Chapter 8
Nanomaterials in Cancer Theranostics

Lei Zhu, Lily Yang and Zhiyang Zhou

Abstract Recent advances in the development of novel nanomaterials and evaluation of their biomedical applications have shown promises of those multifunctional nanomaterials in the development of new approaches for cancer detection and therapy. The unique physicochemical properties of nanomaterials, small size, and large surface-area-to-volume ratio endow them with novel multifunctional capabilities for cancer imaging, drug delivery, and cancer therapy, referred to as theranostics, which are different from the traditional diagnosis and therapy approaches. To facilitate the translation of nanomaterials as imaging agents and drug delivery carriers into clinical applications, great efforts have been made on designing and improving biocompatibility, stability, safety, drug loading ability, targeted delivery, imaging signals, and thermal- or photodynamic responses. With the development of companion new imaging techniques and therapeutic approaches, several nanomaterials have demonstrated great theranostic potential in image-guided therapy of diseases, especially in cancer therapy. In this review, the current status and perspective of nanoparticles in the development of cancer theranostic agents will be discussed with a focus on several representative nanomaterials, including magnetic iron oxide nanoparticles, gold nanoparticles, silica nanoparticles, polymeric nanoparticles, and carbon nanomaterials.

Keywords Nanomaterials · Theranostics · Imaging-guide therapy

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8.1 Introduction

Cancer is characterized by the uncontrolled growth and spreading of abnormal cells. It has been a public health issue in many countries all over the world, including the US [1, 2]. Although progresses have been made in cancer diagnosis and treatment, the survival rate of cancer patients is still low, especially for those diagnosed at the later stage. Therefore, sensitive and specific diagnostic and effective therapeutic approaches are needed for the improvement of prognosis of cancer patients [3].

Nanoparticles, composed of different types of materials as the small particles in a nanoscale range, can be classified as organic and inorganic nanoparticles [4] (Fig. 8.1). Specifically, inorganic nanoparticles include metal nanoparticles, carbon nanoparticles, and quantum dots, while organic nanoparticles usually contain biocompatible materials, such as lipids, polymers, liposomes, polymeric micelles, dendrimers, and engineered peptides and nucleic acids. Nanoparticles have high ratio of the surface area-to-body volume, various chemical compositions, and biological characteristics that enable their ability of surface modification for conjugation or encapsulation of targeting, drug loading, and imaging contrast agents [5]. Moreover, surface characteristics play a vital role in metabolism and distribution of nanoparticles in the blood circulation. Various approaches have been developed to reduce nonspecific uptake by macrophages in the reticuloendothelial system (RES), such as polyethylene glycol (PEG) or antifouling polymer coating of the surface of nanoparticles [6, 7]. It is well accepted that after modification with PEG, nanoparticles could increase physiological stability, reduce nonspecific interaction with serum proteins and macrophages, and therefore prolong the half-life time in the blood circulation, which improve the passive targeting to tumor sites. Additionally, the shape of nanoparticles affects the blood half-life, macrophage uptake, extravasation, and internalization by cells. It has been reported that oblong-shaped nanoparticles can circulate in vivo for longer time than nanospheres due to the low level of macrophage uptake [8, 9].

A marked feature of nanoparticle-mediated drug delivery following systemic delivery is that small size nanoparticle drug carriers (<200 nm) can be delivered into and accumulated in tumors by the enhanced permeability and retention (EPR) effect through the leaking tumor vasculatures [10]. Drug delivery utilizing passively targeted nanoparticles have shown improved intratumoral delivery efficiency and therapeutic efficacy in preclinical and clinical studies. Most of the U.S. Food and Drug Administration (FDA) approved imaging and therapeutic nanoparticles that are currently used in cancer patients or in clinical trials are nontargeted nanoparticles (Table 8.1).

In human tumors, distribution, structure, and permeability of tumor vessels are highly heterogeneous [11]. To increase the efficiency of nanoparticle delivery and retention in tumors, targeting ligands to certain receptors that are highly expressed in tumor vasculatures, tumor stromal cells, and tumor cells have been conjugated onto the nanoparticles [12]. Those include antibodies or engineered antibody fragments, natural ligands, peptides, structured DNA and RNA molecules, and

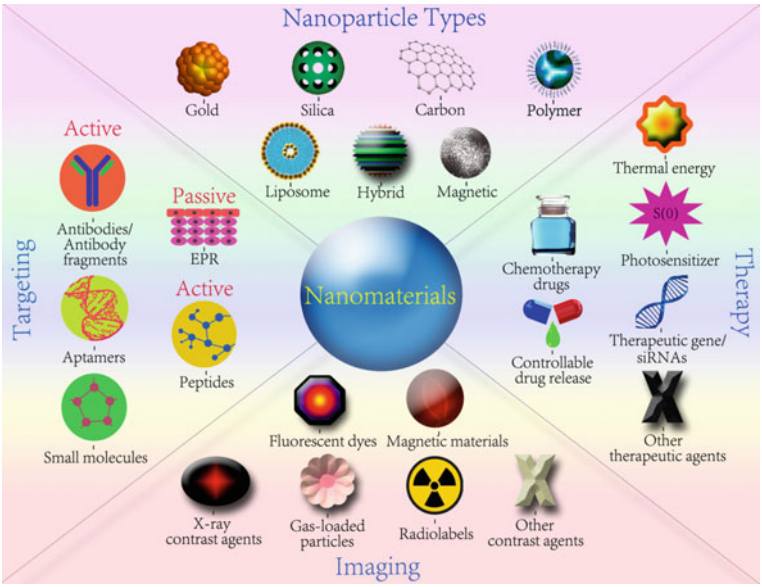

Fig. 8.1 Classification, modification, and functionalization of theranostic nanoparticles in biomedical applications

