Published in final edited form as:
Drug Resist Updat. 2014 April ; 17(0): 13–23. doi:10.1016/j.drup.2014.04.001.

Nanoways to Overcome Docetaxel Resistance in Prostate Cancer

Aditya Ganju[1,2], **Murali M. Yallapu**[1,*], **Sheema Khan**[1], **Stephen W. Behrman**[3], **Subhash C. Chauhan**[1,*], and **Meena Jaggi**[1,*]

[1]Department of Pharmaceutical Sciences and the Center for Cancer Research, College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN 38163, USA

[2]College of Graduate Health Sciences, University of Tennessee Health Science Center, Memphis, TN 38163, USA

[3]Department of Surgery, University of Tennessee Health Science Center, Memphis, Tennessee 38163, USA

Abstract

Prostate cancer is the most common non-cutaneous malignancy in American men. Docetaxel is a useful chemotherapeutic agent for prostate cancer that has been available for over a decade, but the length of the treatment and systemic side effects hamper compliance. Additionally, docetaxel resistance invariably emerges, leading to disease relapse. Docetaxel resistance is either intrinsic or acquired by adopting various mechanisms that are highly associated with genetic alterations, decreased influx and increased efflux of drugs. Several combination therapies and small P-glycoprotein inhibitors have been proposed to improve the therapeutic potential of docetaxel in prostate cancer. Novel therapeutic strategies that may allow reversal of docetaxel resistance include alterations of enzymes, improving drug uptake and enhancement of apoptosis. In this review, we provide the most current docetaxel reversal approaches utilizing nanotechnology. Nanotechnology mediated docetaxel delivery is superior to existing therapeutic strategies and a more effective method to induce P-glycoprotein inhibition, enhance cellular uptake, maintain sustained drug release, and improve bioavailability.

Corresponding authors: Dr. Murali M Yallapu, Cancer Research Building, University of Tennessee Health Science Center, 19 South Manassas, Memphis, TN 38163; Phone: 901-448-7313; Fax: 901-448-1051; myallapu@uthsc.edu. Prof. Subhash C. Chauhan, Cancer Research Building, University of Tennessee Health Science Center, 19 South Manassas, Memphis, TN 38163; Phone: 901-448-2175; Fax: 901-448-1051; schauha1@uthsc.edu. Dr. Meena Jaggi, Cancer Research Building, University of Tennessee Health Science Center, 19 South Manassas, Memphis, TN 38163; Phone: 901-448-6848; Fax: 901-448-6801; mjaggi@uthsc.edu.

Competing interests
The authors declare that they have no competing interests in this work.

Disclaimer
The views, opinions and statements expressed in this review are those of the authors and do not reflect the official policy or position of the University of Tennessee Health Science Center, Department of Defense and the National Institutes of Health.

Keywords

Docetaxel; chemoresistance; nanotechnology; nanomedicine; nanoparticles; drug delivery; drug targeting; prostate cancer

1. Introduction

It is estimated that over 200,000 new prostate cases and over 29,000 deaths will occur in the United States in 2013 (Siegel et al., 2013). Current treatment options include surgery, radiation, and chemotherapy. The risk of prostate cancer death has decreased in the past few years due to screening by serum prostate specific antigen (PSA) for early detection and tumor progression (Nelson et al., 2013; Penney et al., 2013). Four stages of prostate cancer have been identified based upon "Tumor Node Metastasis" system (http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-staging). The majority of metastatic prostate cancers can be effectively treated with docetaxel. In prostate cancer stage I, the cancer is found only in the prostate. In this stage the cancer is hormone-naïve and asymptomatic or minimally symptomatic. In stage I prostate cancer, chemotherapeutic agents are not recommended; instead, tumors are subjected to surgery, brachytherapy (Johnson and Roach, 2014) and other forms of treatment such as cryosurgery (Al Ekish et al., 2013), and High Intensity Focused Ultrasound (HIFU) (Komura et al., 2013). However, for most of the other stages of metastatic prostate cancer, docetaxel is used. In stage II, prostate cancer typically grows inside the prostate with the intact basement membrane. Cancer in this stage is fully symptomatic. Docetaxel, mitoxantrone (Song et al., 2013), and platinum/etoposide (Aparicio et al., 2013) treatments are used at this stage to treat cancer. In stage III, prostate cancer sparsely spreads outside the prostate. Such cancer can also be treated with docetaxel but in some instances cancer develops resistance to it. Radiation followed by treatment with chemotherapy such as docetaxel, cabazitaxel (Fernandez et al., 2013), mitoxantrone (Song et al., 2013), and abiraterone (Sorensen et al., 2013) is the standard treatment regime for this stage. Stage IV prostate cancer is the stage where cancer has spread outside the prostate and metastasized to other organs/tissues. The standard treatment options for stage IV prostate cancer include external-beam and palliative radiation therapy or surgery with transurethral resection of the prostate and watchful waiting or active surveillance.

Prostate cancer at the beginning stage is androgen (AR) sensitive and it can be treated with either an androgen-receptor antagonist or chemical castration but as the cancer progresses the majority become androgen-resistant; response to these treatments is poor, leading to high rates of mortality and morbidity (Goldberg et al., 2013). Hormone therapy has been frequently used to treat advanced stage prostate cancer (Teixeira et al., 2013) and this therapy also works efficiently on androgen sensitive prostate cancer. After a certain period the majority of prostate cancer cells develops resistance to hormone treatment and become androgen independent. Docetaxel (Taxotere®) is a clinically approved drug by the Food and Drug Administration to treat various metastatic prostate cancers including androgen independent and castration resistant prostate cancer (Bahl et al., 2013). However, resistance to docetaxel is a significant clinical problem that has been a challenge since it was

established as a front-line therapy for metastatic castrate-resistant prostate cancer. Newer chemotherapeutic drugs developed to treat docetaxel resistant patients carry significant hematological toxicities that may outweigh their benefits. Therefore, this review aims to discuss recent nanotechnology based approaches and future directions for overcoming docetaxel-resistance for effective prostate cancer treatment.

2. Transport, metabolism, molecular mechanism and action of docetaxel in cancer cells

Docetaxel is considered the most promising anticancer drug for prostate cancer treatment. It is a semi-synthetic analog of paclitaxel with proven low systemic toxicity and higher cellular retention (Jones et al., 2005). It thereby provides benefit in progression free survival. It promotes microtubule stabilization which can lead to cell cycle arrest at G_2M phase and further leads to initiation of apoptosis and cytotoxicity in cancer cells (Clarke and Rivory, 1999). Docetaxel is a more potent drug than paclitaxel; thus, a smaller dose of docetaxel was able to cause significant apoptosis induced cancer cell death than a higher dose of paclitaxel (Grant et al., 2003). Docetaxel (chemical formula, $C_{43}H_{53}NO_{14}$ and M.W. 807.9 g mol^{-1}) is a well-established water insoluble anti-mitotic chemotherapeutic agent but it is readily dissolved in 0.1N hydrochloric acid, chloroform, ethanol and methanol. Because of its hydrophobic nature, its transportation inside the cell occurs with the help of plasma proteins such as lipoproteins, albumin and α1 acid glycoprotein (Clarke and Rivory, 1999). Once it is internalized, hydroxylation occurs at the methyl group of the *tert*-butyl group at the C_{13} side chain which is further oxidized and converted into a cyclical form in animals and humans (Monegier et al., 1994; Royer et al., 1996). This cyclic form of docetaxel is responsible for binding to the microtubule and stabilizing the microtubule structure. Such microtubule polymer hyperstabilization ultimately leads to G_2M phase cell cycle arrest and cell death (Verweij et al., 1994). Metabolism of docetaxel occurs in liver and the cytochrome P450 member, CYP3A4, is a major enzyme responsible for its breakdown (Kruijtzer et al., 2002).

Docetaxel suppresses AR nuclear translocation through microtubule bundling, leading to cytoplasmic accumulation of the AR. Although tubulin mutations at the taxane binding site may account for clinical taxane resistance including paclitaxel, it does not affect the binding of docetaxel or its inhibition of nuclear AR localization, even though the binding site is shared. This phenomenon is largely due to different binding modes of docetaxel and paclitaxel such that mutation may affect the binding of one but not the other (Darshan et al., 2011; Giannakakou et al., 2000; Nettles et al., 2004). Subsequent gene alteration rendering AR trafficking independent of microtubule control leads to docetaxel resistance (Darshan et al., 2011). Furthermore, docetaxel resistance in prostate cancer cells can develop due to increased drug efflux, which lowers the drug concentration inside the cell. Docetaxel resistance in part is due to increased expression of an ATP-binding cassette (ABC) transporter, P-glycoprotein (P-gp), the product of the *MDR1*/*ABCB1* gene (Ueda et al., 1987). P-glycoprotein is a broad spectrum multidrug efflux pump which binds to the hydrophobic substrate through its transmembrane domain and ATP hydrolysis causes conformational change in the transporter leading to release of the drug to the outer leaflet or the extracellular space (Gottesman et al., 2002). Drug resistance can also be developed due

to increased cellular metabolism of drug detoxifying proteins, such as glutathione-S-transferase, or alterations in β-tubulin isotypes with different kinetics of microtubule formation (O'Neill et al., 2011). Solid tumors are heterogeneous in vasculature and increase interstitial fluid pressure (IFP) due to higher vascular permeability and absence of a lymphatic system. In addition, solid tumors with an acidic environment and a lack of oxygen also contribute to the drug resistance.

In addition to activation of the androgen receptor (AR) and overexpression of ABC or P-gp transporters that account for increased drug efflux, other drug resistance mechanisms include hypoxia, increased IFP, mutation of β-tubulin, overexpression of βIII-tubulin/MAP, and activated RTK, EGFR, IGFR-1, AKT, and Erk1/2 (Fig. 1). Importantly, altered proliferative and anti-apoptotic mechanisms, aberrant angiogenesis and a favorable tumor microenvironment with expression of ECM endothelin receptor A, also contribute to the drug resistance (Fig. 1).

