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Nanotechnology: Future of Oncotherapy

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Abstract

Recent advances in nanotechnology have established its importance in several areas including medicine. The myriad of applications in oncology range from detection and diagnosis to drug delivery and treatment. Although nanotechnology has attracted a lot of attention, the practical application of nanotechnology to clinical cancer care is still in its infancy. This review summarizes the role that nanotechnology has played in improving cancer therapy, its potential for affecting all aspects of cancer care, and the challenges that must be overcome to realize its full promise.

Introduction

Nanomedicine offers unique opportunities for improving current ways of treating cancer and other diseases (Fig. 1). These stem from the potential of nanoformulations to improve drug delivery and achieve targeted delivery, thereby reducing systemic toxicity (1). Various nanoparticle formulations such as quantum dots, liposomes, polymeric nanoparticles, carbon nanotubes, metallic nanoparticles, or dendrimers have been investigated in preclinical and clinical settings for drug or gene delivery, photothermal therapy, immunotherapy and imaging (Table 1). Although few formulations have been approved by the FDA (Table 2), the full potential of nanotechnology in the clinical setting is yet to be realized. Here, we review the successes of nanotechnology in cancer care and provide a critical appraisal of its future applications.

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Nanoparticles for Drug Delivery

Small molecule drug delivery

Chemotherapy drugs are used for many cancer types, but conventional chemotherapy is nonspecific and can lead to intolerable toxicities, compromising patients' quality of life. Nanotechnology has the potential to overcome such hurdles. Targeted delivery, reduced toxicity, improved pharmacokinetics and bioavailability are some of the potential advantages offered by nanotechnology.

Among various nanoparticle platforms, liposomes are the most advanced with regard to integration into clinical care. Liposomal incorporation of doxorubicin and daunorubicin increase plasma concentration, reduce clearance rate, and volume of distribution, thus, increasing bioavailability of the drug (2, 3). Moreover, there is substantial decrease in cardiac and other toxicities with liposomal doxorubicin as compared to free doxorubicin (4). Further improvement in the safety and pharmacokinetics was achieved by using polyethylene glycol (PEG) to coat liposomes (5–7).

Polymeric nanoparticles have also been instrumental in improving the therapeutic window of conventional drugs. For instance, the use of cremophor with paclitaxel contributes to hypersensitivity reactions and neuropathy, but albumin nanoparticle-based formulation of paclitaxel facilitates endothelial transcytosis to achieve significant accumulation in the tumor (8). Phase I evaluation established that maximum tolerated dose (MTD) dose of such nanoparticles was about 70% higher than traditional paclitaxel (9). This formulation is associated with lower neutropenia and hypersensitivity while achieving higher response rate than standard paclitaxel (10). Paclitaxel poliglumex is another polymeric formulation (poly(L-glutamic acid, PG) with increased water solubility of paclitaxel, increased plasma half-life, tumor uptake, increased anti-tumor activity and improved safety profile compared to free paclitaxel (11, 12).

The nanoparticle platforms discussed above rely predominantly on passive accumulation of nanoparticles at tumor sites based on enhanced permeability and retention (EPR) effect. Tumor selectivity can be further enhanced by attaching tumor-specific ligands (e.g., folic acid, HER2 antibody, aptamers, and transferrin) to nanoparticles to enhance tumor accumulation, increased cellular internalization and increased anti-tumor effects (13–17). For example, MCC-465 (PEGylated immunoliposome conjugated with F(ab′)2 fragment of GAH and encapsulates doxorubicin) was well tolerated in preclinical and early clinical testing. (18). MM-302 is a HER-2 targeted PEGylated liposome containing doxorubicin that has shown improved cardiac toxicity profile in combination with trastuzumab (19). Phase 1 testing of cetuximab conjugated doxorubicin liposome was also well tolerated (20). Additional formulations (e.g., MBP-426 and SGT53 (p53) are in clinical testing (21).

