromolecules and nanoparticles passively extravasate from leaky tumor vasculature containing wide interendothelial junctions, incomplete or absent basement membranes, dysfunctional lymphatics, and numerous transendothelial channels (Jain 1999). In contrast, active targeting is facilitated by functionalizing the gold nanoparticle with biomolecules including peptides, antibodies, and oligonucleotides that are specific to the target of interest (Han et al. 2000; Khan et al. 2008; Loo et al. 2005; Lowery et al. 2006).

The seminal report on the use of systemically administered nontargeted NIR-activatable gold nanoshells for thermal ablation of tumors in an animal model (Hirsch et al. 2003) built on the initial characterization of laser dosimetry studies and pharmacokinetic and biodistribution analyses. A subsequent efficacy study in BALB/c mice inoculated subcutaneously with CT26/wt murine colorectal cancer cells demonstrated that 100 μL of 2.4×10^{11} nanoshells/mL administered intravenously resulted in tumor accumulation at 6 hours – NIR laser treatment at 4 W/cm^2 for 3 minutes resulted in 90% survival of nanoshell-treated and irradiated mice and 0% survival of nanoshell-treated and unirradiated controls

and 0% survival of saline-treated and irradiated controls (O'Neal et al. 2004). Subsequently, several studies have been reported on the use of gold nanoparticles such as gold nanorods and nanocages for the thermal therapy of cancer (Dickerson et al. 2008; Hu et al. 2006; Huang et al. 2006; Huang et al. 2008a; Huff et al. 2007; Skrabalak et al. 2007; von Maltzahn et al. 2009; Wu et al. 2009). More recently, the feasibility of using gold nanoshells and optical fiber-based NIR illumination for interstitial thermoablation of intracranial tumors was demonstrated (Schwartz et al. 2009). While these reports involve passive targeting of gold nanoparticles to achieve the photothermal ablation, several other studies document the feasibility and efficacy of tumor-specific active targeting of gold nanoparticles for photothermal therapy of tumors (Bernardi et al. 2008; Cheng et al. 2009; Huang et al. 2008b; Kawano et al. 2009; Kumar et al. 2008; Liu et al. 2009; Ma et al. 2009; Sokolov et al. 2003). Gold nanoshells have also been used to induce mild temperature hyperthermia in murine tumor models to enhance the therapeutic efficacy of RT. Initial experiments defined the laser parameters for mild temperature hyperthermia and demonstrated that non-invasive magnetic resonance thermal imaging accurately predicted temperature measurements obtained using thermocouples inserted into the tumors (see Figure 2). When mild temperature hyperthermia (41°C for 20 minutes) was followed immediately by a single 10 Gy dose of radiation (125 kV X-rays), there was an approximately 2-fold increase in tumor growth delay (time taken for tumors to double in volume) when compared to the animals treated with radiation alone (Diagaradjane et al. 2008b). As expected, hyperthermia led to an immediate increase in perfusion of the center of tumors (documented on dynamic contrast enhanced magnetic resonance imaging). Unexpectedly, however, there were large areas of necrosis in the combined treatment group at a later time point. This necrotic pattern of tumor cytotoxicity was attributed to a decrease in microvessel density, possibly due to focal vascular disruption mediated by perivascularly concentrated gold nanoshells that generate intense focal temperature elevations. Presumably, gold nanoshells that are too large to diffuse freely into tumor interstitium but large enough to leak out of tumor vasculature remain sequestered in the perivascular region. Conceivably, as an extension of this concept, gold nanorods that are smaller than nanoshells will penetrate deeper into tumors and provide more global temperature elevations within tumors, particularly if they are conjugated to tumor-specific biomarkers. In spite of these extensive reports on the use of gold nanoparticle-mediated ablation and hyperthermic radiosensitization, very few reports document its utility in the treatment of prostate cancer. *In vitro* studies of gold nanoshell-mediated photothermal ablation of PC-3 and C4-2 prostate cancer cells demonstrated a complete loss of cell viability while maintaining intact cellular morphology (Stern et al. 2007). This observation correlates well with the intact cellular morphology of clinical biopsies obtained after radiofrequency ablation (Margulis et al. 2004). A subsequent *in vivo* study on a murine subcutaneous prostate cancer model compared the therapeutic efficacy of two doses of gold nanoshells (7 μ L/gm and 8.5 μ L/gm of body weight) and demonstrated enhanced therapeutic efficacy (93% tumor necrosis and regression with an average temperature rise to 65.4°C) with the high concentration of gold nanoshells (Stern et al. 2008). Targeted thermal therapy of PC-3 prostate cancer cell lines using prostate-specific EphrinA1-conjugated gold nanoshells demonstrated localized thermal damage to cells that were bound to the conjugates (Gobin et al. 2008). Prostate cancer cell specific uptake and toxicity studies of different nanoparticles (gold nanoshells and gold nanorods) have also demonstrated size dependent uptake and negligible toxicity (Malugin and Ghandehari 2009). It is reasonable to assume that findings from other tumors can be reproduced in prostate cancers to provide justification for advancing gold nanoparticle-mediated hyperthermia in clinical scenarios.