3. How to overcome docetaxel resistance

The main cause of resistance in prostate cancer is activation of AR in an androgen independent manner leading to translocation of AR to the nucleus, thus activating oncogenes and development of resistance. A potent antagonist of AR translocation to nucleus, Enzalutamide (Xtandi® and formerly known as MDV3100), has been used to overcome resistance (Tran et al., 2009). This drug in phase I/II human studies has shown some promising results in patients already treated with docetaxel and phase III studies are currently underway. Agents which inhibit both AR and mutation of cytochrome P-45017 alpha gene (CYP17) are being developed to overcome AR mediated resistance (Ahmed et al., 2014). The other mechanism to counter resistance is to target proliferative and survival pathways (Mimeault et al., 2012). Combination therapy using monoclonal antibody against proliferative pathways such as EGFR and IGFR-1 with chemotherapy is underway in phase II clinical trials (Diane Lauren Reidy, 2010). Monoclonal antibody against IL-6, which is involved in resistance, didn't improve overall outcome when used in a combination therapy with mitoxantrone (Fizazi et al., 2012). Treatment with chemotherapy often elevates the survival pathway leading to resistance in prostate cancer cells and treatment with antisense RNA, such as custirsen, against Bcl-2 mRNA has shown promising results when used in combination with docetaxel or mitoxantrone (Saad et al., 2011). Custirsen is an antisense oligonucleotide, currently under Phase III evaluation for second-line metastatic castrate-resistant prostate cancer. Custirsen binds to the translation initiation site of clusterin mRNA, an ATP-dependent heat shock protein, and inhibits cell survival protein synthesis (Higano, 2013). Custirsen differs from other antisense oligonucleotide systems as 2′-methoxyethyl is located on the ribose group at the end of the phosphorothioate backbone. The effect of antisense oligonucleotides on inhibitors of apoptosis and other anti-apoptotic Bcl-2 family of proteins is currently being evaluated in clinical trials. Targeting VEGFR signaling by different anti-angiogenic molecules to improve drug delivery to the target organ is currently under trial. Agents that target different receptor tyrosine kinases in combination with chemotherapy are also undergoing trials.

A number of microRNAs (miRNAs) such as miRNA-125b-2, miRNA-136, miRNA-151-3p, miRNA-200a, miRNA-744a, miRNA-9, miRNA-9, miRNA-99a, miRNA-126, miRNA-142-5p, miRNA-18b, miRNA-27a, miRNA-27b, and miRNA-30a have shown oncogenic activity (are upregulated) while other miRNAs such as miRNA-205, miRNA-106b, miRNA-16, miRNA-363 act as tumor suppressor genes (are downregulated) in both local PrCa and metastasis PrCa (Watahiki et al., 2013). However, in hormone refractory advanced state and metastasis PrCa, various independent gene sequencing analyses report that miR-205 has shown a signature downregulation compared to all other tumor suppressor miRNAs (Gandellini et al., 2009a; Gandellini et al., 2009b; Schaefer et al., 2010; Watahiki et al., 2013). Thus, miR-205 has been considered a suitable single miRNA in replacement therapy to reestablish tumor suppression functions in PrCa (Coppola et al., 2010; Porkka et al., 2007). MiR-205 acts as a tumor suppressor in human PrCa, as its exogenous expression in PrCa cells reverts EMT, restores basement membrane (BM) deposition and attenuates cancer progression (Gandellini et al., 2012) (Fig. 2). Its downregulation expression also enhances invasive properties favoring metastasis in clinically localized carcinomas (Gandellini et al., 2012) (Fig. 2). Downregulation of miR-205 also confers resistance to chemo/radiotherapy-induced apoptosis in PrCa cells derived from advanced metastatic cancers (Bhatnagar et al., 2010). All these studies suggest miR-205 can regulate and target multiple oncogenes and oncogenic pathways to improve PrCa response to Dtxl chemotherapy.

Targeting tumor microenvironment is another way to counter resistance in prostate cancer but such targeted approaches have not yielded any significant results. Alternatively, a combination therapy that targets Endothelin receptor A along with docetaxel is currently undergoing trial. Some promising results have been shown with radiopharmaceuticals that have a potent effect on both metastatic prostate cancer cells and host cells and many such drugs in combination with docetaxel and mitoxantrone are currently under trial. Drugs that are structurally similar to docetaxel but less likely to be a substrate for drug efflux by P-gp have been studied and are currently under trial. Third generation taxanes and epothilones are also being studied and under trial.

4. Using nanotechnology to overcome docetaxel resistance

Nanoparticle (NP) drug delivery systems could prove to be a promising adjunct to improve the therapeutic effect of docetaxel. NPs maximize the permeability and retention of drugs in solid tumors and thus can reduce non-specific toxicity (Hu and Zhang, 2009). Here we describe some nanoformulations that can potentially inhibit docetaxel resistance in prostate cancer. There has been significant interest among nanotechnologists to generate safe and effective drug (docetaxel) nanoformulations for cancer therapy (Fig. 3). The concept of targeting of therapeutic agents to cancer cells is not new and in fact it had been proposed a century ago (Elliott, 2012; Strebhardt and Ullrich, 2008). During the last two decades, targeted drug nanoformulations with the potential to improve solubility or circulation efficiency and permeability while decreasing toxicity of chemotherapeutic agents has received increasing attention. Intense research has been focused on various nano-based approaches but few types of nanoparticles have been utilized for docetaxel delivery. These systems include liposomal, polymer, hybrid/composite, polymer micelles, and docetaxel

conjugates (Fig. 4). Table 1 describes each formulation involved to reverse docetaxel resistance. Data relative to the utilization of nanoparticles in humans has been sparse.

4.1. Liposomes

Liposomal encapsulated docetaxel is an attractive and promising route for prostate cancer therapy. Liposomes increase drug solubility, provide protection from drug degradation and drug related toxicity and help overcome multidrug resistance mediated by P-glycoproteins. Deeken et al. (Deeken et al., 2013) developed a negatively charged cardiolipin based liposomal formulation that can bind with positively charged docetaxel to maximize its efficacy, distribution and pharmacokinetics. These superior characteristics increase the uptake of drug and counter the effect of overexpression of ABC or P-gp transporter, thereby inhibiting activation of proliferative and anti-apoptotic pathways. Another liposomal formulation composed of phosphatidylethanolamine (PE) and oleic acid is also capable of encapsulating docetaxel efficiently and as soon as the formulation reaches the acidic environment of the tumor, docetaxel is selectively released by undergoing a transition from double to hexagonal phase by repulsion of PE and oleic acid (Zhang et al., 2012a). Higher retention and cellular release of docetaxel by liposomal mediated delivery *via* intravenous route (Zhang et al., 2012a) has been shown to decrease docetaxel resistance compared to free drug administration.

Magneto-liposome bound docetaxel formulation has been found to potentiate the inhibition of proliferation in prostate cancer cells and their bone metastasis in a rat model (Kobayashi et al., 2013) by the inhibition of receptor tyrosine kinase pathways such as EGFR, PI3K/AKT and Erk1/2 mediated MAP Kinase activation. Further, this magnetic liposomal formulation reduced the tumor volume by 66% as compared to free drug and induced activation of IFN-gamma and IL-2 expression (Yoshida et al., 2012). This treatment regime has been found to reduce multidrug resistance by inhibiting overexpression of ABC transporter, anti-apoptotic pathway and receptor tyrosine kinase mediated proliferative signaling. Thus, the chances of relapse are reduced as the cells, if not killed by docetaxel, can be killed by heating under the radiofrequency.

Another successful approach using a PEGylated vitamin E (D-alpha-tocopheryl polyethylene glycol 1000 succinate monoester, TPGS) coated liposomal docetaxel formulation is capable of improving docetaxel solubility, inhibiting P-glycoprotein mediated multi-drug resistance and increasing oral bioavailability (Muthu et al., 2012). Additionally, this liposomal formulation also results in a 10-fold increase in cytotoxic activity as compared to free drug after 24 hours of drug administration, implying efficient drug release and uptake by cells. A modified PEGylated liposomal formulation, constructed with N-octyl-O-sulfate chitosan and phospholipid bilayers *via* hydrogen bond and hydrophobic interactions, promotes the uptake, sustained release and longer drug circulation time of docetaxel (Qu et al., 2012). The most efficient way to deliver docetaxel specifically to the prostate tumor is through an antibody conjugated liposomal bound docetaxel formulation (Raju et al., 2013; van der Meel et al., 2013). Prostate cancer cells express high levels of folate receptor, which allows specific binding with folate-conjugated liposomes, receptor mediated endocytosis, superior internalization and enables docetaxel release inside (Li et al.,

2011; Yuan et al., 2010). These formulations prevent efflux of the drug by P-glycoproteins and thus inhibit the buildup of multi-drug resistance (Yamamoto et al., 2011).

4.2. Polymeric nanoparticles

Polymer nanoparticles have great potential to improve the efficacy of chemotherapeutic molecules. A conventional nanoprecipitation process yields < 5% drug loading while emulsion or solvent evaporation methods result in up to 14% drug loading. The most commonly used nanocarrier system for delivery is poly(lactic-*co*-glycolic acid) (PLGA) based nanoparticles but they require sufficient hydrophilic coating, optimal particle size (less than 200 nm) and negative zeta potential in order to avoid opsonization by the reticuloendothelial system (RES) (Dinarvand et al., 2011; Yallapu et al., 2012a; Yallapu et al., 2010b). *In situ* modification of the PLGA nanoparticle's surface with human serum albumin (HSA) leads to a more efficient targeted drug delivery (Manoocheheri et al., 2013; Yallapu et al., 2013a). Bound HSA hydrophilic chains can enhance the cellular uptake by receptor mediated endocytosis or fluid-phase endocytosis. This enables uptake of the drug by the cell and inhibits P-gp accumulation, thus preventing resistance by the cells. The bound HSA PLGA nanoparticle showed a 4-fold increased cytotoxic effect as compared to free drug after 72-hour incubation. This formulation also leads to higher intracellular delivery of the drug. Similar effects can also be attained by coating PLGA nanoparticles with some Food and Drug Administration approved "Generally Recognized As Safe" substances including natural polymers, polyethylene glycol and its derivatives, and pluronic polymers or mixed pluronic polymers which are known to shut down the expression of pumps of the ATP-binding cassette superfamily (Sosnik, 2013). Tao et al. (Tao et al., 2013) synthesized a PLGA and TPGS which improved solubility of the docetaxel and allowed improved permeability through membrane. TPGS inhibits P-gp and thereby inhibits emergence of resistance in cell. Another modification of TPGS polymer with ditocopherol 1000 succinate resulted in a star shaped polymer that showed sensitization to acidic pH may trigger rapid release of drug molecule in tumor cells (Zhao et al., 2013b). Similar copolymer formulations of TPGS and poly(*β*-amino ester) (PBAE) copolymers significantly inhibited the activity of the ABC transporter protein involved in multidrug resistance and caused more cytotoxicity than free docetaxel (Devalapally et al., 2007; Shenoy et al., 2005). This nanoparticle formulation showed up to 69% cell viability as compared to 100% cell viability in the drug solution.