Several nanoparticle strategies have been developed for targeting stromal populations such as endothelial cells, macrophages and cancer stem cells. Paclitaxel loaded into PLGA nanoparticles decorated with CD133 antibody resulted in enhanced survival in preclinical cancer models (22). Combination therapy with epigenetic-targeted decitabine and doxorubicin nanoparticles targeting cancer stem cells was shown to be more beneficial than

free decitabine and doxorubicin in chemoresistant breast cancer models (23). Chitosan nanoparticles decorated with RGD peptides localize to the tumor vasculature and exert anti-angiogenic effects (24). The next generation nanoparticles aim to achieve further selectivity by allowing spatiotemporal control over drug release. These nanoparticles are designed to selectively release drugs in response to stimuli such as an alternating magnetic field, UV or near infra-red radiation or low pH in the tumor microenvironment (25–29). However, issues related to tumor heterogeneity, cost considerations and changes in characteristics of a nanoparticle after ligand conjugation will require careful consideration during drug development.

Nucleotide delivery

Nucleotide therapies hold an important place in cancer therapy since many of the undruggable genes can be targeted using antisense oligonucleotides (ASO) or siRNAs. Several ASOs are now in clinical trials, but the success has been modest (30). SiRNAs may be a better alternative to ASOs due to ease of synthesis and ability to achieve greater silencing at lower concentration than ASOs. However, several challenges associated with siRNA (e.g., enzymatic degradation in plasma, inefficient uptake by cells, and immunostimulation) must be overcome. Several nanoparticle platforms have been investigated to overcome these hurdles in siRNA delivery. While some cationic liposomes are efficacious, these carriers can cause toxicities (e.g., activation of complement system and inflammatory responses) (31–33). Formulations such as AtuPLEX showed that toxicity can be reduced by incorporation of helper neutral lipids and PEGylation (34). The lipoplex Atu027 containing siPKN3 is currently in clinical trials for advanced solid cancers. Although preclinical studies showed anti-tumor effect, it should be noted that the PKN3 mRNA reduction was more pronounced in liver and lung compared to tumor (35). Stable nucleic acid lipid particles (SNALP) formulations such as ALN-VSP02 (first generation SNALP containing siVEGF and siKSP) showed moderate gene knockdown (36), and some liver and spleen toxicities were noted. The next generation SNALP, TKM-080301, was formulated with more stable PEG-lipids in the nanoparticles. The clinical trial with siPLK1 showed better immune profile along with increased drug exposure compared to the earlier generation of SNALPs (37). Neutral nanoliposomes (e.g., DOPC) have shown improved delivery (approximately 10-fold) of siRNA and anti-tumor effects with systemic delivery (38). Moreover, in a hepatocarcinoma mouse model, neutral liposome containing doxorubicin showed better biodistribution profile and anti-tumor efficacy compared to their cationic counterparts (39).

Once inside the tumor cells, it is important to overcome barriers such as endosomal uptake (40). Systems such as polymer-based dynamic polyconjugate (DPC) delivery system, which contains endosomolytic *N*-acetylgalactosamine–conjugated melittin-like peptide, may allow specific endosomal release of siRNA from its nanocarrier, thus lowering siRNA EC_{50} (37, 41).

Nanoparticles for Immunotherapy

One of the unmet needs in the field of immunotherapy is the lack of efficient delivery systems for cytokines and antigens. Success of systemic administration of cytokines has

been limited because of their early degradation, non-specific binding to proteins, quick excretion and undesired toxic effects. Gold nanoparticles conjugated with TNF-alpha are currently being investigated in clinical trials (42). Early results suggest that such a formulation may be safer with higher MTD than free recombinant TNF-alpha (43). In addition, studies with IL-2 and IL-12 have also shown that nanoparticle incorporation increased plasma retention time (44, 45).

Successful antigen vaccination can be achieved by ensuring a) sufficient concentration of antigen in antigen presenting cells (APCs), b) sustained release of antigen for prolonged exposure to APCs and c) cytoplasmic delivery of antigen for MHC class I processing. Incorporation of an antigen into target specific nanoparticles can increase the concentration of antigens in dendritic cells (46–48). Nanoparticles can also incorporate adjuvants and antigens in the same vehicle (46, 47, 49). For example, conjugation of polyribocytidylic acid (adjuvant) with DOTAP containing a tumor lysate (antigen) not only increased toll-like receptor signaling, but also led to increased DC maturation and enhanced anti-immune response (47). Since DOTAP can lead to ROS production and apoptosis of DC cells (50), safer and more effective systems are needed.