small molecules [12] (Fig. 8.1). Extensive preclinical studies have been conducted using different tumor targeting ligand conjugated nanoparticles, either as imaging probes or drug carriers [5, 13]. Improved drug delivery efficiency and therapeutic response have been demonstrated in various animal tumor models. Several targeted nanoparticle formulated drugs are currently in clinical trials to determine the therapeutic effect of targeted nanoparticles in human cancer patients (Table 8.1). Although theranostic nanoparticles have not been tested in human patients so far, preclinical studies have demonstrated the feasibility of further development of the nanoparticle platforms that have been tested in human patients into theranostic nanoparticles by conjugation or encapsulation of imaging contrasts, such as radioisotopes, optical dyes, gadolinium, or magnetic iron oxide nanoparticles [13–15]

For the development of effective targeted theranostic nanoparticles for cancer therapy, several major challenges are well recognized. First, it is important to identify an imaging and therapy suitable biomarker that is highly expressed in tumor cells but is absent or expressed at a low level in normal cells. There should also be an available corresponding targeting ligand that binds to the receptor with a high affinity and can be produced in large quantities for in vivo applications in the experimental animals and humans. For the development of a theranostic agent, it is critical for the nanoparticles to be stable, biocompatible, biodegradable, and low or no toxic. As a theranostic agent, it also requires the nanoparticle to have the capability of carrying and releasing therapeutic payloads after entering tumor

Table 8.1 Representative nanoparticle drug carriers in clinical trials or FDA-approved cancer nanotherapeutics

NP type	Name and formulation	Application	Status	Ref.
Iron oxide NP	Feridex® Sterile aqueous colloid of superparamagnetic iron oxide coated with dextran	MRI; focal hepatic lesions	FDA-approved	[16–18]
	Combidex® Ultrasmall superparamagnetic iron oxide covered with low molecular weight dextran	MRI; metastatic cancer lesions	Approved in Europe	[19, 20]
	Resovist® Superparamagnetic iron oxide nanoparticles coated with carboxyl dextran	MRI; focal hepatic lesions	Approved in Europe	[21–23]
	Gastromark® Aqueous suspension of silicone-coated, superparamagnetic iron oxide	MRI; gastrointestinal lumen imaging	FDA-approved	[15, 24]
Liposome NP	Doxil®, Lipodox® (Doxorubicin HCl liposome injection) DaunoXome® (Daunorubicin Citrate Liposome Injection)	Recurrent ovarian cancer, AIDS-related Kaposi's sarcoma, metastatic breast cancer	FDA-approved	[25–31]
	DepoCyt® Cytarabine liposome injection	Lymphomatous meningitis	FDA-approved	[32–34]
	Myocet® Liposomal doxorubicin	Metastatic breast cancer	Approved in Europe	[35, 36]
	LiPlaCis® Liposomal cisplatin	Solid tumors	Clinical trial	[37]
	DOTAP Liposomal transfection reagent	Gene transfer; lung cancer	Clinical trial	[38]
	Onivyde® Irinotecan liposome	Chemotherapy; metastatic pancreatic cancer	FDA-approved	[39]
Polymeric NP	Genexol® PM Cremophor EL-free polymeric micelle formulation of paclitaxel	Advanced non-small cell lung cancer, metastatic breast cancer	FDA-approved	[40–42]
	CALAA-01 Transferrin receptor-targeted anti-RRM2 siRNA	Solid malignancies	Clinical trial	[43, 44]
	DEP™ docetaxel Dendrimer-docetaxel	Solid tumors including breast, lung and prostate cancers	Clinical trial	[45, 46]
	Oncaspar® L-asparaginase (L-asparagine amidohydrolase) covalently conjugated to mono-methoxypolyethylene glycol (mPEG)	Acute lymphoblastic leukemia	FDA-approved	[47, 48]
	Opaxio® Polyglutamate polymer-paclitaxel	Lung cancer, ovarian cancer	Clinical trial	[49–51]

tissues or cancer cells. In addition to the all above criteria for a nanotherapeutic agent, theranostic nanoparticles should be able to generate stable and strong imaging signals or contrasts for noninvasive imaging of intratumoral nanoparticle drug delivery and tumor response to the therapy. To achieve this goal, specific and sensitive imaging techniques that are tailored to detect nanoparticle specific imaging signals will also be needed.

Theranostic nanoparticles can be engineered to have unique physicochemical properties that respond to external treatment to activate their antitumor effect. For example, in response to a laser irradiation, gold nanoparticles, carbon nanotubes, and near-infrared dye-conjugated nanoparticles are able to generate heat to kill surrounding tumor cells by photothermal therapy (PTT). Furthermore, photodynamic therapy (PDT) involves in nanoparticles conjugated with photosensitizers that can be activated by specific wavelength of light and then produces reactive oxygen species (ROS) to kill tumor cells.