Magnetic nanoparticle induced hyperthermia

Thermotherapy using magnetic nanoparticles involves the coupling of an external magnetic field to tumor laden magnetic particles to generate high-energy photons through a magnetic field induced locally in the vicinity of the nanoparticle. These high-energy photons result in the observed magnetic hyperthermia effect by the Neel's relaxation process (Hildebrandt et al. 2002). Although the concept of magnetic hyperthermia was introduced 50 years ago, its clinical potential has recently been recognized based on the achievable selective and relatively homogenous temperature distribution in deep-seated tumors when compared to conventional hyperthermia modalities (Moroz et al. 2002). Initial studies on the physical evaluation of ferromagnetic particles and magnetic fluids suggested that intratumoral power absorption from a moderate concentration of 5 mg ferrite per gram tumor (i.e. 0.5% w/w) and clinically acceptable magnetic fields is comparable to radiofrequency heating with local applicators and superior to regional radiofrequency heating (by comparison with clinical specific absorption rate measurements from regional and local hyperthermia treatments), which is attributed to the much larger number and surface area of magnetic particles (Jordan et al. 1993). Subsequent *in vivo* studies were performed in murine models of mammary carcinoma with intratumoral injection of 1.5×10^{-2} mg ferrite/mm³ followed 20–30 minutes later by intratumoral hyperthermia (steady-state temperatures of 47°C for 30 minutes) generated by whole-body alternating magnetic fields of 6–12.5 kA/m at 520 kHz. In spite of the inhomogeneity in the intratumoral distribution of magnetic nanoparticles and local tumor regrowth, widespread tumor necrosis was observed after hyperthermia treatment and tumor growth was slightly delayed in comparison with untreated controls (Jordan et al. 1997). The first *in vivo* preliminary evaluation in a rat model of prostate cancer demonstrated successful intraprostatic nanoparticle infiltration, excellent tolerability and stable steady-state thermoablative intratumoral temperatures (50°C using a field strength of 15 kA/m) induced by an alternating magnetic field (Johannsen et al. 2004). Further investigation of an orthotopic Dunning R3327 rat prostate cancer model revealed an intra-prostatic temperature of 70°C with a maximum field strength of 18 kA/m resulting in significant growth inhibition of 44–51% over control animals (Johannsen et al. 2005b). Subsequent studies of magnetic nanoparticle-mediated hyperthermia in combination with RT (20 Gy) in a rat prostate cancer model demonstrated a therapeutic efficacy equivalent to a single radiation of 60 Gy (Johannsen et al. 2006). Similar results were observed with complete tumor regression 30 days after hyperthermic treatment of DMBA-induced rat mammary cancers using magnetic nanoparticles (Motoyama et al. 2008). In an animal model of metastatic prostate cancer to bone, application of an alternating magnetic field to magnetic nanoparticles conjugated to cationic liposomes demonstrated potent suppression of tumor proliferation in the bone microenvironment (Kawai et al. 2008). The promising preclinical activity of magnetic nanoparticle-mediated hyperthermia has now been advanced to early clinical experiences discussed later.