Poly-lactic-co-glycolic acid (PLGA) nanoparticles have been shown to act as intracellular antigen reservoirs for DCs, minimizing degradation of antigens and the need of repeated dosing (51). Such sustained antigen presentation leads to stronger immune responses and consequently better anti-tumor effects. However, precise knowledge of degradation and release kinetics is essential to formulate effective sustained release nanoparticles. Once inside the cells, it is important that the antigens are released in the cytosol for preferential processing through MHC class I pathway to prime $CD8^+$ T-cells. Use of poly-(gamma–glutamic acid), conjugation of pH responsive peptide bonds, or incorporation of cell penetrating peptide R8, are some of the strategies to achieve enhanced cytoplasmic release of antigens (52–54). Immunogenicity of certain nanomaterials is a potential concern (e.g., PEG coated nanoparticles can activate the complement system and lead to PEG specific IgM antibodies) (55, 56); strategies to overcome these unexpected side effects are needed.

Nanoparticle as an Individual Active Agent for Therapy and Imaging

Photothermal ablation for tumoricidal effect

Photothermal ablation involves exposure of tissues to high temperature for membrane lysis and subsequent cell death (57). Increased susceptibility of cancer cells to hyperthermia is on account of their higher metabolic rates than normal cells (58), however, this selectivity is minimal. The main concern with photothermal therapy (PTT) is the non-specific effect on surrounding normal tissues. Localized heating, enabled with the use of nanoparticles, can avoid toxicity to normal cells. Blood and tissues are relatively transmissive in near infra-red (NIR) range. NIR has thus been effective for PTT since it achieves optimal tissue penetration to reach deeply localized tumor tissues. Initial preclinical studies were conducted using FDA approved NIR free dyes (e.g., indocyanine green). Although it showed anti-tumor effect, the strategy mainly suffered because of the low circulation time of ICG (3 minutes) and damage to normal tissues (59). Incorporation of these dyes into

polymeric nanoparticles improved solubility and stability, increased photothermal ablation while keeping toxicity at minimum (60–62).

Gold nanoparticles are widely used for PTT (57, 63, 64). Nanoshells with silica core coated with thin gold layer have been studied extensively in preclinical studies and are currently in clinical trials for head and neck and metastatic lung cancer patients (65, 66). The temperatures achieved by these nanoparticles ($\Delta T = 37.4 \pm 6.6°C$) were significantly higher than those achieved by laser treatment alone ($\Delta T < 10°C$) (65). In the treatment arm, tumor growth was significantly lower and survival was significantly higher. Further studies demonstrated that malignant cells required less than half of the laser density (~20W/cm^2) for ablation compared to normal cells (57 W/cm^2) when incubated with EGFR conjugated gold nanoshells (67, 68). Smaller hollow gold nanospheres have also been developed for simultaneous laser triggered drug delivery of doxorubicin, with significantly better anti-tumor effects compared to PTT alone (69), and have a favorable safety profile (70). Copper sulfide (CuS) nanoparticles are also being investigated for PTT. PEG-CuS nanoparticles plus laser treatment resulted in significantly higher tumor tissue necrosis (~65%) compared to saline plus laser treatment (~5%) (71). Several attractive features (smaller size (<15nm), better renal clearance, ease of synthesis, and low cost) make them promising candidates for PTT (71, 72).

Clinical applicability of a nanoparticle can be further improved if it can also be used as an imaging agent for MR imaging and spatiotemporal monitoring of the nanoparticles (73). Similar to previously discussed nanoparticles, gold and iron oxide nanoparticles also have certain toxicity issues (74–77) that will require additional work.

Tumor imaging

The limitations of current imaging modalities, such as iodine and gadolinium based CT, X-ray and MRI scans, are lack of sensitivity in detecting small tumor nodules, lack of specificity, shorter imaging time, and toxic effects. Novel nanoparticle platforms may help to overcome these limitations. For example, ferumoxtran-10, an iron oxide nanoparticle showed significantly higher sensitivity (90.5% vs. 35.4%) in detecting lymph node metastasis as compared to conventional MRI scans (78, 79). Iron oxide nanoparticles, when compared with gadolinium (Gd) chelates, showed lower diffusion from tumor site, increased internalization by cancer cells, and enhanced detection of lesions in the brain (80). Polymeric dendrimers used as nanocarriers for Gd proved as a better tool for detecting lymph nodes compared to free Gd chelates; such sensitivity was achieved at 1/2500th of the molar concentration of the clinical Gd dose (81). Owing to the high atomic number and electron density, gold nanoparticles have higher absorption coefficient than conventional iodine and are better contrast agents for PET and X-rays (82). Ability to coat them with PEG and functionalize the surface with targeting ligands makes it possible to increase circulation time and achieve high tumor cell specificity (83, 84). Nanoparticle formulations have also been used to reduce the toxicity of conventional contrast agents. Gadolinium containing agents can cause nephrogenic systemic fibrosis, which can be prevented with nanoparticle incorporation (85, 86).