8.2 Nanomaterials for the Development of Theranostic Nanoparticles

Theranostic nanomaterials are designed to contain both imaging and therapeutic agents. Up to date, various single or multiple imaging modality nanoparticles have been developed for optical, PET, SPECT, MRI, and photoacoustic imaging. In addition to the promising imaging property, theranostic nanoparticles have been produced to carry a single therapeutic agent or the combination of drugs [52], including chemotherapy drugs, small molecules, photosensitizers, and siRNAs. Significant advantages of nanoparticle formulated drug delivery include: (1) increasing in the drug dose by selective delivery of a large amount of drug molecules, especially highly insoluble drug-loaded nanoparticles, into the tumor while reducing systemic side effects [53]; (2) protecting drug molecules or biological therapeutic agents (siRNAs or peptides) from degradation before reaching target tissues and cells [43]; and (3) targeted delivery through cell receptors that bypasses multidrug-resistant mechanisms on tumor cell membrane [54]. For example, Doxil is a pegylated liposomal doxorubicin drug that is currently used in the clinic for cancer therapy. Liposomal formulated doxorubicin significantly reduced the risk for cumulative cardiac toxicity of the drug [55]. Abraxane is an FDA-approved cancer nanotherapeutic that contains 50–150 nm size nanoparticles composited of clusters of human albumin bound with paclitaxel. Paclitaxel is an effective antitumor drug but has a very poor water solubility that requires a special solvent, Cremophor EL (polyoxyethylated castor oil), in the drug formulation, which may induce inflammatory responses. Many patients had to be pretreated with steroid medications before administration of the anticancer drug. However, albumin-bound paclitaxel can be administrated into cancer patients at a higher dose (260 mg/m^2) with reduced systemic toxicity than the conventional paclitaxel with i.v. dose of

175 mg/m^2 [56]. A recent FDA-approved liposomal irinotecan formulation, Onivyde, in combination with conventional fluorouracil and leucovorin, to treat patients with metastatic pancreatic cancer that were resistant to gemcitabine treatment prolonged survival of the patients for 1.9 months [57].

Encouraged by clinical successes of nanodrugs, great efforts have been made toward the development of new and improved nanoparticle drugs or theranostic nanoparticles in preclinical and clinical studies. It is well known that human cancers are highly heterogeneous in their vascular structures and distribution, tumor stromal components, and tumor cells. To improve therapeutic efficacy, it is important to accurately assess the efficiency of intratumoral drug delivery, especially nanoparticle-mediated drug delivery, in individual patients using a noninvasive imaging. Such a precision oncology approach using image-guided drug delivery should allow timely assessment and adjustment of treatment strategies for cancer patients. Therefore, the development of theranostic nanoparticles with the ability of targeted drug delivery and imaging has the potential to contribute significantly to the personalized and effective cancer treatment. In the following sections, current status and results of the development of theranostic nanoparticles using different nanomaterials will be discussed.

8.2.1 Magnetic Nanomaterials

Magnetic nanomaterials refer to a class of nanocomplexes with a metal core, which can be iron, nickel, cobalt, gadolinium, or their oxide or chelated compounds [58]. The magnetism of magnetic nanomaterials makes them applicable as magnetic resonance imaging (MRI) contrast agents. One of the most widely applied magnetic nanomaterials is iron oxide nanoparticles that have been used as MRI contrasts in experimental animals and human patients [59, 60]. At present, magnetic iron oxide nanoparticles are one of the few FDA-approved nanomaterials that have been used in humans for clinical MRI applications (Table 8.1).

MRI has high imaging resolution, 3D-imaging capability, and anatomical information in soft tissues for the detection of intratumoral nanoparticle drug delivery and distribution. Extensive investigations have been done to develop targeted MRI contrast agents based on iron oxide nanoparticles to improve their tumor accumulation and imaging specificity and sensitivity. For example, peptides, antibodies, or antibody fragments that specifically bind to receptors overexpressed in tumor cells, such as MUC-1, αVβ3 integrin, epidermal growth factor receptor (EGFR), HER2/neu, urokinase plasminogen activator receptor (uPAR), and prostate specific membrane antigen (PSMA), were conjugated to the surface of polymer coated iron oxide nanoparticles. Systemic delivery of those MRI nanoparticle imaging probes led to the targeted accumulation and retention of the iron oxide nanoparticles in tumor tissues, enabling MRI T_2 contrast decreases and detection of tumors by MRI [61]. Furthermore, receptor-mediated endocytosis further increases intratumoral cell delivery of the nanoparticles and relative long-term retention of the

nanoparticles in tumors for imaging drug delivery and tumor responses to the therapy [62].

To improve MRI contrasts of the nanoparticles, various iron nanoparticle core sizes and surface modifications have been studied for their MR imaging properties. Although magnetic iron oxide nanoparticles have been generally considered as T_2 contrasts or dark effect MRI agents, the effect of the particle size on MRI contrast property is recognized by several studies. It has been shown that T_2 contrast increases as the size of iron oxide nanoparticles becomes larger [63]. When the nanoparticle core size is smaller (<5 nm), T_1 signal is dominant and gives rise to bright T_1 contrast. The production of strong T_1 MRI contrast from sub 5 nm core size iron oxide nanoparticles has been demonstrated in vitro in solution and in animal tumor models in vivo [6].

A recently study also showed that protein-coated iron oxide nanoparticles, such as milk casein protein, have prominent T_2 enhancing capability following intratumoral cell delivery of the nanoparticle MRI contrast [6]. Singe-chain anti-EGFR antibody-conjugated and milk casein protein-coated iron oxide nanoparticles showed targeted nanoparticle accumulation in a human breast cancer xenograft model in nude mice, producing strong T_2 MRI contrast [6].

To reduce nonspecific macrophage uptake and improve blood circulation time and biodistribution of the iron oxide nanoparticles, an anti-biofouling polymer-PEO-block-poly(γ-methacryloxypropyltrimethoxysilane) (PEO-b-PγMPS) has been developed to coat magnetic iron oxide nanoparticles [64]. Compared with other surface modified strategies for stabilizing the nanoparticles, PEO-b-PγMPS coated nanoparticles have enhanced cell targeting ability. In a recent study, HER2 antibody and ScFvEGFR were covalently conjugated to iron oxide nanoparticles. Both in vitro and in vivo results showed that anti-biofouling polymer coated iron oxide nanoparticles accumulated at a high level in breast tumors with reduced uptake in macrophages in the liver and spleen, suggesting the potential of using this system for improved tumor targeting and nanoparticle drug delivery tumor [65].