DeSimone's group has developed a biodegradable nanoparticle formulation of docetaxel utilizing a soft-lithography template based approach, i.e., PRINT® (particle replication in nonwetting templates) technology (Enlow et al., 2011). This technology generates poly(lactic acid-*co*-glycolic acid) nanoparticles with high and efficient loadings of docetaxel, up to ~ 40% with encapsulation efficiency of > 90%. PRINT nanoparticles (Chu et al., 2013) exhibit improved docetaxel plasma levels compared to a free docetaxel drug formulation in mouse models. A more significant outcome was noticed with a PLGA targeted nanoformulation of docetaxel generated by a team from MIT, Harvard and BIND Biosciences (Hrkach et al., 2012). This formulation utilized nanoparticles of varying size, PEG molecular weight, polymer/copolymer compositions, lactide/glycolide ratio and encapsulation process. The final product has been ideal in targeting prostate cancer cells in

mice and in humans in a Phase I clinical trial (Hrkach et al., 2012). Photoswitchable nanoparticles are another route to effectively deliver docetaxel to the tumor site. Nanoparticles are delivered in large number to tumor site due to enhanced permeation and retention effect but their effect is often compromised due to a lack of lymphatic vessels and the tumor microenvironment. Photoswitchable nanoparticles utilize the ability to trigger reversible change in nanoparticles on exposure to light and this causes enhanced drug release and tissue penetration (Tong et al., 2013). An *in vivo* study of photoswitchable nanoparticles demonstrated enhanced tumor reduction as compared to nanoparticle drug not exposed to light. This formulation showed no *in vivo* systemic toxicity and a six-fold higher blood plasma concentration as compared to free drug, leading to enhanced efficacy and penetration of the drug in tumor cells.

4.3. Composite and hybrid nanoparticles

Wang et al. demonstrated that docetaxel or 8-hydroxyquinone loaded in mesoporous silica nanoparticle-supported lipid bilayers of hyaluronic acid nanocomposite formulation has produced the strongest antitumor efficacy in xenograft mouse models (Wang et al., 2013). This targeted delivery platform is very effective in accumulating drug in the cancerous cell mass and if conjugated with androgen receptors or CD133 receptor can be an effective treatment modality for prostate cancer. Drug uptake occurs *via* receptor-mediated endocytosis and prevents the accumulation of multi-drug resistance build-up in prostate cancer cells. A copolymer polyethylene glycol (PEG) and poly(ε-caprolactone) (PCL) with a tumor specific gelatinases cleavable peptide insertion was not only able to inhibit cancer cells but also cancer stem cells when docetaxel was conjugated to a miRNA 200c. The miRNA 200c is downregulated in prostate cancer as it inhibits motility and progression from epithelial to mesenchymal transition in prostate cancer (Kim et al., 2013). The cytotoxicity of free drug with a docetaxel equivalent of 64 ng/ml concentration was just 27% whereas the siRNA based nanoparticle formulation had cytotoxicity of 45% (Liu et al., 2013a). This formulation also accompanied a 7-fold increase in E-cadherin levels in each cell. MiR 200c high level expression maintains epithelial phenotype and loss of miR 200c is associated with drug resistance (Kopp et al., 2012). MiR 200c regulates downstream targets such as TrkB and Bmi1. TrkB is a tyrosine kinase family member protein, involved in cell proliferation and anoikis resistance is targeted and silenced by miR 200c. Bmi1 regulates self-renewal and senescence, which confers docetaxel resistance in prostate cancer, and miR200c silences Bim1 and thus inhibits docetaxel resistance. A docetaxel loaded nanocomposite of mesoporous silica and magnetic nanoparticles was able to deliver the drug to the target under magnetic field and is readily taken up by the cells (El-Toni et al., 2013). Mesoporous silica nanoparticles also help to overcome P-gp overexpression in prostate cancer cells (Shen et al., 2011). Lipid-polymer hybrid nanoparticles are highly attractive as a platform for targeted drug delivery (Hadinoto et al., 2013). Such lipid-polymer hybrid nanoparticle showed up to 60% efficient drug entrapment. Docetaxel loaded gold nanoparticles conjugated with folate receptor have high affinity for the prostate specific membrane antigen (PSMA) and help to internalize the drug loaded nanoparticle into the cancer cells (de Oliveira et al., 2013). These gold nanoparticle formulations were less effective in the first 48 hours when compared to free drug but showed significantly improved effect 144 hours after of administration. Calcium phosphate hybrid nanoparticles can be self-assembled in aqueous

phase by oppositely charged polyelectrolytes (Zhao et al., 2013c). Mukherjee's group has established novel strategies to further improve pharmacokinetics, tumor uptake and biodistribution of gold nanoparticles by engineering the surface of nanoparticles and targeting moiety (Arvizo et al., 2012; Arvizo et al., 2011; Bhattacharyya et al., 2011). These calcium phosphate hybrid nanoparticles have a distinct advantage over other nanoparticles due to their high drug loading capacity, pH induced drug release, biodegradability and ability to conjugate to any functional molecule. They also provide greater surface area and higher stability (Min et al., 2012). The added advantage of this calcium phosphate hybrid is that it interacts with surrounding cells and tissues, thus regulating cancer associated stromal cells. Increasing attention has been given to develop magnetic nanoparticles. Fe_3O_4 magnetic nanoparticles (MNP) are an exciting delivery system that has proven advantageous to enhance the biological activity of pharmaceutical ingredients. These magnetic nanoparticles have shown increased reactive oxygen species levels in prostate cancer cells and lower cell viability leading to enhanced cell death and increased expression of NF-κB in DU145 cells (Sato et al., 2013). Recent studies suggest that multi-layer magnetic nanoparticle system(s) has been highly encouraged due to their theranostic (therapy and imaging/diagnosis) applications in cancer (Yallapu et al., 2013b; Yallapu et al., 2010a; Yallapu et al., 2012b; Yallapu et al., 2011). Yazdi et al. (Yazdi et al., 2012) synthesized a magnetic nanoparticle loaded with docetaxel which showed higher cytotoxicity than the free drug in cancer cells and this delivery system can be used to inhibit development of resistance in cancer cells. This formulation has shown to be effective even at very low concentration levels.

4.4. Polymeric Micelles

Another system for efficient delivery of docetaxel to prostate cancer cells is by micelles (Yallapu et al., 2010c). A most suitable carrier is polypeptide cationic-based micelles (Zheng et al., 2013). These micelles are made up of copolymer blocks and show great activity in terms of solubility, toxicity and resistance. This system has an outer core made up of PEG and the inside has positively charged copolymer lipid molecules that can bind to the negatively charged docetaxel. This delivery system has an added advantage: it can deliver other small molecules in combination with the drug. Mikhail et al. (Mikhail et al., 2013) tested these docetaxel loaded block copolymers in 3-D cultures and confirmed that the optimum dose concentration to achieve a cytotoxic effect went down to nanogram levels and caused growth inhibition. These copolymer block micelles showed 6- to 9-fold increases in cytotoxic activity in monoculture of different human cancer cell lines. Often the cytotoxic effect of a drug molecule observed in cell culture or 2-D culture doesn't replicate as well *in vivo*; thus, using 3-D cultures and targeting the drug molecule using copolymer micelles eventually inhibited the growth of tumor in both cell culture experiments as well as in mice experiments. These copolymeric micelles demonstrated better therapeutic effect than the free drug in culture environment that closely reflects tumor environment. These copolymeric micelles are taken up by the cell; their small size increases their permeability and retention in tumor cells (Nair et al., 2011). TPGS based immuno-micelles contain the immunoglobin against a specific cell surface receptor highly expressed in tumor cells (Zhao et al., 2013a). This drug formulation had 55% and 70% drug release in absence and presence of glutathione in the medium after 120 hours of incubation, respectively. This delivery system

can be further used to deliver other small molecules such as siRNA or other small molecules along with drug molecules and this interaction is stable and effectively delivers the drug to its intended target. TPGS inhibits P-gp and thus inhibits drug resistance in the cells, whereas specific miRNAs can target the tyrosine kinase-signaling pathway inhibiting proliferative signaling in these cells. Yu et al. (Yu et al., 2013) synthesized methoxy PEG-cholesterol micelles, which can effectively entrap the drug and has a higher drug loading capacity than other micelles. This formulation minimized the particle size and displayed a greater cytotoxic effect on cells than the free drug. Due to its reduced size, this drug is easily taken up by the tumor cells, i.e., has higher preference for tumor cells, and enhanced retention mediates the cytotoxic effect on tumor cells. It also helped to inhibit resistance as PEG inhibits P-gp. Moreover, this formulation provided a sustained drug release, which is pH sensitive. A very similar drug formulation, the only difference being polylactic acid was used instead of cholesterol to form methoxy PEG-polylactic acid polymeric micelles (Li et al., 2012), has displayed higher entrapment efficiency and drug loading capacity than the other polymeric micelles and it selectively accumulated in solid tumors. Recently, an emulsion diffusion method was used to synthesize nanomicelle-loaded docetaxel, which showed superior drug entrapment and high stability over a 12 hour time period. This delivery system was tested in mice and reduced tumor growth significantly. The tumor weight was reduced by up to 72% and 80% inhibition of tumor volume was achieved with this formulation as compared to free drug (Ma et al., 2012). This formulation showed little toxicity and had higher retention levels of drug in blood and tumors. Another docetaxel encapsulated phospholipid micelle composed of copolymeric diblock, methoxy polyethylene glycol-distearoylphosphatidylethanolamine (PEG-DSPE), has displayed strong antitumor effects and decreased toxicity (Tong et al., 2012). This drug formulation achieved almost 98% efficient drug entrapment and 3% drug loading. When used against a Taxotere® control, this formulation showed greater antitumor effects and higher drug entrapment efficiency. Phospholipid coating helps the drug pass through the cell membrane due to its hydrophobic nature and release the drug molecule inside the cells preventing accumulation of P-gp on the cell surface. An amphiphilic drug micelle made up of poly(2-methyl-2-carboxytrimethylene carbonate-*co*-D,L-lactide)-graft-poly(ethylene glycol) displayed greater retention in solid tumor and less resistance toward the drug molecule as PEG inhibits P-gp overexpression within these cells (Ho et al., 2012). A novel thermo sensitive docetaxel loaded micelle showed enhanced antitumor activity compared to the free drug molecule (Liu et al., 2008). When tested in mice, these micelles resulted in lower weight loss in mice than the conventional drug therapy. Nanoxel-PM™ is a docetaxel-loaded methoxy-poly(ethylene glycol)-*block*-poly(d,l-lactide) micellar formulation and is an alternative and better bioequivalent compared to Taxotere® (Lee et al., 2011). Pluronic P123 conjugated docetaxel formed core shell type micelles in aqueous solution. DTX conjugated to P123 showed 13.69% drug loading at a lower critical micellar concentration than free P123 and showed increased efficacy and lower toxicity in both *in vitro* and *in vivo* systems. These micelles showed pH-dependent degradation at lower pH, indicating enhanced drug release at the tumor site due to lower pH of the tumor microenvironment (Liu et al., 2013b).