Certain nanoparticles such as self-assembled nanocages facilitate interaction between water molecules and Gd, allowing higher MR signal at much lower Gd concentration (87). Same was the case with free NIR dyes, where non-specific accumulation of dyes in lungs and testicles had raised concerns, but nanoparticle formulations improved biodistribution and significantly reduced toxicity (88). Carbon nanotubes (CNT) are being investigated for X-ray imaging, but may be limited by potential carcinogenic effects (89).

Oncolytic Viruses

Oncolytic viruses are natural or genetically modified viruses that specifically kill cancer cells either by intensive cytopathic effect or inducing strong immune response in tumor microenvironment. JX-594 poxvirus, genetically modified to express GM-CSF, has been shown to increase anti-tumor immune response. The intratumoral injections had limited side effects and resulted in partial remission or stable disease in patients with liver cancer (90). Talimogene laherparepvec (T-vec) is a Herpes simplex virus expressing GM-CSF, which has shown promising results in patients with advanced melanoma. ONYX-015, an adenovirus specifically targeting tumors with inactivated p53 has also shown promising results in phase 1 and 2 trials (91). A similar virus (H101) has already gained approval for the treatment of head and neck cancer in China. Systemic administration can lead to the production of neutralizing antibodies, which may require immunosuppressive treatments prior to viral therapy (92). Combination of oncolytic viral therapy with chemotherapy or radiation may further enhance its activity (91).

Challenges and Future Perspectives

Nanotechnology has transformed the field of medicine by crafting promising avenues in therapeutics and diagnosis (Fig. 2), but there is clearly room for further improvement. Considering the heterogeneity of tumor, extent of hypoxia or expression of specific enzymes required for drug release may not be the same at all metastatic sites, potentially making drug release unpredictable. A possible solution to increase tumor specificity is to use dual stimuli responsive triggers (93–96), but particular attention must be given to characterizing these systems further and improving the scalability of the formulations. Regarding the multidrug carrying nanoparticles, optimized ratiometric loading and compatibility of their efficacy and toxicity profiles are important aspects to be considered. For theranostic nanoparticles, care must be taken to avoid compromising imaging quality or therapeutic efficacy. Pharmacokinetic (PK) and pharamacodynamic (PD) requirements are also different for imaging and drug delivery vehicles. For examples, long circulation times that are ideal for effective drug delivery may not be suitable for imaging purposes and will give high background signal (97, 98). Collectively, several factors must be considered to improve the translation of nanomedicines from bench to bedside. Here, we discuss key issues and ways to accelerate the development of clinically feasible nanosystems.

Use of relevant preclinical models to predict EPR effect

Most nanoparticles are thought to rely on the EPR effect to accumulate in tumors. Reliable methods for assessing delivery are needed. A recent study with NIRF labelled polymeric nanoparticles showed that tumors with high vascularity accumulated a greater density of nanoparticles (99). Although the study used fairly small nanoparticles (10 nm), the concept

of predicting EPR effects by simple ultrasound imaging of vasculature should be explored further in relevant pre-clinical and clinical models.

Discrepancies between pre-clinical studies and clinical trials

It is now recognized that *in vitro* models may not reliably predict the utility of nanoparticles. For example, a dual targeted (Tf and mAb 2C5) nanoparticle system failed to reproduce the in *vitro* effectiveness when tested in mouse models (100). Whether 3D biomimetic tumor models can help bridge this gap to some extent is not fully understood (101). The current 3D systems could potentially be improved by incorporating relevant stromal cells, ECM proteins or even relevant mechanical forces. These factors will help to closely simulate the tumor microenvironment and will make 3D systems a reliable platform for designing of subsequent preclinical studies.