Iron oxide nanoparticles are promising drug carriers for the development of clinically applicable theranostic agents since they are biodegradable and have low toxicity. Furthermore, MRI is a commonly used clinical imaging modality, making the translation of MRI-guided drug delivery in cancer patients a feasible approach [12]. For example, to overcome the physical barrier of the stroma in drug delivery, theranostic nanoparticles targeting uPAR that is highly expressed in both pancreatic cancer cells and tumor associated stromal cells have been developed and their antitumor effects have been examined in a human pancreatic cancer xenograft model in nude mice. uPAR targeting ligands, derived from the amino-terminal fragment (ATF) peptides of urokinase plasminogen activator(uPA), were conjugated onto iron oxide nanoparticles (IONPs) carrying a conditional release chemotherapy drug, gemcitabine (Gem) (ATF-IONP-Gem) [66]. Systemic delivery of uPAR-targeted ATF-IONP-Gem resulted in a significant growth inhibition of pancreatic tumors. Nanoparticle drug delivery and changes in MRI contrasts and tumor sizes could be detected by MRI. To detect drug-resistant residual tumors, an

ultrashort TE MRI scan method was developed and produced MR images with bright T_1 contrasts in the resistant tumors containing delivered ATF-IONP-Gem [66]. Resistance to chemotherapy is a major and unmet challenge. Recent studies have demonstrated the ability of overcoming drug-resistant mechanism on the tumor cell membrane by nanoparticle-mediated internalization of nanoparticle drug complexes. It has been shown that hollow iron oxide nanoparticles (HIONPs) modified with human serum albumin (HSA) and incorporated with doxorubicin (DOX) had significantly higher level of intratumoral cell nanoparticle-DOX delivery compared to conventional DOX treatment in a multidrug-resistant human ovarian cancer OVCAR8-ADR cell line [54], which might be caused by decreased efflux of nanoparticle drugs by P-glycoprotein that located on the cellular membrane and transported free drugs out of cells.

Increasing evidence shows that insulin-like growth factor 1 receptor (IGF1R) is highly expressed in drug-resistant tumor cells and tumor stromal cells [67]. Recombinant human IGF1 has been used as a targeting ligand to be conjugated to theranostic IONPs carrying DOX. The effect of the theranostic IONPs was evaluated in an orthotopic human pancreatic cancer patient tissue derived xenograft model that recapitulated heterogeneous tumor cells and enriched tumor stroma in human pancreatic cancer [67]. Results of this study showed that IGF1R targeted IGF1-INOP-DOX theranostic nanoparticles efficiently targeted pancreatic tumors and were detectable by optical and MR imaging. Repeated delivery of IGF1-IONP-DOX led to breaking tumor stromal drug delivery barriers and significant tumor growth inhibition in this human pancreatic cancer tumor xenograft model in nude mice (Fig. 8.2). Histological analysis also revealed the inhibition of cell proliferation and induction of cell apoptosis in pancreatic cancer cells following IFG1-IONP-DOX treatment, suggesting that the IGF-1R-targeted theranostic IONP is a promising drug delivery system for further development of effective approaches for cancer treatment.

A. transmission electron microscopic (TEM) image of DOX capsulated NIR830-IGF1-IONPs. B. Pre- and post-24 h T_2-weighted MR images. Numbers shown are relative mean MRI signal intensities of the entire tumor. Pink arrows indicate the location of orthotopic pancreatic tumors. C. Tumor growth inhibition. The mean tumor weight (navy bar) and individual tumor weight distributions as color symbols after the treatment are shown. D. whole body NIR optical imaging 24 h after IONP administration. Optical images were overlaid with X-ray images of the mice. Red numbers shown are the mean signal intensities of tumor areas. E. Prussian blue staining of frozen tumor sections. Blue: IONP-positive cells. Red: nuclear fast red. Adapted with permission from [67]. Copyright 2015 American Chemical Society.

Unlike chemotherapy, hyperthermia induces cancerous cells undergoing apoptosis under high-temperature conditions. It also sensitizes cancer cells to radiation therapy or chemotherapy. In addition, external magnetic field induces superparamagnetism in magnetic nanoparticles, at the same time, could locally convert magnetic field energy to thermal energy, which is called magnetic hyperthermia [68–70]. For example, magnetic hyperthermia mediated by iron oxide nanoparticles