4.5. Nanoconjugates

Ring opening polymerization is a powerful strategy to develop polymer-docetaxel nanodelivery systems for improved cancer treatment (Tong and Cheng, 2012). Shimoda et al. (Shimoda and Kubota, 2011) used a docetaxel prodrug conjugated to monosaccharide for better solubility and to induce greater cytotoxic effects. The water solubility of this drug conjugate was at 27μM, which is 52-fold higher than the free docetaxel. Lipid docetaxel conjugates have desired advantages: they have low toxicity, provide sustained release and can penetrate the leaky vasculature of the tumors (Feng et al., 2011). These docetaxel conjugates provided 10-fold increased solubility in Miglyol 88 and were independent of their chain length dependency in mouse plasma as compared to free docetaxel, which showed chain length dependency. The cytotoxic effect of all three docetaxel conjugates was lower than free docetaxel although it showed dose dependent cytotoxicity in human cancer cell lines. The half-life of the docetaxel conjugates was superior to free docetaxel by about 1.9 to 3.4 times. Taurocholic acid linked heparin-docetaxel conjugate improves adsorption and activity of docetaxel in an oral route (Khatun et al., 2013). This drug-conjugate formulation provided higher anticancer effects in human cancer cell lines even after 72 hours of treatment. This oral formulation was taken up by the tumor site specifically within 24 hours after oral administration in animal models and showed up to 37% greater tumor volume reduction as compared to free drug. Zhou et al. identified that intravenous administration of N-(2-hydroxypropyl) methacrylamide (HPMA) conjugated docetaxel formulation not only inhibited tumor growth in xenograft model but also reduced the population of prostate cancer stem cells (CSC) when used along with a cyclopamine conjugate (Zhou et al., 2013). The level of growth inhibition in the xenograft model improved with a combination treatment of HPMA copolymer drug conjugates compared to an individual conjugate formulation or free drug. This formulation showed greater cytotoxic effect in human cancer cell lines even after 10 days of treatment when compared to free drug. The combination treatment didn't show an immediate effect but suppressed growth for a longer period. Esmaeili et al. (Esmaeili et al., 2009) synthesized an albumin conjugated docetaxel formulation because albumin results in higher bioavailability and biodegradability and ease of modification *in vivo*. This drug formulation was particularly useful as it showed a 6-fold increase in cytotoxic effects on human cancer cell lines and retained this effect at lower concentration even after 96 hours of treatment. Up to 20% of the drug was released from this conjugate and higher uptake of drug is due to gp60 receptors, which are specific to albumin and on activation transport albumin into tumor tissue.

Similarly, docetaxel can be conjugated to carbon nanontubes (CNTs) which exhibit the highest drug entrapment (Mody et al., 2014). Use of Single-walled carbon nanotubes (SWCNTs) is a novel drug delivery vehicle that is being explored in *in-vitro* systems for delivery of drugs, proteins, plasmid DNA and RNAi (Wang et al., 2011). These SWCNTs are insoluble in water but by surface modification can be made soluble in water. SWCNTs conjugated to Doxorubicin (DOX), when functionalized by adding P-gp (P-glycoprotein) antibody, lead to a 23-fold higher uptake by tumor cells (Wong et al., 2013). Conjugation with P-gp antibody leads to selective uptake by resistant cells and intracellular concentration of DOX was significantly higher due to the inability of P-gp pump to efflux the drug out and steric hindrance created by the interaction of P-gp with its antibody conjugated SWCNTs.

Recent studies have indicated that CNTs are able to increase intracellular ROS levels by activating MAPK/Erk levels (Manna et al., 2005). In separate study, SWCNTs were able to sensitize ovarian cancer cells to PTX, leading to enhanced cell death (Zhang et al., 2012b).

5. Conclusion and opinion

Docetaxel chemotherapy plays a vital role in the clinical oncology of prostate cancer. Although this therapy has had great success in the eradication of tumor(s) or controlling the tumor(s) growth and metastasis, dose-dependent adverse reactions and the emergence of chemoresistance limits its use. The documented reports described in this review delineate the feasibility of nanotechnology mediated docetaxel therapeutics in the clinical arena. Docetaxel nanoformulations in combination with multidrug (chemo-sensitizers or synergetic agents), targeting moiety, siRNA, miRNA, and immunoactivation compositions are excellent mechanisms to overcome drug resistance and circumvent target tumor cells. Additionally, these docetaxel nanoformulations reduce the chemotherapeutic dose required for therapy due to improved targeting of drug, increased intracellular accumulation and sustained release for superior pharmacological actions. These characteristics significantly reduce the chemotherapy related adverse effects and relapse. Based on literature, clinically relevant and successful docetaxel nanoformulations for prostate cancer therapy possess a suitable particle size (≤ 100 nm) possibly with negative zeta potential, must use safe, proper and approved technology, identify appropriate stabilization step, engineer accurate targeting moiety, and induce multi-functionality for theranostic purpose. This review shows that various nanoformulations of docetaxel can reverse docetaxel resistance by inhibiting or altering whole pathways that are responsible for resistance. The preclinical and clinical results (Table 2) indicate that docetaxel nanoparticle mediated delivery is safe and very efficient in overcoming impaired docetaxel delivery and docetaxel resistance. It is also possible to combine the targeted systemic chemotherapies with nanodocetaxel formulations to improve the docetaxel therapeutic outcome through targeting, accumulation and sustained release of docetaxel to combat prostate cancer. In our opinion, a biocompatible nanoparticle formulation of docetaxel with controlled release and multi-functionality that can target the tumor cells utilizing overexpressing ligands/antigens such as prostate stem cell antigen, prostate specific membrane antigen, six transmembrane epithelial antigen of the prostate 1, prostatic acid phosphatase, T cell receptor gamma alternate reading frame protein, transient receptor potential (trp)-p8, and a specific signaling pathway will be proven as a novel and effective approach in prostate cancer therapy and diagnosis (Fig. 5). Such formulation ultimately will overcome most of the docetaxel-associated hurdles and will aid clinical oncology in the near future.

Acknowledgments

This work was partially supported by grants from Department of Defense (PC073887 to SCC and PC073643 MJ); the National Institutes of Health (RO1 CA142736 to SCC and UO1 CA162106A to SCC and MJ) and the College of Pharmacy 2013 Dean's Seed Grant of the University of Tennessee Health Science Center (to MJ and MMY). The authors thank Cathy Christopherson (Sanford Research/USD) for editorial assistance.

References

Ahmed A, Ali S, Sarkar FH. Advances in androgen receptor targeted therapy for prostate cancer. Journal of cellular physiology. 2014; 229:271–276. [PubMed: 24037862]

Al Ekish S, Nayeemuddin M, Maddox M, Pareek G. The role of cryosurgery of the prostate for nonsurgical candidates. JSLS: Journal of the Society of Laparoendoscopic Surgeons/Society of Laparoendoscopic Surgeons. 2013; 17:423–428. [PubMed: 24018080]

Aparicio AM, Harzstark AL, Corn PG, Wen S, Araujo JC, Tu SM, Pagliaro LC, Kim J, Millikan RE, Ryan C, Tannir NM, Zurita AJ, Mathew P, Arap W, Troncoso P, Thall PF, Logothetis CJ. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. 2013; 19:3621–3630. [PubMed: 23649003]

Arvizo RR, Bhattacharyya S, Kudgus RA, Giri K, Bhattacharya R, Mukherjee P. Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future. Chemical Society reviews. 2012; 41:2943–2970. [PubMed: 22388295]

Arvizo RR, Miranda OR, Moyano DF, Walden CA, Giri K, Bhattacharya R, Robertson JD, Rotello VM, Reid JM, Mukherjee P. Modulating pharmacokinetics, tumor uptake and biodistribution by engineered nanoparticles. PloS one. 2011; 6:e24374. [PubMed: 21931696]

Bahl A, Masson S, Birtle A, Chowdhury S, de Bono J. Second-line treatment options in metastatic castration-resistant prostate cancer: A comparison of key trials with recently approved agents. Cancer treatment reviews. 2013

Bhatnagar N, Li X, Padi SK, Zhang Q, Tang MS, Guo B. Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells. Cell death & disease. 2010; 1:e105. [PubMed: 21368878]

Bhattacharyya S, Khan JA, Curran GL, Robertson JD, Bhattacharya R, Mukherjee P. Efficient delivery of gold nanoparticles by dual receptor targeting. Adv Mater. 2011; 23:5034–5038. [PubMed: 21971980]

Chu KS, Schorzman AN, Finniss MC, Bowerman CJ, Peng L, Luft JC, Madden AJ, Wang AZ, Zamboni WC, DeSimone JM. Nanoparticle drug loading as a design parameter to improve docetaxel pharmacokinetics and efficacy. Biomaterials. 2013; 34:8424–8429. [PubMed: 23899444]

Clarke SJ, Rivory LP. Clinical pharmacokinetics of docetaxel. Clinical pharmacokinetics. 1999; 36:99–114. [PubMed: 10092957]

Coppola V, De Maria R, Bonci D. MicroRNAs and prostate cancer. Endocrine-related cancer. 2010; 17:F1–17. [PubMed: 19779034]

Darshan MS, Loftus MS, Thadani-Mulero M, Levy BP, Escuin D, Zhou XK, Gjyrezi A, Chanel-Vos C, Shen R, Tagawa ST, Bander NH, Nanus DM, Giannakakou P. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. Cancer research. 2011; 71:6019–6029. [PubMed: 21799031]

de Oliveira R, Zhao P, Li N, de Santa Maria LC, Vergnaud J, Ruiz J, Astruc D, Barratt G. Synthesis and in vitro studies of gold nanoparticles loaded with docetaxel. International journal of pharmaceutics. 2013; 454:703–711. [PubMed: 23701998]

Deeken JF, Slack R, Weiss GJ, Ramanathan RK, Pishvaian MJ, Hwang J, Lewandowski K, Subramaniam D, He AR, Cotarla I, Rahman A, Marshall JL. A phase I study of liposomal-encapsulated docetaxel (LE-DT) in patients with advanced solid tumor malignancies. Cancer chemotherapy and pharmacology. 2013; 71:627–633. [PubMed: 23274395]

Devalapally H, Shenoy D, Little S, Langer R, Amiji M. Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs: part 3. Therapeutic efficacy and safety studies in ovarian cancer xenograft model. Cancer Chemother Pharmacol. 2007; 59:477–484. [PubMed: 16862429]

Diane Lauren Reidy EV, Fakih Marwan G, Saif Muhammad Wasif, Hecht Joel Randolph, Goodman-Davis Noah, Hollywood Ellen, Shia Jinru, Schwartz Jonathan, Chandrawansa Kumari, Dontabhaktuni Aruna, Youssoufian Hagop, Solit David B, Saltz Leonard B. Randomized, Phase II Study of the Insulin-Like Growth Factor-1 Receptor Inhibitor IMC-A12, With or Without