Carbon nanotube induced hyperthermia

Carbon nanotubes (CNT) are another class of nanomaterials that holds great potential for various biomedical applications including extrinsically activated hyperthermia. CNTs are nested, cylindrical grapheme structures with diameters ranging from a few to hundreds of nanometers and lengths up to a few micrometers (Zheng et al. 2004). The extraordinary photon-to-thermal energy conversion efficiency of CNTs with high absorption cross-section in the NIR region of the electromagnetic spectrum stimulated several investigations to exploit their potential for anticancer therapy (Kam et al. 2005; O'Connell et al. 2002). Several *in vitro* studies have demonstrated the use of targeted and non-targeted CNTs (single walled) for photothermal ablation of cancer cells (Biris et al. 2009; Chakravarty et al. 2008; Kam et al. 2005; Mahmood et al. 2009; Torti et al. 2007; Wang et al. 2009). While these studies have used NIR irradiation to generate hyperthermia, radiofrequency fields have also

been shown to induce thermal toxicity in malignant cells. In this study, internalized single walled CNTs (SWCNTs) in human cancer cells were exposed to a 13.56 MHz radiofrequency field to induce noninvasive, selective, concentration dependent thermal destruction. Direct intratumoral injection of SWCNTs followed by radiofrequency treatment at 48 hrs demonstrated complete necrosis of tumors when compared to the controls (Gannon et al. 2007). *In vivo* obliteration of solid human epidermoid tumor xenografts in mice without harmful side effects or tumor recurrence for 6 months was demonstrated by combining intratumoral injections of SWCNTs (~ 120 mg/ml, 100 μ L) with NIR irradiation (808 nm, 76 W/cm³) for 3 min. SWCNTs were completely excreted (in 2 months) via the biliary or urinary pathways (Moon et al. 2009). Recently, multi walled CNTs (MWCNTs) have been explored as a mediator for photothermal therapy of cancer because of their enhanced absorption cross-section when compared to SWCNTs (Kam et al. 2005). A long-term survival study following a single treatment of kidney tumors with MWCNTs (100 μ g/mouse) and NIR radiation (1064 nm; 3W/cm²) for 30 seconds demonstrated tumor ablation with minimal local or systemic toxicity. The tumor ablation achieved with a relatively low laser power and very minimal exposure time suggests that the photothermal efficacy of MWCNTs is considerably greater than SWCNTs (Burke et al. 2009). More recently, treatment of prostate cancer xenografts in nude mice with MWCNTs demonstrated that DNA-encasement enhanced the heat emission from MWCNTs following NIR irradiation with a 3-fold lower concentration of MWCNTs than that required to impart a 10 °C temperature increase in bulk solution. A single intratumoral injection of MWCNTs (100 μ L of a 500 μ g/mL solution) followed by laser irradiation at 1064 nm, 2.5 W/cm² resulted in complete eradication of PC3 xenograft tumors (Ghosh et al. 2009). Despite these promising results, toxicity concerns about carbon nanotubes have been attributed to factors such as surface chemistry, degree of aggregation, and chemical functionalization (Dumortier et al. 2006; Magrez et al. 2006; Sayes et al. 2006; Wick et al. 2007). In addition, the route of administration also contributes the likelihood of toxicity. For instance, exposing the mesothelial lining of the body cavity of mice to long multiwalled carbon nanotubes resulted in granuloma formation similar to that noted with asbestos exposure (Poland et al. 2008). Similarly, in a manner reminiscent of asbestos-associated pleural fibrosis and mesothelioma formation, multiwalled carbon nanotubes reach the subpleura in mice after a single inhalation exposure (Ryman-Rasmussen et al. 2009). Nonetheless, at low doses, ranging from 20 – 850 μ g/kg body weight, carbon nanotubes are non-toxic in mice (Liu et al. 2007; Liu et al. 2008; Schipper et al. 2008; Singh et al. 2006). Even at high oral doses of 1000 mg/kg body weight, a more recent study has demonstrated that carbon nanotubes are non-toxic (Kolosnjaj-Tabi et al.). Clearly, the toxicity of carbon nanotubes needs to be carefully evaluated in parallel with continued exploration of the use of carbon nanotubes for biomedical applications.