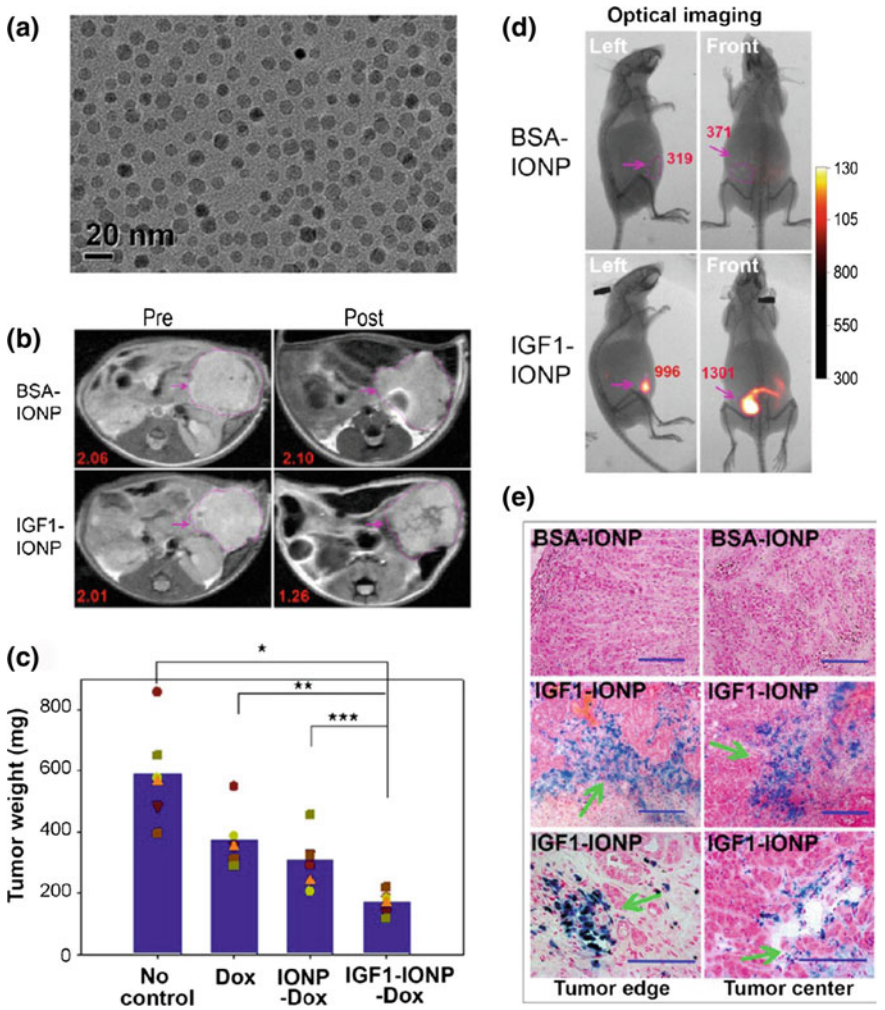

Fig. 8.2 Evaluation of the effect of IGF-1R targeted IONP carrying DOX for targeted and image-guided tumor therapy in a human pancreatic cancer patient tissue derived xenograft model. Reprinted with permission from [67]. Copyright © 2015, American Chemical Society

could increase temperature in the tumor center to >40 °C after exposed to alternating magnetic field [71], resulting in tumor growth inhibition in a human head and neck tumor xenograft model. Iron oxide nanoparticle-facilitated magnetic hyperthermia has been translated in human patients in clinical trails [72]. After receiving iron oxide nanoparticle-induced hyperthermia and low dosage radiotherapy, a significant increase in survival of the patients with recurrent glioblastoma was observed in the combination treatment group comparing to the control groups. No serious complications were found in the clinical trials, suggesting that the

combination of thermo- and radiotherapy is a safe and effective approach. As aforementioned, iron oxide nanoparticles mediated magnetic hyperthermia triggered by the external magnetic field not only ablated cancer cells, but also increased the effectiveness of other treatments. In comparison with laser-triggered photothermal therapy, magnetic hyperthermia therapy is more promising in translation due to the unlimited tissue penetration ability and the reduced skin damage. Although there may be some magnetic-thermal conversion efficient concern, it can be solved by the combined therapy, such as radiotherapy/magnetic hyperthermia or chemotherapy/magnetic hyperthermia.

Considering the potential and growing applications of MNPs, it is required to evaluate and clarify the toxicity of Magnetic nanoparticles. Typically, IONPs are internalized and degraded by Kupffer cells in liver and macrophages of spleen [73]. Once degraded, free iron will be released from IONP and participate in Fenton reaction to generate hydroxyl radicals. In addition, free irons will be stored in the form of protein complex, for example ferritin, for further applications. Unfortunately, the over amount of these iron–protein complex will induce an expression of ROS which is a major reason behind cell death [74]. A well design of shape, size, and surface charge of IONP will be a way of optimizing IONP in vivo behavior and reducing the potential systemic toxicity.

8.2.2 Gold Nanoparticles

Gold nanoparticles (GNPs), including gold nanorods, nanoshells, nanospheres, and nanocages, have been intensively studied for many years due to their unique surface plasmon resonance (SPR) effect, strong NIR light absorption, and the potential to integrate different entities at the same time for cancer diagnosis, and treatment.

GNPs with strong absorption and scattering intensity at a selected light wavelength [75] allow them as contrast agents for computed tomography (CT) imaging, optical imaging, photoacoustic imaging and surface-enhanced Raman spectroscopy imaging [76, 77] A folic acid (FA) targeting dendrimer stabilized gold nanoparticle (Au DSNPs) has shown the ability as a CT imaging contrast in a head and neck cancer xenograft model [78]. A notably higher CT value was observed in Au DSNPs treated tumor than that of a conventional CT contrast agent, Omnipaque. However, due to the fact that a large amount of the contrast agent is needed to produce a satisfying CT imaging, GNPs may not be the perfect choice clinically, considering the cost and safety. Alternatively, photoacoustic or Raman imaging has a higher sensitivity than CT imaging and can be used when GNPs will be used as the contrasts for imaging applications [79].