Cetuximab, in Patients With Cetuximab- or Panitumumab-Refractory Metastatic Colorectal Cancer. Journal of Clinical Oncology. 2010; 28:4240–4246. [PubMed: 20713879]

Dinarvand R, Sepehri N, Manoochehri S, Rouhani H, Atyabi F. Polylactide-co-glycolide nanoparticles for controlled delivery of anticancer agents. International journal of nanomedicine. 2011; 6:877–895. [PubMed: 21720501]

El-Toni AM, Ibrahim MA, Labis JP, Khan A, Alhoshan M. Optimization of synthesis parameters for mesoporous shell formation on magnetic nanocores and their application as nanocarriers for docetaxel cancer drug. International journal of molecular sciences. 2013; 14:11496–11509. [PubMed: 23722659]

Elliott RL. Combination cancer immunotherapy “Expanding Paul Ehrlich’s Magic Bullet Concept”. Surgical oncology. 2012; 21:53–55. [PubMed: 20338747]

Enlow EM, Luft JC, Napier ME, DeSimone JM. Potent engineered PLGA nanoparticles by virtue of exceptionally high chemotherapeutic loadings. Nano letters. 2011; 11:808–813. [PubMed: 21265552]

Esmaeili F, Dinarvand R, Ghahremani MH, Amini M, Rouhani H, Sepehri N, Ostad SN, Atyabi F. Docetaxel-albumin conjugates: preparation, in vitro evaluation and biodistribution studies. Journal of pharmaceutical sciences. 2009; 98:2718–2730. [PubMed: 18972321]

Feng L, Wu H, Ma P, Mumper RJ, Benhabbour SR. Development and optimization of oil-filled lipid nanoparticles containing docetaxel conjugates designed to control the drug release rate in vitro and in vivo. International journal of nanomedicine. 2011; 6:2545–2556. [PubMed: 22072889]

Fernandez O, Afonso J, Vazquez S, Campos B, Lazaro M, Leon L, Anton Aparicio LM. Metastatic castration-resistant prostate cancer: changing landscape with cabazitaxel. Anti-cancer drugs. 2013

Fizazi K, De Bono JS, Flechon A, Heidenreich A, Voog E, Davis NB, Qi M, Bandekar R, Vermeulen JT, Cornfeld M, Hudes GR. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. European journal of cancer (Oxford, England: 1990). 2012; 48:85–93.

Gale S, Croasdell G. 28th Annual JPMorgan Healthcare Conference--Exelixis and Nektar Therapeutics. IDrugs: the investigational drugs journal. 2010; 13:139–141. [PubMed: 20191424]

Gandellini P, Folini M, Longoni N, Pennati M, Binda M, Colecchia M, Salvioni R, Supino R, Moretti R, Limonta P, Valdagni R, Daidone MG, Zaffaroni N. miR-205 Exerts tumor-suppressive functions in human prostate through down-regulation of protein kinase Cepsilon. Cancer research. 2009a; 69:2287–2295. [PubMed: 19244118]

Gandellini P, Folini M, Zaffaroni N. Towards the definition of prostate cancer-related microRNAs: where are we now? Trends in molecular medicine. 2009b; 15:381–390. [PubMed: 19716766]

Gandellini P, Profumo V, Casamichele A, Fenderico N, Borrelli S, Petrovich G, Santilli G, Callari M, Colecchia M, Pozzi S, De Cesare M, Folini M, Valdagni R, Mantovani R, Zaffaroni N. miR-205 regulates basement membrane deposition in human prostate: implications for cancer development. Cell death and differentiation. 2012; 19:1750–1760. [PubMed: 22555458]

Giannakakou P, Gussio R, Nogales E, Downing KH, Zaharevitz D, Bollbuck B, Poy G, Sackett D, Nicolaou KC, Fojo T. A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97:2904–2909. [PubMed: 10688884]

Goldberg AA, Titorenko VI, Beach A, Sanderson JT. Bile acids induce apoptosis selectively in androgen-dependent and -independent prostate cancer cells. PeerJ. 2013; 1:e122. [PubMed: 23940835]

Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nature reviews Cancer. 2002; 2:48–58.

Grant DS, Williams TL, Zahaczewsky M, Dicker AP. Comparison of antiangiogenic activities using paclitaxel (taxol) and docetaxel (taxotere). International journal of cancer Journal international du cancer. 2003; 104:121–129. [PubMed: 12532428]

Hadinoto K, Sundaresan A, Cheow WS. Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: A review. European journal of pharmaceutics and

biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V. 2013

Higano CS. Potential use of custirsen to treat prostate cancer. OncoTargets and therapy. 2013; 6:785–797. [PubMed: 23836992]

Ho KS, Aman AM, Al-awar RS, Shoichet MS. Amphiphilic micelles of poly(2-methyl-2-carboxytrimethylene carbonate-co-D,L-lactide)-graft-poly(ethylene glycol) for anti-cancer drug delivery to solid tumours. Biomaterials. 2012; 33:2223–2229. [PubMed: 22182751]

Hrkach J, Von Hoff D, Mukkaram Ali M, Andrianova E, Auer J, Campbell T, De Witt D, Figa M, Figueiredo M, Horhota A, Low S, McDonnell K, Peeke E, Retnarajan B, Sabnis A, Schnipper E, Song JJ, Song YH, Summa J, Tompsett D, Troiano G, Van Geen Hoven T, Wright J, LoRusso P, Kantoff PW, Bander NH, Sweeney C, Farokhzad OC, Langer R, Zale S. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Science translational medicine. 2012; 4:128ra139.

Hu CM, Zhang L. Therapeutic nanoparticles to combat cancer drug resistance. Current drug metabolism. 2009; 10:836–841. [PubMed: 20214578]

Johnson J, Roach M 3rd. Prostate cancer: Impact of national guidelines on brachytherapy monotherapy. Nature reviews. Urology. 2014

Jones SE, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower E, Laufman L, Sundaram S, Urba WJ, Pritchard KI, Mennel R, Richards D, Olsen S, Meyers ML, Ravdin PM. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2005; 23:5542–5551. [PubMed: 16110015]

Khatun Z, Nurunnabi M, Reeck GR, Cho KJ, Lee YK. Oral delivery of taurocholic acid linked heparin-docetaxel conjugates for cancer therapy. Journal of controlled release: official journal of the Controlled Release Society. 2013; 170:74–82. [PubMed: 23665255]

Kim J, Wu L, Zhao JC, Jin HJ, Yu J. TMPRSS2-ERG gene fusions induce prostate tumorigenesis by modulating microRNA miR-200c. Oncogene. 2013

Kobayashi D, Kawai N, Sato S, Naiki T, Yamada K, Yasui T, Tozawa K, Kobayashi T, Takahashi S, Kohri K. Thermotherapy using magnetic cationic liposomes powerfully suppresses prostate cancer bone metastasis in a novel rat model. The Prostate. 2013; 73:913–922. [PubMed: 23334935]

Komura K, Inamoto T, Takai T, Uchimoto T, Saito K, Tanda N, Kono J, Minami K, Uehara H, Fujisue Y, Takahara K, Hirano H, Nomi H, Watsuji T, Kiyama S, Azuma H. Single session of high-intensity focused ultrasound for localized prostate cancer: treatment outcomes and potential effect as a primary therapy. World journal of urology. 2013

Kopp F, Oak PS, Wagner E, Roidl A. miR-200c sensitizes breast cancer cells to doxorubicin treatment by decreasing TrkB and Bmi1 expression. PloS one. 2012; 7:e50469. [PubMed: 23209748]

Kruijtzer CM, Beijnen JH, Schellens JH. Improvement of oral drug treatment by temporary inhibition of drug transporters and/or cytochrome P450 in the gastrointestinal tract and liver: an overview. The oncologist. 2002; 7:516–530. [PubMed: 12490739]

Lee SW, Yun MH, Jeong SW, In CH, Kim JY, Seo MH, Pai CM, Kim SO. Development of docetaxel-loaded intravenous formulation, Nanoxel-PM using polymer-based delivery system. Journal of controlled release: official journal of the Controlled Release Society. 2011; 155:262–271. [PubMed: 21704664]

Li X, Tian X, Zhang J, Zhao X, Chen X, Jiang Y, Wang D, Pan W. In vitro and in vivo evaluation of folate receptor-targeting amphiphilic copolymer-modified liposomes loaded with docetaxel. International journal of nanomedicine. 2011; 6:1167–1184. [PubMed: 21852896]

Li Y, Yang F, Chen W, Liu J, Huang W, Jin M, Gao Z. A novel monomethoxy polyethylene glycol-polylactic acid polymeric micelles with higher loading capacity for docetaxel and well-reconstitution characteristics and its anti-metastasis study. Chemical & pharmaceutical bulletin. 2012; 60:1146–1154. [PubMed: 22976323]

Liu B, Yang M, Li R, Ding Y, Qian X, Yu L, Jiang X. The antitumor effect of novel docetaxel-loaded thermosensitive micelles. European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e V. 2008; 69:527–534. [PubMed: 18359617]

Liu Q, Li RT, Qian HQ, Wei J, Xie L, Shen J, Yang M, Qian XP, Yu LX, Jiang XQ, Liu BR. Targeted delivery of miR-200c/DOC to inhibit cancer stem cells and cancer cells by the gelatinases-stimuli nanoparticles. Biomaterials. 2013a; 34:7191–7203. [PubMed: 23806972]

Liu Z, Wang Y, Zhang J, Li M, Liu Y, Zhang N. Pluronic P123-docetaxel conjugate micelles: synthesis, characterization, and antitumor activity. Journal of biomedical nanotechnology. 2013b; 9:2007–2016. [PubMed: 24266256]

Ma M, Hao Y, Liu N, Yin Z, Wang L, Liang X, Zhang X. A novel lipid-based nanomicelle of docetaxel: evaluation of antitumor activity and biodistribution. International journal of nanomedicine. 2012; 7:3389–3398. [PubMed: 22848167]

Manna SK, Sarkar S, Barr J, Wise K, Barrera EV, Jejelowo O, Rice-Ficht AC, Ramesh GT. Single-walled carbon nanotube induces oxidative stress and activates nuclear transcription factor-kappaB in human keratinocytes. Nano letters. 2005; 5:1676–1684. [PubMed: 16159204]

Manoocheheri S, Darvishi B, Kamalinia G, Amini M, Fallah M, Ostad SN, Atyabi F, Dinarvand R. Surface modification of PLGA nanoparticles via human serum albumin conjugation for controlled delivery of docetaxel. Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2013; 21:58.