Clinical experience

The first indication of clinical feasibility of nanoparticle-based hyperthermia treatment was provided by a German pilot study in 10 patients with biopsy-proven locally recurrent prostate cancer following prior RT. In the absence of an extant standard treatment for recurrent prostate cancer, patients were eligible as long as they were either not suitable for or refused salvage radical prostatectomy. In an approach similar to prostate brachytherapy, patients under general anesthesia underwent transrectal ultrasound/fluoroscopy-guided external template-assisted transperineal intraprostatic injection of a nanoparticle dispersion to achieve a three-dimensional distribution paralleling a preplan (Johannsen et al. 2005a). The magnetic nanoparticles had an average core size of 15 nm with an aminosilane-type shell and remained stable in the injected location for all six weeks of treatment. Computed tomography images allowed visualization of the spatial distribution of nearly 90% of all magnetic nanoparticles in suspension (112 mg/ml of ferrites in aqueous solution) whereas

ultrasound and MRI were incapable of providing similar anatomic definition. A customized magnetic field applicator MFH 300F (MagForce Nanotechnologies) (Gneveckow et al. 2004) provided the 100 kHz alternating magnetic field at a variable field strength of beginning at 2.5 kA/m and escalated to 18 kA/m as tolerated by the unanesthetized patient. A median temperature of 40.1°C was attained in 90% of prostates and a median CEM 43°C T₉₀ of 7.8 min was achieved over six 60-min weekly treatments. A 4–5 kA/m constant magnetic field strength was tolerated for the entire hour by all patients. With a median follow-up of 17.5 months, no systemic toxicity was noted (Johannsen et al. 2007a). Acute urinary retention occurred in 4 patients with pre-existing urethral strictures. Quality of life assessments detected acute (midway through and upon completion of 6-week course) decline in social and sexual functioning, and increased fatigue, pain, and urinary symptoms. Later (3–6 months from treatment), only deterioration in social functioning was recorded.

Challenges with nanoparticle-mediated hyperthermia

Biodistribution

Even a single injection of nanoparticles directly into the prostate, in an idealized hypothetical scenario, leads to a non-uniform spatial distribution of particles that is defined by the injection volume, the injection rate, the concentration of the particles and the resilience of the tissue (Salloum et al. 2008). The heterogeneity in intraprostatic biodistribution of nanoparticles is compounded by the need for multiple injections to encompass the entire prostate. It is well recognized that the spatial distribution of nanoparticles dominates the resulting spatial distribution of temperature within the prostate (Salloum et al. 2009). In the case of systemically delivered nanoparticles not only is there heterogeneous accumulation within tumors, there is also considerable variability in organ/tissue biodistribution and pharmacokinetics. For instance, the kinetics of accumulation within tumors is influenced by the hydrodynamic diameter (Choi et al. 2007), shape (Champion and Mitragotri 2009), surface charge (Akiyama et al. 2009), and the extent (Akiyama et al. 2009), length (Choi et al. 2009) and branching (Veronese 2001) of the polyethylene glycol surface coating often used to confer “stealth” properties for immune evasion from the reticuloendothelial system. Experimental evidence suggests that spherical nanoparticles with a hydrodynamic diameter of approximately 5.5 nm and a zwitterionic surface charge are cleared by the kidneys and not entrapped within the reticuloendothelial system (Choi et al. 2007) whereas larger nanoparticles (20 nm) are captured by the reticuloendothelial macrophages (Diagaradjane et al. 2008a). At the tissue-level, leaky vascular fenestrations and chaotic immature vascular architecture largely determine the geographic distribution of nanoparticles within tumors - untargeted nanoparticles, irrespective of their size, leak out of tumor vasculature and remain sequestered and spatially confined to the perivascular zone (Diagaradjane et al. 2008a) (Diagaradjane et al. 2008b). The heterogeneity in vascular architecture and the consequent heterogeneity in intratumoral distribution of nanoparticles results in non-uniform temperature profiles within tumors when these nanoparticles are activated. Some reports would suggest that this heterogeneity is advantageous when combined with radiation since focal vascular disruption may ensue following the juxtaposition of this form of hyperthermia with RT (Diagaradjane et al. 2008b). Therefore, in contrast to the vascular compartment of tumors serving as a heat sink with traditional forms of hyperthermia, in this instance the preferential heating of nanoparticles entrapped within perivascular spaces focuses thermal energy on endothelial cells, a prime target for radiosensitization strategies. Despite this potential advantage, the heterogeneous distribution of nanoparticles, the inhomogeneity of NIR density (greater intensity closer to the illumination source), and difficulty with modeling and dosimetry make nanoparticle-mediated hyperthermia challenging. To some extent, the heterogeneity in the nanoparticle distribution can be overcome by specifically targeting tumor interstitium-