Besides the imaging ability, GNPs have been investigated as delivery scaffolds for tumor therapeutic agents. GNPs are feasible to encapsulate drug molecules to improve their solubility. Moreover, attachment of targeting ligands further improves the selective accumulation of therapeutic drugs into target sites. At present, GNPs carrying various therapeutic agents, including DOX, camptothecin,

irinotecan, topotecan, and paclitaxel [80–82], have been developed by many research groups and their antitumor effects have been reported in various mouse tumor models [83]. For example, You et al constructed a doxorubicin loaded hollow GNPs for tumor treatment. Significantly greater killing of the MDA-MB-231 breast cancer cells was observed after NIR laser triggered DOX release [84], suggesting that GNPs are promising carriers for chemotherapy drugs.

One of the theranostic functions of GNPs could be achieved by application of external activation laser sources. Photothermal therapy (PTT) induces tumor cell death in the tumor cells or tumor areas containing GNPs by converting photon energy into heat [76]. In the view of strong absorptions at different wavelength, GNPs were identified as superior PTT agents [85]. A study showed that intravenously injected 15 nm core GNPs conjugated with EGFR antibody induced effective tumor ablation but had minimal normal tissue damage in human squamous cell carcinoma A431 tumor xenografts in nude mice [86]. Besides antibodies, peptide and small molecules were both reported labeled on GNPs as recognition ligands for tumor targeting and PTT [87–89]. In addition to PTT, photodynamic therapy (PDT) is another emerging new cancer treatment approach that kills cancer cells through laser irradiation [90]. By modifications with photosensitizers, the efficiency of various GNPs in PTT or PDT has been investigated, including nanoshells [91], nanorods [92], nanocages [93], nanospheres [94], and nanostars [87]. Nearly all types of GNPs showed strong PDT or PTT effects. However, most gold nanomaterial based PTT/PDT therapeutic complexes required two wavelength laser for irradiation due to the absorbance differences between photosensitizer and gold nanoparticles. Recently, a monolayer of modified GNPs has been used to compose gold nanovesicles, which have capability to encapsulate photosensitizer, chlorin e6 (Ce6), in the interior hollow [79]. The gold vesicles hold a strong absorption at 671 nm, which is close to the absorbance of Ce6 for PDT. In this study, 671 nm laser radiation was used to excite gold vesicles for PTT and chlorin e6 for PDT, which solved the challenge of two different wavelengths laser for simultaneous PDT and PTT. Significantly improved tumor ablation efficacy of the multifunctional GNPs system was achieved under the fluorescence and photoacoustic imaging guidance (Fig. 8.3).

As described above, GNPs are excellent platforms for multimodal tumor imaging and various therapeutic approaches. Compared with the other nanomaterials, the inherent PTT ability and the controlled morphology suggested that GNPs are promising phototherapy agents. By clarification of the relationships between GNP shape and PTT effects, it is hopefully to apply this newly developed strategy for the treatment of human tumors located at relatively to the body surface, such as melanoma, head and neck cancer, breast cancer, and prostate cancer. With the development of endoscopic imaging devices, it is also feasible to treat tumors on the mucosal surface of the colon, esophagus, stomach, and bladder.

Although multifunctional GNPs have many potential applications for cancer imaging and therapy, a major challenge in the development of GNPs for human use is the concern of their biodegradability, long-term toxicity, and high cost [95]. Extensive investigations of these nanoparticle systems should be required to fully

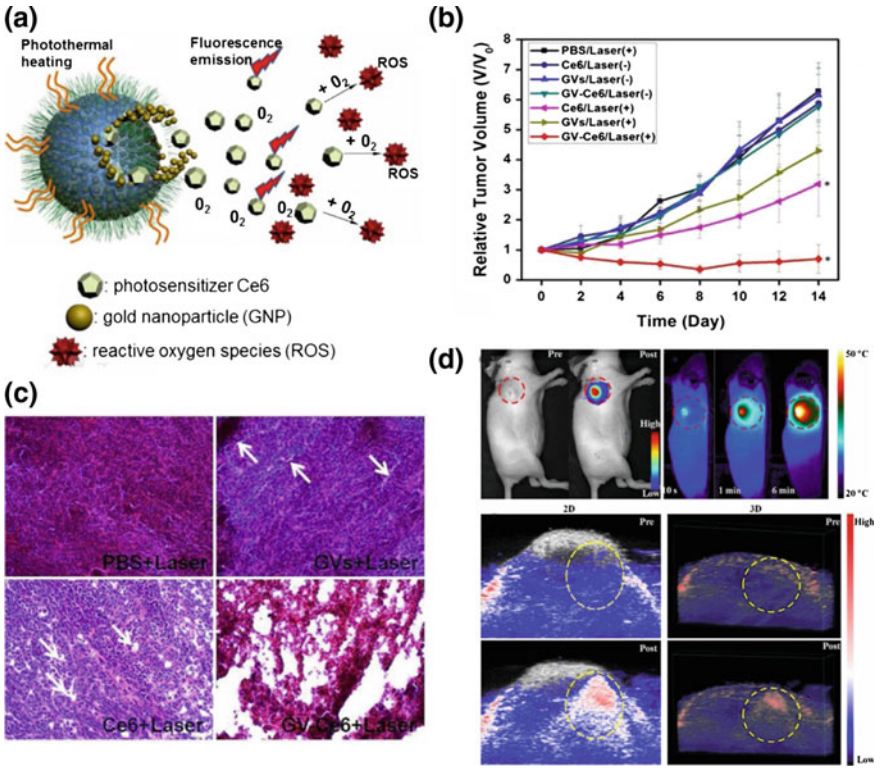

Fig. 8.3 Designed gold nanocomplex for tumor theranostic applications. **a** Schematic illustration of photosensitizer (Ce6)-loaded plasmonic gold vesicles. **b** Tumor growth curves of different groups in tumor-bearing mice after treatment. **c** H&E staining of tumors from different groups of mice 14 days post treatment. **d** NIR fluorescence images, thermal images and photoacoustic images of MDA-MB-435 tumor-bearing mice. Adapted with permission from [79]. Copyright © 2015 American Chemical Society

understand their pharmacokinetics, interactions with the immune system and other normal cells, the extent of cytotoxicity due to surface and size of the AuNPs, in vivo biodistribution and mechanisms of clearance. Appropriate surface tailoring and geometric manipulation may have an important role in improving the stabilities, biocompatibilities, and targeting ability with reduced toxicities of GNPs [96–99]. For example, it has been shown that GNPs smaller than 5 nm were able to be cleared out from the kidney. Novel GNPs that could disassemble themselves following in vivo delivery under specific conditions to allow in vivo clearance [100].