Mikhail AS, Eetezadi S, Allen C. Multicellular tumor spheroids for evaluation of cytotoxicity and tumor growth inhibitory effects of nanomedicines in vitro: a comparison of docetaxel-loaded block copolymer micelles and Taxotere(R). PloS one. 2013; 8:e62630. [PubMed: 23626842]

Mimeault M, Johansson SL, Batra SK. Pathobiological implications of the expression of EGFR, pAkt, NF-kappaB and MIC-1 in prostate cancer stem cells and their progenies. PloS one. 2012; 7:e31919. [PubMed: 22384099]

Min KH, Lee HJ, Kim K, Kwon IC, Jeong SY, Lee SC. The tumor accumulation and therapeutic efficacy of doxorubicin carried in calcium phosphate-reinforced polymer nanoparticles. Biomaterials. 2012; 33:5788–5797. [PubMed: 22591612]

Mody N, Tekade RK, Mehra NK, Chopdey P, Jain NK. Dendrimer, Liposomes, Carbon Nanotubes and PLGA Nanoparticles: One Platform Assessment of Drug Delivery Potential. AAPS Pharm Sci Tech. 2014

Monegier B, Gaillard C, Sablé S, Vuilhorgne M. Structures of the major human metabolites of docetaxel (RP 56976 - Taxotere®). Tetrahedron Letters. 1994; 35:3715–3718.

Muthu MS, Kulkarni SA, Raju A, Feng SS. Theranostic liposomes of TPGS coating for targeted co-delivery of docetaxel and quantum dots. Biomaterials. 2012; 33:3494–3501. [PubMed: 22306020]

Nair KL, Jagadeeshan S, Nair SA, Kumar GS. Evaluation of triblock copolymeric micelles of delta-valerolactone and poly (ethylene glycol) as a competent vector for doxorubicin delivery against cancer. Journal of nanobiotechnology. 2011; 9:42. [PubMed: 21943300]

Nelson SJ, Kurhanewicz J, Vigneron DB, Larson PE, Harzstark AL, Ferrone M, van Criekinge M, Chang JW, Bok R, Park I, Reed G, Carvajal L, Small EJ, Munster P, Weinberg VK, Ardenkjaer-Larsen JH, Chen AP, Hurd RE, Odegardstuen LI, Robb FJ, Tropp J, Murray JA. Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-13C]Pyruvate. Science translational medicine. 2013; 5:198ra108.

Nettles JH, Li H, Cornett B, Krahn JM, Snyder JP, Downing KH. The binding mode of epothilone A on alpha,beta-tubulin by electron crystallography. Science (New York, NY). 2004; 305:866–869.

O'Neill AJ, Prencipe M, Dowling C, Fan Y, Mulrane L, Gallagher WM, O'Connor D, O'Connor R, Devery A, Corcoran C, Rani S, O'Driscoll L, Fitzpatrick JM, Watson RW. Characterisation and manipulation of docetaxel resistant prostate cancer cell lines. Molecular cancer. 2011; 10:126. [PubMed: 21982118]

Penney KL, Stampfer MJ, Jahn JL, Sinnott JA, Flavin R, Rider JR, Finn S, Giovannucci E, Sesso HD, Loda M, Mucci LA, Fiorentino M. Gleason Grade Progression Is Uncommon. Cancer research. 2013; 73:5163–5168. [PubMed: 23946472]

Porkka KP, Pfeiffer MJ, Waltering KK, Vessella RL, Tammela TL, Visakorpi T. MicroRNA expression profiling in prostate cancer. Cancer research. 2007; 67:6130–6135. [PubMed: 17616669]

Qu G, Wu X, Yin L, Zhang C. N-octyl-O-sulfate chitosan-modified liposomes for delivery of docetaxel: preparation, characterization, and pharmacokinetics. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2012; 66:46–51. [PubMed: 22264883]

Raju A, Muthu MS, Feng SS. Trastuzumab-conjugated vitamin E TPGS liposomes for sustained and targeted delivery of docetaxel. Expert opinion on drug delivery. 2013; 10:747–760. [PubMed: 23458409]

Royer I, Monsarrat B, Sonnier M, Wright M, Cresteil T. Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. Cancer research. 1996; 56:58–65. [PubMed: 8548776]

Saad F, Hotte S, North S, Eigl B, Chi K, Czaykowski P, Wood L, Pollak M, Berry S, Lattouf JB, Mukherjee SD, Gleave M, Winquist E. Randomized phase II trial of Custirsen (OGX-011) in combination with docetaxel or mitoxantrone as second-line therapy in patients with metastatic castrate-resistant prostate cancer progressing after first-line docetaxel: CUOG trial P-06c. Clinical cancer research: an official journal of the American Association for Cancer Research. 2011; 17:5765–5773. [PubMed: 21788353]

Sato A, Itcho N, Ishiguro H, Okamoto D, Kobayashi N, Kawai K, Kasai H, Kurioka D, Uemura H, Kubota Y, Watanabe M. Magnetic nanoparticles of Fe3O4 enhance docetaxel-induced prostate cancer cell death. International journal of nanomedicine. 2013; 8:3151–3160. [PubMed: 23990723]

Schaefer A, Stephan C, Busch J, Yousef GM, Jung K. Diagnostic, prognostic and therapeutic implications of microRNAs in urologic tumors. Nature reviews Urology. 2010; 7:286–297.

Shen J, He Q, Gao Y, Shi J, Li Y. Mesoporous silica nanoparticles loading doxorubicin reverse multidrug resistance: performance and mechanism. Nanoscale. 2011; 3:4314–4322. [PubMed: 21892492]

Shenoy D, Little S, Langer R, Amiji M. Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs. 1. In vitro evaluations. Molecular pharmaceutics. 2005; 2:357–366. [PubMed: 16196488]

Shimoda K, Kubota N. Chemo-enzymatic synthesis of ester-linked docetaxel-monosaccharide conjugates as water-soluble prodrugs. Molecules (Basel, Switzerland). 2011; 16:6769–6777.

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA: a cancer journal for clinicians. 2013; 63:11–30. [PubMed: 23335087]

Song G, Lee C, You D, Jeong IG, Hong JH, Ahn H, Kim CS. Prostate-specific antigen response rate of sequential chemotherapy in castration-resistant prostate cancer: the results of real life practice. Prostate international. 2013; 1:125–132. [PubMed: 24223414]

Sorensen S, Ellis L, Wu Y, Hutchins V, Linnehan JE, Senbetta M. Budgetary impact on a u.s. Health plan adopting abiraterone acetate plus prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. Journal of managed care pharmacy: JMCP. 2013; 19:799–808. [PubMed: 24156649]

Sosnik A. Reversal of multidrug resistance by the inhibition of ATP-binding cassette pumps employing “Generally Recognized As Safe” (GRAS) nanopharmaceuticals: A review. Advanced drug delivery reviews. 2013; 65:1828–1851. [PubMed: 24055628]

Strebhardt K, Ullrich A. Paul Ehrlich’s magic bullet concept: 100 years of progress. Nature reviews Cancer. 2008; 8:473–480.

Svenson S. What nanomedicine in the clinic right now really forms nanoparticles? Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology. 2014; 6:125–135. [PubMed: 24415653]

Tan Q, Liu X, Fu X, Li Q, Dou J, Zhai G. Current development in nanoformulations of docetaxel. Expert opinion on drug delivery. 2012; 9:975–990. [PubMed: 22703284]

Tao W, Zeng X, Liu T, Wang Z, Xiong Q, Ouyang C, Huang L, Mei L. Docetaxel-loaded nanoparticles based on star-shaped mannitol-core PLGA-TPGS diblock copolymer for breast cancer therapy. Acta biomaterialia. 2013; 9:8910–8920. [PubMed: 23816645]

Teixeira AL, Gomes M, Nogueira A, Azevedo AS, Assis J, Dias F, Santos JI, Lobo F, Morais A, Mauricio J, Medeiros R. Improvement of a Predictive Model of Castration-Resistant Prostate

Cancer: Functional Genetic Variants in TGFbeta1 Signaling Pathway Modulation. PloS one. 2013; 8:e72419. [PubMed: 23951322]

Tong R, Cheng J. Drug-Initiated, Controlled Ring-Opening Polymerization for the Synthesis of Polymer-Drug Conjugates. Macromolecules. 2012; 45:2225–2232. [PubMed: 23357880]

Tong R, Chiang HH, Kohane DS. Photoswitchable nanoparticles for in vivo cancer chemotherapy. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110:19048–19053. [PubMed: 24191048]

Tong SW, Xiang B, Dong DW, Qi XR. Enhanced antitumor efficacy and decreased toxicity by self-associated docetaxel in phospholipid-based micelles. International journal of pharmaceutics. 2012; 434:413–419. [PubMed: 22698861]

Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen CD, Higano CS, Beer TM, Hung DT, Scher HI, Jung ME, Sawyers CL. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science (New York, NY). 2009; 324:787–790.

Ueda K, Cardarelli C, Gottesman MM, Pastan I. Expression of a full-length cDNA for the human "MDR1" gene confers resistance to colchicine, doxorubicin, and vinblastine. Proceedings of the National Academy of Sciences of the United States of America. 1987; 84:3004–3008. [PubMed: 3472246]

van der Meel R, Vehmeijer LJ, Kok RJ, Storm G, van Gaal EV. Ligand-targeted particulate nanomedicines undergoing clinical evaluation: current status. Advanced drug delivery reviews. 2013; 65:1284–1298. [PubMed: 24018362]

Verweij J, Clavel M, Chevalier B. Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind. Annals of oncology: official journal of the European Society for Medical Oncology/ESMO. 1994; 5:495–505. [PubMed: 7918121]

Wang D, Huang J, Wang X, Yu Y, Zhang H, Chen Y, Liu J, Sun Z, Zou H, Sun D, Zhou G, Zhang G, Lu Y, Zhong Y. The eradication of breast cancer cells and stem cells by 8-hydroxyquinoline-loaded hyaluronan modified mesoporous silica nanoparticle-supported lipid bilayers containing docetaxel. Biomaterials. 2013; 34:7662–7673. [PubMed: 23859657]

Wang L, Zhang M, Zhang N, Shi J, Zhang H, Li M, Lu C, Zhang Z. Synergistic enhancement of cancer therapy using a combination of docetaxel and photothermal ablation induced by single-walled carbon nanotubes. International journal of nanomedicine. 2011; 6:2641–2652. [PubMed: 22114495]

Watahiki A, Macfarlane RJ, Gleave ME, Crea F, Wang Y, Helgason CD, Chi KN. Plasma miRNAs as Biomarkers to Identify Patients with Castration-Resistant Metastatic Prostate Cancer. International journal of molecular sciences. 2013; 14:7757–7770. [PubMed: 23574937]