penetrating small nanoparticles to tumor-specific biomarkers for a relatively uniform and homogeneous distribution (Diagaradjane et al. 2008a).

Quantification and visualization

One of the challenges of using nanoparticles for cancer therapy is the inability to readily quantify and/or visualize these particles after they have accumulated within tumors. As noted above, magnetic nanoparticles are not visualized on MRI due to a signal void in the areas containing high concentrations of interstitially injected iron oxide nanoparticles (Johannsen et al. 2007b). Similarly, they are not readily visualized on transrectal ultrasound. CT imaging was able to detect large deposits of injected magnetic nanoparticles but this sensitivity would be much lower if the concentration of nanoparticles is considerably lower, as in the case of systemically administered nanoparticles. For such instances, dedicated techniques are needed to quantify the amount of nanoparticles globally present within tumors as well as to visualize geographic locations of these nanoparticles within tumors. In the case of gold nanoparticles, one technique that non-invasively estimates the quantity of gold (and therefore, the number of gold nanoparticles) within tumors in real time is diffuse optical spectroscopy (DOS). In DOS, light is delivered to and collected from tissue via an optical fiber probe and the specific reflectance spectra of gold nanoparticles are used to indirectly measure gold concentrations after accounting for the contribution of oxy-hemoglobin and deoxy-hemoglobin. In one such study, DOS measurements accurately quantified the concentration of gold nanoshells in tissue phantoms within 10% of the known concentration as well as *in vivo* where gold content measurements were validated by neutron activation analysis, the standard method of measuring gold nanoshell concentrations in tissues that are excised, dehydrated and irradiated within a nuclear reactor (Zaman et al. 2007). While DOS provides a global estimate of gold nanoparticle concentration within tumors, it does not provide spatial information on the distribution of these nanoparticles within tumors. One technique that offers this option is narrowband imaging which capitalizes on the strong NIR absorption of gold nanoshells to distinguish between blood and nanoshells in the tumor by imaging in narrow wavelength bands in the visible and NIR, respectively (Puvanakrishnan et al. 2009). By clearly discriminating between blood and gold nanoshells, this technique allows imaging of the heterogeneous spatial distribution of nanoshells within tumors. This geographic distribution imaging can be verified *ex vivo* by two-photon luminescence imaging. Alternative strategies include radiolabeling the nanoparticle for visualization by positron emission tomography or single photon emission computed tomography, fluorescent dye labeling for optical tomography of enhanced fluorescence (Bardhan et al. 2009), optical coherence tomography (Gobin et al. 2007), or NIR diffuse optical tomography (Wu et al. 2005).

Modeling and dosimetry

Visualizing and quantifying gold nanoparticles accurately in tumors is a prelude to modeling and mapping the temperature elevations within tumors and generating dosimetry outputs similar to RT. For instance, continued development and clinical translation of gold nanoshell-mediated thermal therapy requires computational tools for estimating heat distribution within the tumor and surrounding tissues. One model for estimating heat from NIR laser activation of gold nanoshells uses a modified bioheat equation with a finite element model based on alterations in the optical properties of the medium when laden with nanoshells to predict temperature rise and magnetic resonance thermal imaging to validate it (Elliott et al. 2008). However, this model requires prior knowledge of the altered optical properties of the medium with nanoshells, which might not be readily obtained during routine *in-vivo* experiments or in future clinical applications. An alternative technique is to use the light transport theory with a diffusion approximation to model the temperature rise within nanoshell-free media due to NIR laser power dissipation and combine this with