Additionally, most imaging devices for GNPs are still under preclinical development. For translation of gold-based theranostic nanoparticles for image-guided drug delivery, it is also important for translational development of imaging equipments that are tailored for the detection of imaging signals of GNPs.

8.2.3 Silica Nanoparticles

Silica nanoparticles (SNPs) have attracted great attentions due to the versatile exterior, interior surface chemistry, and highly tunable structures such as size and pore volume [101]. They are highly soluble in aqueous solutions due to a high concentration of silanol groups on their surface [102]. Generally, SNPs can be classified as mesoporous SNPs (MSNPs) and nonporous/solid SNPs [103–106].

A concern for the application of clinical MRI contrast agents like Gd-based compounds is the potential toxicity of the released Gd following in vivo delivery. Various attempts of developing new Gd- or Mn-based T_1 MRI contrast agents have been made to alleviate side effects and toxicities, but only few progresses were achieved. To address this issue, synthesized silica-coated iron oxide nanoparticles that exhibited excellent biocompatibility both in vitro and in vivo were used. Result of this study showed that the hybrid nanoparticles have high T_1-weighted MRI contrasts and could be promising imaging contrast agents for MRI [107]. More interestingly, a trimodality imaging agent, an iodinated oil-loaded fluorescent mesoporous silica-coated iron oxide nanoparticle, was prepared to integrate fluorescence, CT and MRI imaging approaches into a single nanoparticle platform. The trimodal imaging nanoparticle showed intensified fluorescence and enhanced CT and MRI contrasts [108].

Besides improving the in vivo behavior of imaging agents, SNPs are also applied as drug carriers for tumor ablations. To improve the ability of tumor targeting and reduce undesired accumulation, peptides or antibodies are usually used for modification of SNPs, which yield selective tumor targeting SNPs [109]. For example, a CD105 antibody modified SNP was recently reported by Cai group for successful PET/fluorescent imaging of a mouse breast tumor in the 4T1 mouse mammary tumor model [110].

MSNPs have the capability of loading large amounts of drug molecules and even different types of drugs. For example, camptothecin (CPT) was encapsulated into the inner pore and arsenic trioxide was coated onto the external surface of MSNPs [111]. MSNPs carry dual drugs significantly enhanced the inhibitory effect on tumor cell growth, and lowered the concentration of drugs that were required for the same treatment efficacy. Another approach of improving the treatment efficacy is to initiate treatment at desired locations, such as releasing drugs by certain stimuli when drugs accumulate mostly in tumors. MSNPs have the capabilities of loading targeting molecules on the external surfaces to enhance tumor selectivity, and placing diverse moieties on the outlets of pores to serve as gatekeeper to empower controllable drug release [112]. PEG modified MSNPs functionalized with folate acid and amino-β-cyclodextrin (β-CD) have been shown to be able to block DOX in the pores of SNPs (Fig. 8.4) [113]. This folate receptor-targeted SNP remarkably improved specific uptake of the nanoparticle by tumor cells, and showed stronger therapeutic efficacy in vivo compared with free drug or nontargeted groups. Acidic conditions or the presence of glutathione induced the chemical or physical change of β-CD that triggered the release of chemotherapeutic drugs, which considerably