Wong BS, Yoong SL, Jagusiak A, Panczyk T, Ho HK, Ang WH, Pastorin G. Carbon nanotubes for delivery of small molecule drugs. Advanced drug delivery reviews. 2013; 65:1964–2015. [PubMed: 23954402]

Yallapu MM, Dobberpuhl MR, Maher DM, Jaggi M, Chauhan SC. Design of curcumin loaded cellulose nanoparticles for prostate cancer. Current drug metabolism. 2012a; 13:120–128. [PubMed: 21892919]

Yallapu MM, Ebeling MC, Jaggi M, Chauhan SC. Plasma proteins interaction with curcumin nanoparticles: implications in cancer therapeutics. Current drug metabolism. 2013a; 14:504–515. [PubMed: 23566382]

Yallapu MM, Ebeling MC, Khan S, Sundram V, Chauhan N, Gupta BK, Puumala SE, Jaggi M, Chauhan SC. Novel curcumin-loaded magnetic nanoparticles for pancreatic cancer treatment. Molecular cancer therapeutics. 2013b; 12:1471–1480. [PubMed: 23704793]

Yallapu MM, Foy SP, Jain TK, Labhasetwar V. PEG-functionalized magnetic nanoparticles for drug delivery and magnetic resonance imaging applications. Pharmaceutical research. 2010a; 27:2283–2295. [PubMed: 20845067]

Yallapu MM, Gupta BK, Jaggi M, Chauhan SC. Fabrication of curcumin encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells. Journal of colloid and interface science. 2010b; 351:19–29. [PubMed: 20627257]

Yallapu MM, Jaggi M, Chauhan SC. Scope of nanotechnology in ovarian cancer therapeutics. Journal of ovarian research. 2010c; 3:19. [PubMed: 20691083]

Yallapu MM, Othman SF, Curtis ET, Bauer NA, Chauhan N, Kumar D, Jaggi M, Chauhan SC. Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications. International journal of nanomedicine. 2012b; 7:1761–1779. [PubMed: 22619526]

Yallapu MM, Othman SF, Curtis ET, Gupta BK, Jaggi M, Chauhan SC. Multi-functional magnetic nanoparticles for magnetic resonance imaging and cancer therapy. Biomaterials. 2011; 32:1890–1905. [PubMed: 21167595]

Yamamoto Y, Yoshida M, Sato M, Sato K, Kikuchi S, Sugishita H, Kuwabara J, Matsuno Y, Kojima Y, Morimoto M, Horiuchi A, Watanabe Y. Feasibility of tailored, selective and effective anticancer chemotherapy by direct injection of docetaxel-loaded immunoliposomes into Her2/neu positive gastric tumor xenografts. International journal of oncology. 2011; 38:33–39. [PubMed: 21109923]

Yazdi M, Najafi ZN, Khorramizadeh M, Amini M, Shahverdi A. Fabrication of docetaxel surfaced Fe3O4 magnetite nanoparticles and their cytotoxicity on 4 T1 breast cancer cells. Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2012; 20:15.

Yoshida M, Sato M, Yamamoto Y, Maehara T, Naohara T, Aono H, Sugishita H, Sato K, Watanabe Y. Tumor local chemohyperthermia using docetaxel-embedded magnetoliposomes: Interaction of chemotherapy and hyperthermia. Journal of gastroenterology and hepatology. 2012; 27:406–411. [PubMed: 22098478]

Yu Y, He Y, Xu B, He Z, Zhang Y, Chen Y, Yang Y, Xie Y, Zheng Y, He G, He J, Song X. Self-assembled methoxy poly(ethylene glycol)-cholesterol micelles for hydrophobic drug delivery. Journal of pharmaceutical sciences. 2013; 102:1054–1062. [PubMed: 23280512]

Yuan Z, Chen D, Zhang S, Zheng Z. Preparation, characterization and evaluation of docetaxel-loaded, folate-conjugated PEG-liposomes. Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan. 2010; 130:1353–1359. [PubMed: 20930488]

Zhang H, Li RY, Lu X, Mou ZZ, Lin GM. Docetaxel-loaded liposomes: preparation, pH sensitivity, pharmacokinetics, and tissue distribution. Journal of Zhejiang University Science B. 2012a; 13:981–989. [PubMed: 23225853]

Zhang W, Zhang D, Tan J, Cong H. Carbon nanotube exposure sensitize human ovarian cancer cells to paclitaxel. Journal of nanoscience and nanotechnology. 2012b; 12:7211–7214. [PubMed: 23035454]

Zhao J, Mi Y, Feng SS. Targeted co-delivery of docetaxel and siPlk1 by herceptin-conjugated vitamin E TPGS based immunomicelles. Biomaterials. 2013a; 34:3411–3421. [PubMed: 23375951]

Zhao S, Tan S, Guo Y, Huang J, Chu M, Liu H, Zhang Z. pH-Sensitive Docetaxel-Loaded d-alpha-Tocopheryl Polyethylene Glycol Succinate-Poly(beta-amino ester) Copolymer Nanoparticles for Overcoming Multidrug Resistance. Biomacromolecules. 2013b; 14:2636–2646. [PubMed: 23815156]

Zhao XY, Zhu YJ, Chen F, Lu BQ, Qi C, Zhao J, Wu J. Calcium phosphate hybrid nanoparticles: self-assembly formation, characterization, and application as an anticancer drug nanocarrier. Chemistry, an Asian journal. 2013c; 8:1306–1312.

Zheng C, Zheng M, Gong P, Deng J, Yi H, Zhang P, Zhang Y, Liu P, Ma Y, Cai L. Polypeptide cationic micelles mediated co-delivery of docetaxel and siRNA for synergistic tumor therapy. Biomaterials. 2013; 34:3431–3438. [PubMed: 23375952]

Zhou Y, Yang J, Rhim JS, Kopecek J. HPMA copolymer-based combination therapy toxic to both prostate cancer stem/progenitor cells and differentiated cells induces durable anti-tumor effects. Journal of controlled release: official journal of the Controlled Release Society. 2013; 172:946–953. [PubMed: 24041709]

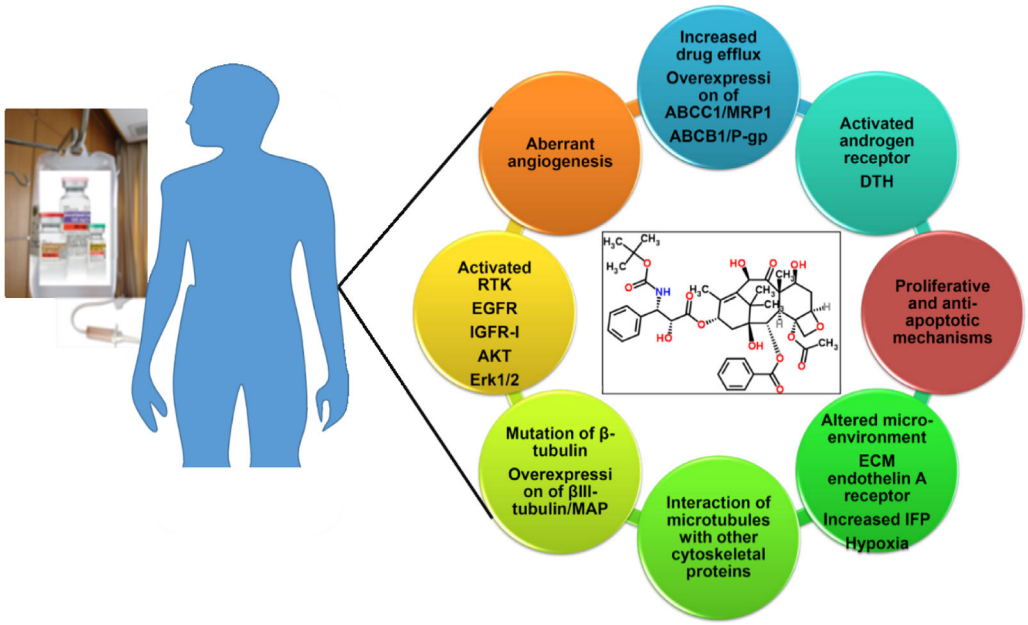

Figure 1.

De novo and acquired resistance mechanisms that mediate docetaxel therapy in many prostate cancer cells and patients.

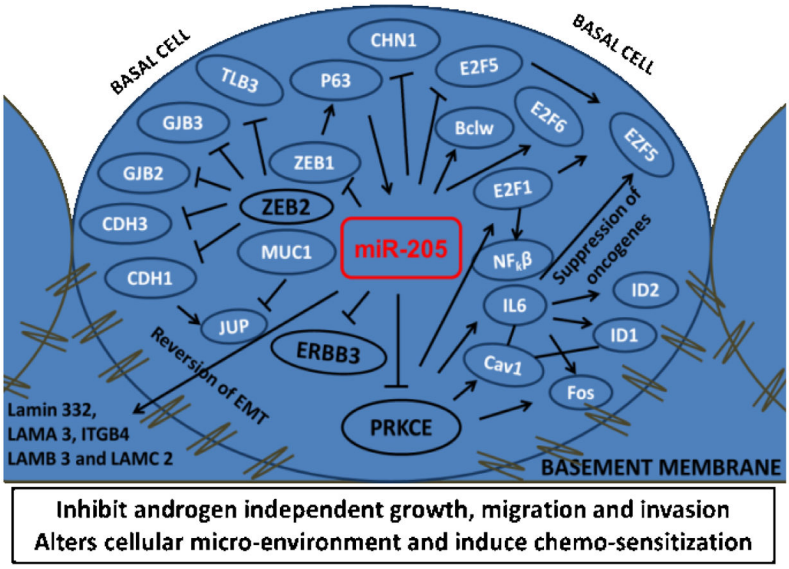

Figure 2.

Importance of miR-205 in various types and stages of prostate cancer to reverse docetaxel resistance.