modeling of plasmonic heat generated by NIR irradiated individual gold nanoshells due to photothermal effect to estimate the global elevation of temperature within nanoshell-laden media (Cheong et al. 2009). This model accounts for the response of tissue to laser illumination as well as the optical and thermal effects due to embedded individual gold nanoshells on the temperature rise in tissues. Similarly, in the clinical study described earlier, real-time thermal measurements in four catheters (2 in each lobe of the prostate) were fitted to thermal dosimetry calculations using the bio-heat transfer equation solved on a finite element basis using iron-mass (derived from CT density), specific absorption rate (SAR) of magnetic nanoparticles, magnetic field strength, and an estimated perfusion (Johannsen et al. 2007b). In the earliest incarnation of individualized noninvasive three-dimensional thermal modeling based on spatial distributions of intraprostatic magnetic nanoparticles, the model overestimated temperatures near the urethra and bladder base, and underestimated temperatures at the prostatic apex and along skin folds. On the flip side, the heterogeneity of nanoparticle distribution (a function of injection flow rate, concentration and firmness of a previously radiated prostate) (Salloum et al. 2008) and consequent non-uniform intraprostatic temperatures also results in an overestimation of actual temperature by intraluminal measurements. Nonetheless, the reasonable agreement between noninvasive temperature calculations and invasive thermometry within the prostate suggests that thermal modeling could provide a global assessment of temperature across a target volume that complements focal thermal monitoring. Admittedly, unlike radiation dosimetry that is based on physical parameters (radiation quality, radiation quantity, tissue density and tissue geometry), thermal dosimetry also needs to account for tissue physiology (heat dissipation and transfer being modulated by vascularity, degree of necrosis/fibrosis, tissue conductivity/perfusion, and the influence of heat itself on these parameters) (Hurwitz 2007). Continued refinement of thermal dosimetry algorithms incorporating normal tissue avoidance constraints could guide the selection of injection coordinates for highly conformal thermotherapy (Salloum et al. 2009). If predictive models do not turn out to be sufficiently accurate, magnetic resonance thermometry currently provides accurate and real-time spatiotemporal resolution of thermal dose without requiring accurate heat-transfer models and precise knowledge of local particle concentrations. Magnetic resonance thermometry capitalizes on the correlation between a shift in proton resonance frequency and elevation of temperature within tissue to facilitate mapping of temperature distributions (Wust et al. 2006). Typically, after obtaining a reference (baseline) scan and a measurement scan, phase subtraction allows computation of a proton resonance frequency shift. Since the proton resonance frequency of adipose tissue does not shift as a function of temperature, nulling these regions (fat correction) can be utilized for calibration and accounting for baseline drift. This novel non-invasive thermal imaging remains one of the most significant technical advances in clinical applications of thermal therapy that allows real-time temperature monitoring, confirmation of adequate thermal dose coverage and adaptive course-correction during treatment.

Biocompatibility

A legitimate concern with all classes of nanoparticles is their toxicity, which is, in turn, determined by the dose, core composition, surface chemistry, and location and duration of confinement to the body. Whereas the use of gold and iron oxide in medicine for many decades offers some degree of familiarity with the safety profile of these bulk metals, the unique properties and biodistribution of nanoscale formulations of these metals calls for systematic evaluation and characterization of their biocompatibility. The National Institutes of Health also recognizes the need for toxicity testing of nanoparticles to parallel pre-clinical efficacy assessment - the Nanotechnology Characterization Laboratory, working in concert with the National Institute of Standards and Technology (NIST) and the U.S. Food and Drug Administration (FDA), facilitates such testing and regulatory review. Gold nanoshells have

been extensively tested preclinically and are now in clinical trials as investigational new devices.