Testing the biodistribution and efficacy of nanoparticles in relevant animal models is crucial to move the therapy into the clinic. Ideally, animal models that are reflective of human disease should be utilized for such studies. Subcutaneous models are likely to be the least reliable due to aberrant stromal and vascular biology compared to the orthotopic sites (102). Design of preclinical trials is crucial for predicting the efficacy and safety of the nanoparticles. Moreover, it is also important to assess immunological parameters (e.g., changes in cytokine levels or number of immune cells) during preclinical testing. Such comprehensive analysis will help in predicting efficacy and toxicity profile of a nano-therapy in patients. In addition, phase 0 studies should be employed to improve clinical translatability of nanoparticles. PK profile and tumor localization potential of a given nanocarrier in humans can be assessed in a timely manner in Phase 0 trials. They are much cheaper to conduct compared to phase 1 trials and researchers can also obtain feedback on the clinical feasibility of a given nanosystem much more quickly.

Selection of clinically relevant route of administration

Nanodrugs should ideally be administered the same way in the preclinical models as it is expected to be delivered in patients. For instance, pre-clinical studies with oncolytic viral therapy typically use intratumoral injections (103). Many other studies using non-viral nanocarriers also try to prove better efficacy using intratumoral injections (104, 105). However, this would have limited utility in patients with widely metastatic disease. Unlike intratumoral injections; intravenous injections can expose the particles to various biological barriers and thus will not be as effective as intartumoral route.

Choosing the right ligand for targeted delivery

Ligand targeted therapies have been shown to superior in terms of tumor specificity and low off-target effects. (106–108). In preclinical studies, greater accumulation of nanoparticles can be achieved by choosing a tumor model overexpressing the specific receptor. (105). However, there is heterogeneity in receptor expression in tumors (109, 110), and a single ligand could ultimately lead to selection of cells that lack target expression. Multi-ligand approach has been shown to be more specific and leads to better uptake of nanoparticles (111–113). With increased specificity, multi-ligand nanoparticles are less likely to be taken up by normal cells and thus have less toxicity issues (112, 114).

In summary, the versatility of formulations, targeted delivery and biocompatibility have garnered a lot of interest in nanotechnology. However, we must first address several practical issues. Every new nanomaterial and added complexities require additional controls and toxicity checks, making FDA approval potentially more difficult. Batch-to-batch variations in these cases further complicate scaling up the production. Thus, the clinical benefit and toxicity profile has to be far superior compared to the conventional drugs to justify the cost. Moreover, it is important to understand the intricacies of nanotechnology *in vivo* and predict the behavior, distribution, and kinetics with certainty. Then, we can develop strategies for scaling up production and distribution with the ultimate goal of direct clinical translation and patient benefit.

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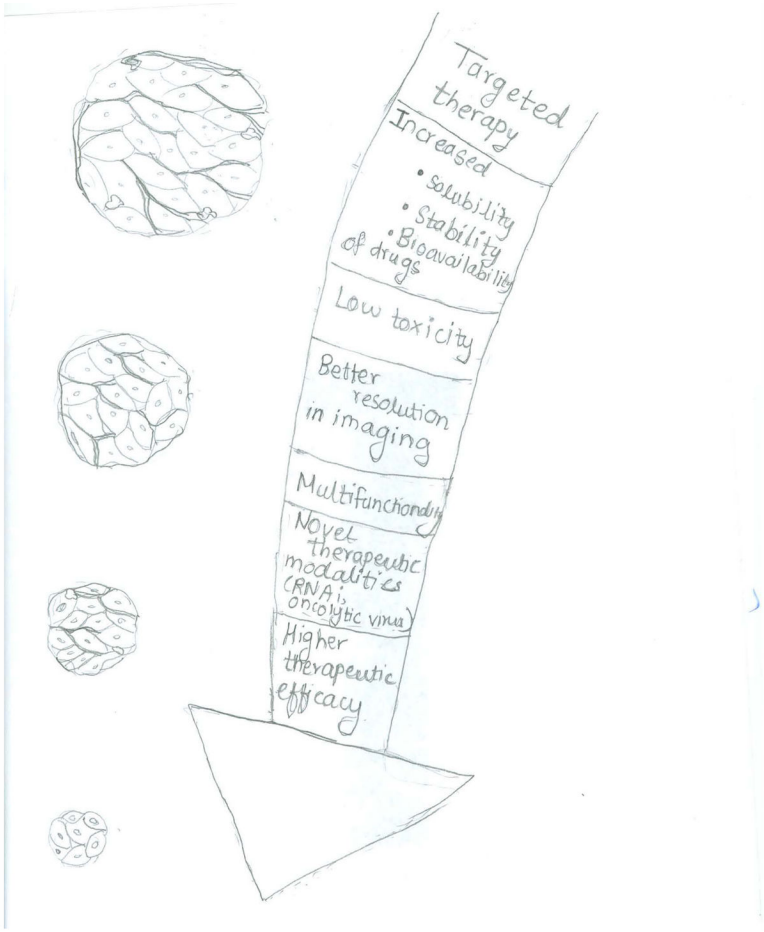