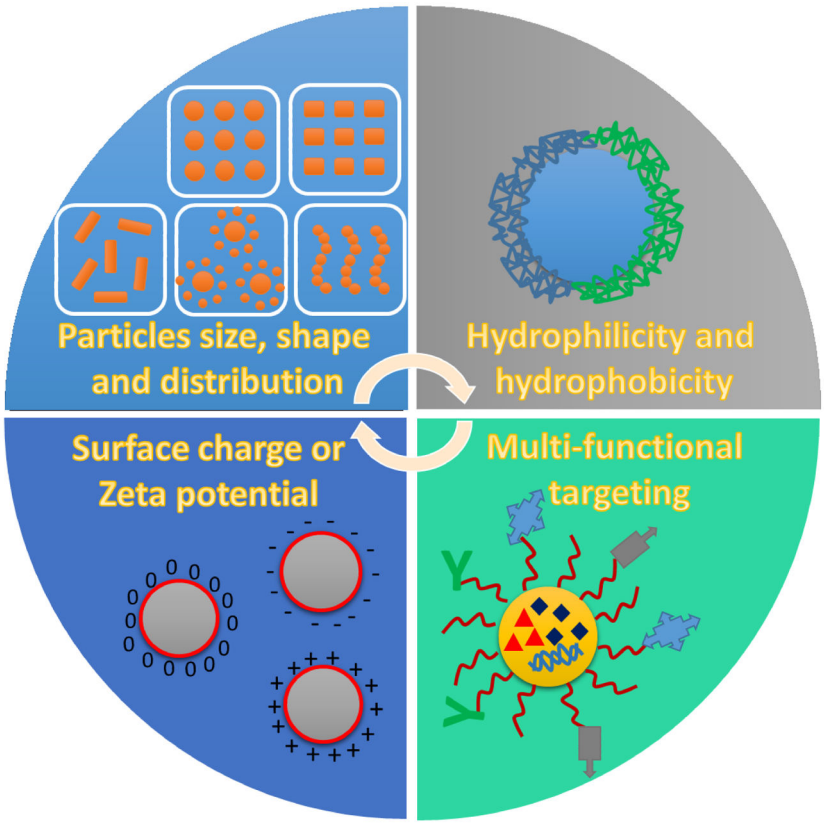

Figure 3.

Nanoformulation architecture for efficient delivery of docetaxel to cancer cells or tumors. This putative diagram represents various factors such particle size, shape, hydrophilicity/ hydrophobicity, surface charge and multi-functionality that influence the engineering of a successful nanoformulation. The development of a nanoformulation appropriate for a clinical trial formulation that will improve cancer therapeutics needs to achieve specific criteria: particle size (<100 nm), hydrophilicity (less body clearance), negative zeta potential (for low systemic toxicity), and targeting and diagnosis moiety (for improve therapeutic potential).

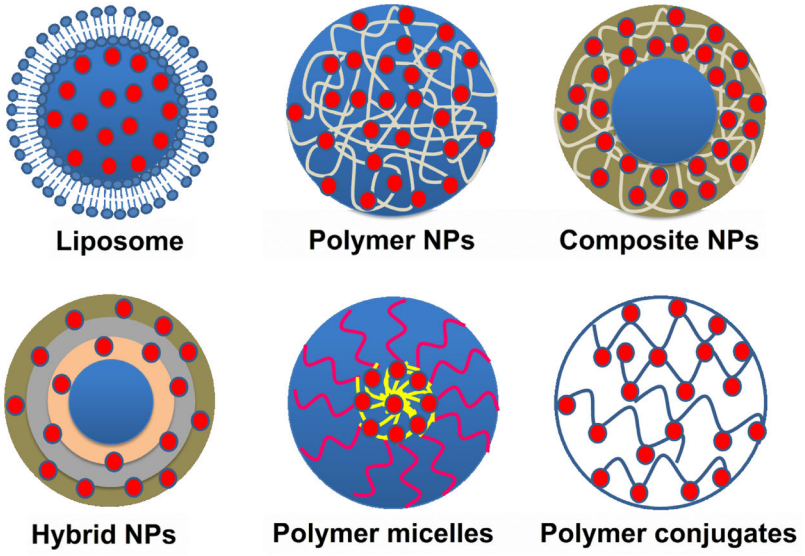

Figure 4.
Structurally varied docetaxel nanoformulations for therapeutic applications.

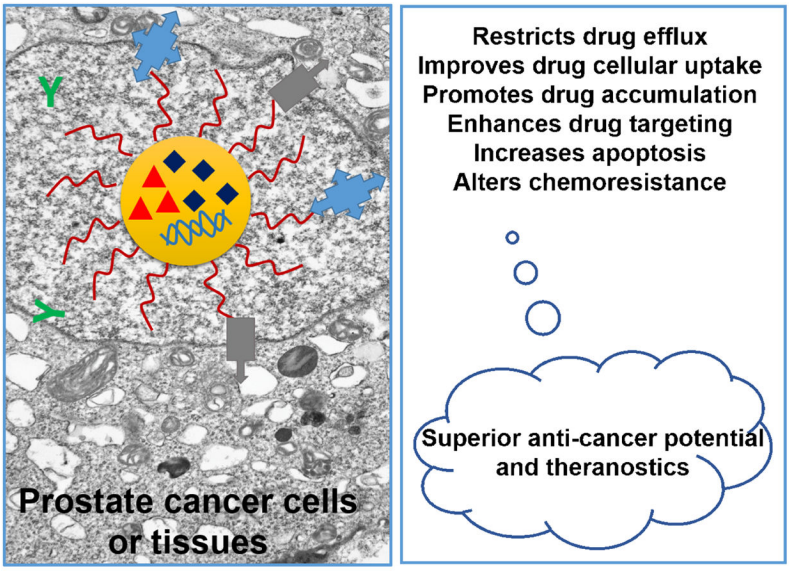

Figure 5.

A multi-functional nanoformulation with appropriate targeting potential addresses conventional docetaxel resistance by altering the tumor microenvironment in order to regulate drug efflux. This approach may lead to improved docetaxel cellular uptake, accumulation, targeting and thus improved apoptosis and anti-cancer effects.

Table 1

Docetaxel nanoformulations can reverse docetaxel resistance mechanisms by improving availability and activity at tumor sites.

Formulations	Overcome resistance mechanism					
	ABC transporters and P-gp	Altered microenvironment and hypoxia	Androgen receptor, DTH, and other receptors	Proliferative and anti-apoptotic mechanisms	RTK/EGFR/IGFR-1/AKT/ERK/Angiogenesis	Mutation of β-tubulin
Liposomes	✓	✓	?	✓	✓	✗
Polymeric nanoparticles	✓	✓	✓	?	?	✗
Composites and hybrid nanoparticles	✓	✓	✓	?	?	✗
Polymeric micelles	✓	✓	✓	?	?	✗
Nanoconjugates	✓	✓	✓	?	?	✗

Table 2

Beneficial outcome of docetaxel nanoformulations in preclinical or clinical stage trials.

Nanoformulation	Subject	Superior Outcome
Docetaxel-loaded liposomes (Zhang et al., 2012a)	Kunming mice	Increased plasma concentration and half life
Magnetic cationic liposome conjugated DTX (Kobayashi et al., 2013)	Androgen independent prostate cancer tissue, PLS-P transplanted male F344 rats	Increased necrosis and apoptosis, suppressed proliferation and bone destruction and increased tumor immunity
Docetaxel embedded magnetoliposome (DML) (Yoshida et al., 2012)	Human MKN45 gastric cancer cells implanted in Balb-c/nu/nu mice	Increased DTX concentration, cell cycle arrest and increased TNF-α levels
N-octyl—O-sulfate chitosan modified DTX liposome (Qu et al., 2012)	Sprague-Dawley (SD) rats	Higher plasma concentration, higher drug loading and entrapment efficiency
Docetaxel-loaded immunoliposomes (Yamamoto et al., 2011)	NCI-N87 transplanted in BALB/c-nu/nu mice	Higher drug concentration in xenograft tissues, superior antitumor efficacy and cell cycle arrest
Docetaxel loaded Mannitol-core PLGA-TPGS (Tao et al., 2013)	MCF-7 transplanted SCID mice	Reduced tumor volume and higher cellular uptake
Docetaxel loaded PLGA nanoparticle (Chu et al., 2013)	A549 transplanted xenograft and A549-luciferase-c8 transplanted lung orthotopic nude mice	Higher drug concentration at tumor site, Higher maximum tolerated dose, tumor growth inhibition and no systemic toxicity
PSMA targeted docetaxel nanoparticle (Hrkach et al., 2012)	MX-1 breast cancer transplanted Female athymic mice, male Sprague-Dawley (SD) rats, and Cynomolgus monkeys	Higher plasma concentration at 48 hours, increased half-life and tumor inhibition
Single-walled carbon nanotubes –DTX (Wang et al., 2011)	S180 transplanted BALB/c mice	Increased cellular uptake, higher plasma concentration, higher concentration at tumor site and better antitumor efficacy
Photoswitchable docetaxel nanoparticle (Tong et al., 2013)	HT-1080 transplanted nude mice	Enhanced tumor reduction, no systemic toxicity, higher plasma concentration leading to higher antitumor efficacy and cell penetration
Docetaxel loaded mesoporous silica nanoparticle (Wang et al., 2013)	MCF-7 transplanted nude mice	Strong antitumor efficacy, little systemic toxicity, Higher drug loading and encapsulation efficiency, lower cytotoxic effects and reduced tumor growth
Docetaxel conjugated miR-200c nanoparticle (Liu et al., 2013a)	BGC-823 gastric cancer transplanted BALB/c mice	Higher intracellular accumulation and longer retention, inhibited tumor growth and reduced resistance
DTX-loaded PLGA-methoxyPEG micelle (Li et al., 2012)	4T1 implanted in BALB/c Mice, Hartley Guinea pigs (Hemolysis test)	Higher drug loading and entrapment efficacy, better cytotoxic and anti-metastatic ability
Nanomicelle loaded DTX (Ma et al., 2012)	Luciferase expressing M2L tumor cells implanted in BALB/c nude mice	Higher survival rate, longer blood circulation, increased accumulation in tumor and reduced tumor volume
Docetaxel-loaded mPEG-DSPE (Tong et al., 2012)	Female Sprague-Dawley rats (PK studies), MCF-7 transplanted in BALB/c nude mice	Longer circulation effect, enhanced antitumor efficacy and decreased toxicity and inhibition of tumor growth
HPMA conjugated DTX (Zhou et al., 2013)	PC-3 transplanted in Male nude mice	Persistent growth inhibition and selective killing of Cancer initiating cells
Docetaxel-albumin conjugate (Esmaeili et al., 2009)	Female BALB/c mice	Higher Plasma concentration, longer half-life, higher RES evading ability and higher antitumor efficacy
LE-DT (Liposome) (Deeken et al., 2013)	Patients	Well tolerated with expected toxicity, neutropenia, anemia and fatigue
BIND-014 (Docetaxel nanoparticle) (Hrkach et al., 2012)	Patients	Enhanced tumor accumulation, blood circulation and tumor growth inhibition

Nanoformulation	Subject	Superior Outcome
Dendrimer-DTX (Tan et al., 2012)	Patients	Increased solubility, antitumor efficacy and biodistribution
ATI-1123 (Liposomal docetaxel)	Patients (Svenson, 2014)	Phase 1 study
NKTR-105 (PEG-DTX conjugate) (Gale and Croasdell, 2010)	Patients	Ongoing study