Unique opportunities with nanoparticle-mediated hyperthermia

Active targeting

As noted above, a unique feature of systemic administration of nanoparticles for hyperthermia is the ability to potentially target the nanoparticle preferentially to tumor cells, thereby increasing tumor-specificity and reducing collateral damage to surrounding critical structures. This has been demonstrated *in vitro* using ephrinA 1 (Gobin et al. 2008). Similarly, circulating nanoparticles (Gao et al. 2004) could be guided onto prostate-specific membrane antigen, an integraltransmembrane glycoprotein expressed on the surface of prostate carcinoma at all stages of the cancer (Rajasekaran et al. 2005) but highly restricted in extraprostatic tissues and normal endothelial cells (Silver et al. 1997). Alternatively, rather than focusing delivery on prostate cancer cells, the nanoparticles can be delivered to prostate cancer neovasculature by targeting molecules such as integrin $\alpha_v\beta_3$, a cell adhesion molecule that is significantly up-regulated on endothelia during angiogenesis and on fast-growing solid tumor cells, but not on quiescent endothelium and normal tissues (Hood and Cheresh 2002). Nevertheless, although targeted therapy is highly appealing as a means of treating prostate cancer without excessive collateral damage to surrounding normal tissue, a major limitation of such treatments for prostate cancer, which is typically a multifocal disease, is the lack of contemporary diagnostic imaging modalities to visualize localized foci of involvement.

Targeted payload delivery

Another unique feature of nanoparticle-mediated hyperthermia is the possibility of delivering an entirely different payload to the tumor when the nanoparticle concentrates within it. This is in contrast to using hyperthermia to trigger release of payloads contained with separate thermosensitive nanoparticles – this form of hyperthermia-triggered payload release would potentially be applicable to any form of hyperthermia. Instead, this feature refers to hybrid nanoparticles that serve as activatable thermal sources as well as therapeutic payload carriers. As a first step in achieving this goal, it has been shown that pretreatment with intravenously administered TNF- α -coated gold nanoparticles enhances thermally induced tumor growth delay in a mouse model of breast cancer (Visaria et al. 2006). Future applications could entail externally-triggered thermally-mediated release of payloads within the confines of the tumor alone - the payloads could include targeted therapeutic peptides/proteins, toxins, oligonucleotides and small interfering RNA.

Radiation dose enhancement

One additional benefit of combining RT with metal nanoparticle-mediated hyperthermia is the possibility of radiation dose-enhancement due greater photoelectric interactions in the presence of higher atomic number (Z) gold preferentially within tumors. Irradiation of tumor-bearing mice after injecting gold nanoparticles was shown to induce remarkable tumor regression and long-term survival without any significant toxicity when compared to mice irradiated without gold nanoparticles (Hainfeld et al. 2004). This dramatic outcome was attributed to significant increase in the photoelectron fluence within gold nanoparticle-laden tumors and their vasculature during x-ray irradiation (Hainfeld et al. 2008). A subsequent Monte Carlo computational study confirmed that the macroscopic (or average) tumor dose enhancement in the original animal study was dependent on gold concentration within the tumor and the photon beam quality, ranging from several hundred percent for diagnostic x-rays to a few percent for typical megavoltage photon beams (Cho 2005; Roeske et al. 2007). Since low energy gamma rays interact with gold nanoparticles within the tumor

predominantly via photoelectric effect, additional computational studies suggested that macroscopic dose enhancement might be more pronounced in prostate brachytherapy applications (Cho et al. 2009).

Conclusions

Nanoparticle-mediated hyperthermia promises to be a new minimally invasive tool in the armamentarium for the treatment of prostate cancer. A greater understanding and increasing research related to novel particle compositions, geometries, activation strategies, targeting techniques, payload delivery strategies and radiation dose enhancement concepts are likely to energize this field in the coming years. Accurate modeling and dosimetry are likely to facilitate seamless and logical transition from the bench to the bedside.

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Figure 1.
A schematic representation of the typical nanoparticles utilized in thermal therapies.

Figure 2. Spatial temperature map of magnetic resonance thermal imaging indicating temperature rise ($^{\circ}\text{C}$) above the baseline following near infrared illumination of gold nanoshells-laden tumors (Reproduced with permission from.