Figure 1.
Shown are some of the advantages of nanoparticles over conventional therapeutic modalities

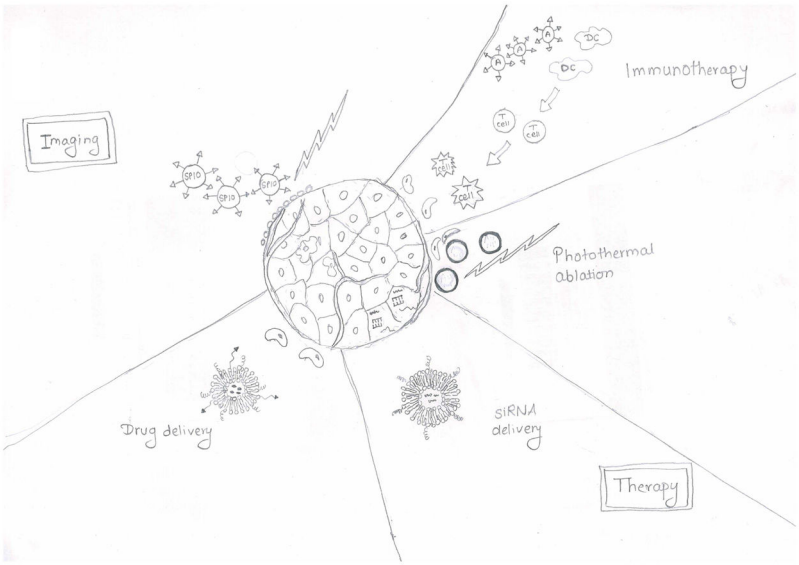

Figure 2.

Nanotechnology offers a wide array of applications for drug delivery, nucleotide delivery, photothermal therapy, immunotherapy and imaging. Shown are some of the commonly used nanoformulations for each of the applications: ligand conjugated, target specific PEGylated liposomes for small molecule drug delivery; PEGylated stable nucleic acid lipid particles (SNALP) for nucleotide (e.g., siRNA) delivery; gold nanoshells for photothermal therapy; ligand conjugated, target specific antigen carrying polymeric nanoparticles for immunotherapy and super paramagnetic iron oxide nanoparticles (SPIO) for imaging. Dendritic cells (DC) are immune cells that process and present antigens to T cells.

Table 1

Types of nanoparticles

Name	Formulation	Advantages	Disadvantages and toxicity	Application
Liposome	Self-assembled bilayers of phospholipid molecules	• Can incorporate hydrophobic molecules in the core and hydrophilic molecules in between the bilayer • Increase circulation time • Biodegradable	Cationic liposomes can lead to hemolysis and blood coagulation	Mainly used for drug delivery (e.g., doxil, daunoxome, etc.)
Polymeric nanoparticles	• Polymer-protein conjugation by chemical conjugation • Polymeric micelles by emulsification, precipitation method	• Biocompatible and biodegradable • Increase circulation time • Reduced toxicity • Surface can be conjugated with ligands	Toxicity at very high doses	Drug delivery (Abraxane), siRNA delivery (currently in clinical trials)
Dendrimers	Highly branched polymeric molecules with a central core	• Chemical composition can be controlled thus PK properties can be predicted • Ability to incorporate drug in the core or conjugating it to the surface • Multivalent structure allows sites for ligand conjugation for targeted delivery	• Difficult to scale up • Cationic dendrimers lead to intravascular coagulation	Drug, siRNA or plasmid delivery
Gold nanoparticle	Reduction and precipitation of ions leads to nanoformulations	• Biocompatible • Surface plasmon resonance • Increased sensitivity as a contrast agent • Can be used as imaging and therapeutic agent simultaneously	Some particle retention after the therapy	Currently in clinical trials for photothermal application MR imaging Drug delivery
Iron oxide nanoparticle	Reduction and precipitation of ions lead to nanoformulation	• Supermagnetic property • Ease of synthesis • Can be used as a theranostic agent	Hydrphobic surface leads to Particle aggregation	MR imaging Photothermal ablation Drug delivery
Carbon nanotubes	Single or multi walled cylindrical graphene sheets	• Ease of internalization by cells • Surface can be functionalized for attaching drugs/proteins/ligands, etc.	• Inflammatory responses after aggregation • Pulmonary toxicities • Possible carcinogenic activity	Imaging Drug delivery

Name	Formulation	Advantages	Disadvantages and toxicity	Application
Quantum dots	Core-shell structure, most common core- Cadmium selenium, Cadmium tellurium Shell- zinc sulfide, zinc selenium	• Ease of formulation • Higher brightness and photosensitivity than conventional dyes • Imaging and delivery agent	• Limited tissue penetration • Low resolution of deeply situated tumor • Release of Cadmium leads to toxicities.	Imaging Drug and gene delivery

Table 2

Nanoformulations currently in clinical trials

Name	Formulation	Indication	Phase status	Trial number
Drug delivery				
Myocet	Liposomal doxorubicin	Metastastic breast cancer	Approved	
Daunoxome	Liposomal daunorubicin	Kaposi's sarcoma	Approved	
Doxil	PEGylated liposomal doxorubicin	Kaposi's sarcoma Recurrent ovarian cancer Metastatic breast cancer Multiple myeloma	Approved	
Marqibo	Liposomal vincristine	Acute lymphoblastic leukemia	Approved	
Abraxane	Albumin bound paclitaxel	Breast cancer Non-small cell lung cancer Pancreatic cancer	Approved	
Paclitaxel poliglumex	Polyamino acid bound paclitaxel	Head and neck cancer Ovarian cancer Glioma Non-small cell lung cancer	Phase I/II Phase III Phase II	NCT00660218 NCT00269828 NCT01402063 NCT00045682
Zinostatin stimalamer	Neocarzinostatin SMANCS (Polymer-protein conjugate)	Hepatocellular carcinoma	Approved	
Oncospar	PEG-L- asparaginase	Acute lymphoblastic leukemia	Approved	
siRNA delivery				
CALAA-01	Transferrin targeted cyclodextrin nanoparticle with siRRM2	Solid tumor	Phase 1	NCT00689065
Atu027	Cationic liposome- siPKN3	Solid tumor	Phase 1	NCT00938574 NCT01808638
TKM 080301	Stable nucleic acid lipid particle-siPLK1	Solid tumor	Phase 1	NCT01262235
ALN-VSP02	Stable nucleic acid lipid particle-siVEGF and siKSP	Solid tumors	Phase 1	NCT01158079
Epharna	Neutral DOPC liposome-siEphA2	Solid tumor	Phase 1	NCT01591356
Immunotherapeutic agents				
CHP-HER2 and CHP-NY- ESO-01	Cholesterol-Bearing hydrophobized pullulan HER2 Protein 146 (CHP- HER2) and NY- ESO-1 Protein (CHP-NY-ESO-1) in combination With OK-432	Esophageal cancer Lung cancer Stomach cancer Breast cancer Ovarian cancer	Phase 1	NCT00291473
CYT004- MelQbG10	Virus like nanoparticle with antigens Melan- A/MART-1 and adjuvant CpG- oligonucleotide (ODn)	Malignant melanoma	Phase 2	NCT00651703
Photothermal and radiotherapy application				
AuroLase	Silico core with gold metal shell and near infrared laser	Head and neck cancer Lung cancer	Phase 1	NCT00848042, NCT01679470
NBTXR3	Hafnium oxide nanocrystals	Soft tissue sarcoma	Phase 1	NCT01946867, NCT01433068
Imaging agents				
SPIO MRI	Ultrasmall Superparamagnetic Iron Oxide Magnetic Resonance Imaging	Pancreatic cancer	Phase 4	NCT00920023

Name	Formulation	Indication	Phase status	Trial number
fluorescent cRGDY-PEG- Cy5.5-C dots	RGD labeled silica nanoparticle with Cy5.5 dye	Solid tumor	Phase 0	NCT02106598
Carbon nanoparticles	Carbon nanoparticles	Advanced gastric cancer	Phase 3	NCT02123407