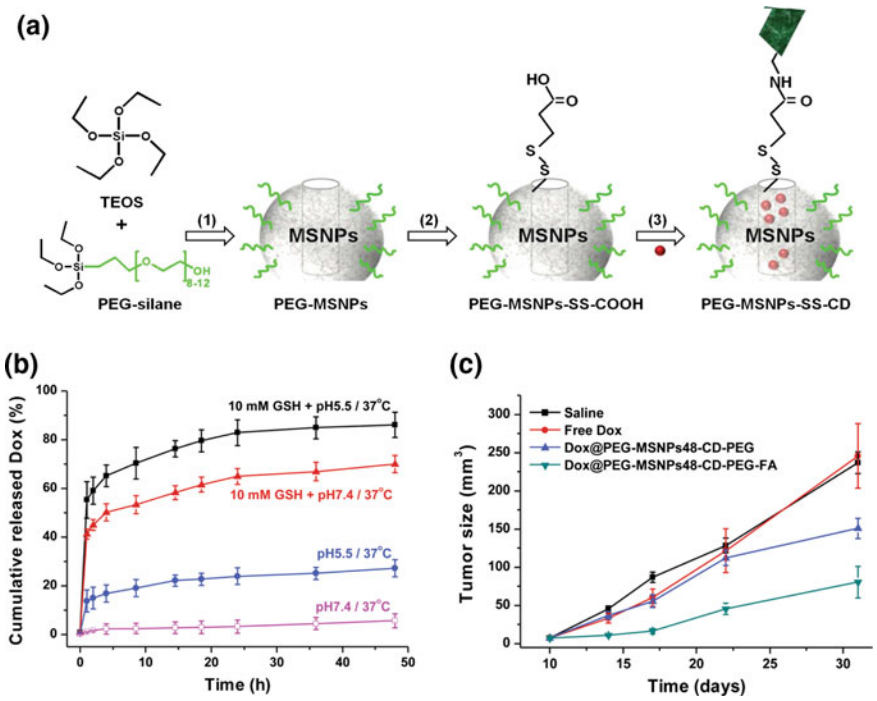

Fig. 8.4 Design of enzyme responsive SNP complex for tumor therapeutic. **a** The preparation of Cargo-encapsulated SNPs. **b** Drug release profile of SNP/drug complex under different conditions. **c** Tumor therapeutic effects of pH-sensitive SNPs. Adapted with permission from [113]. Copyright © 2015 John Wiley & Sons, Ltd.

improved the efficiency of drug delivery and ultimately enhanced tumor-inhibiting effect with reduced side effects.

In addition to chemotherapy, SNPs are also available for other promising therapeutic modalities such as gene therapy, PTT and PDT. MSNPs functionalized with cyclodextrin-grafted polyethylenimine (CP) have been shown to deliver siRNA targeting the M2 isoform of the glycolytic enzyme pyruvate kinase into tumors, resulting in inhibition of tumor cell growth, invasion, and migration, accompanying with effective knockdown of gene expression both in vitro and in vivo [114]. MSNPs coated with a photosensitizer, tetra-substituted carboxyl aluminum phthalocyanine, for PDT and small Pd nanosheets for PTT were developed for tumor phototherapy [111]. In vitro and in vivo studies indicated that simultaneous PDT and PTT had stronger effect on inhibition of tumor cell growth than either PDT or PTT alone. Therefore, results of those studies showed that SNPs are excellent nanoparticle platforms to integrate different types of therapeutic agents due to their tunable size and porosity. Some studies have demonstrated co-delivery of different moieties that can even overcome multidrug resistance, such as SNPs

functionalized with paclitaxel and tetrandrine [115] and SNPs coated with anti-CD44 antibody and chemotherapy drug, DOX [116].

Overall, SNPs are a class of nanomaterials with controllable size and morphology. Their biocompatibility and biodegradability make SNPs as widely applied nanomaterials in bioimaging and therapeutic fields in preclinical studies. With the capacities of receptor-mediated active targeting and controllable drugs release, SNP or SNP-hybrid nanoparticles demonstrated significantly enhanced tumor accumulation. However, safety of SNPs for human use as therapeutics is still a concern. Further preclinical studies on the toxicity, immunogenicity, pharmacokinetics, biodistribution, and clearance of SNPs should shade the light on the translational potential for future clinical theranostic applications.

8.2.4 Carbon Nanomaterials

The first report on fullerenes in 1985 opens the era of carbon nanomaterials, which mainly consist of sp^2 bonded graphitic carbon. Different from the above-mentioned nanomaterials, carbon nanomaterials exist in different low dimensionalities such as zero-dimensional fullerenes, one-dimensional carbon nanotubes (CNT), and two-dimensional graphemes. The nanoscale size (1 nm to 1 μm), extremely large surface area (2600 m^2/g) and unique optical properties make those promising nanomaterials for the development of nanoparticle-based biosensor, and imaging and therapy agents. Besides, some graphitic carbon nanomaterials, like graphene and CNT, hold strong optical absorptions ranging from 650 to 1000 nm, which allowed them to be utilized for photoacoustic imaging and in situ photothermal therapy. Interestingly, the characterized long fluorescent emission of single wall carbon nanotube (SWCNT) at so-called second near-infrared (NIR-II) window (1000–1700 nm) provided a new approach of optical imaging for the detection of tumors in deep tissues. Carbon nanomaterials were also used as tissue scaffolds and Raman scatter enhancers reviewed elsewhere [13, 117]. However, one of the key factors that affect the applications of carbon nanomaterials as nanoparticle drug carriers is their physiological compatibility, because unmodified carbon nanomaterials with a hydrophobic surface are very easily aggregated driven by the π–π interactions and van der Waals forces among themselves [118]. To make these carbon nanomaterials soluble in aqueous conditions, almost all carbon nanomaterials have to be surface modified with biocompatible moieties. Currently, covalently and non-covalently decorations of nanomaterials are two major categories of treating carbon materials, which simultaneously improve their biocompatibility and endow them specific biological functionalities. In this part, we covered the latest progresses of applications of carbon nanomaterials in diseases diagnosis and therapy by focusing on single-wall carbon nanotubes (SWCNTs).

SWCNT, composed of a single graphene sheet that is rolled into a tubular structure, is one of the more striking discoveries in the carbon nanomaterials. Typically, functional materials consisting of a hydrophilic head and hydrophobic

tail are broadly used for CNTs modifications. Through the designed modifications such as surfactants, polymers, gens, peptides/proteins, and other hydrophilic reagents, CNTs are reported advantageous for the development of new nanotechnologies for cancer detection and therapy. For example, PET imaging modality has high sensitivity and wide clinic applications for cancer diagnosis. A PEGylated SWCNT that chemically conjugated with ^{64}Cu-1,4,7,10-tetraazacyclododecane-N, N′, N″, N‴-tetraacetic acid (DOTA) and tumor-targeted arginine-glycine-aspartic acid (RGD) ligand was used for in vivo *detection of* glioblastoma (U87MG) by PET imaging [119]. SWCNT-PEG-RGD showed good tumor targeting with about 13% of injected dose per gram tumor (% ID/g) observed in the tumor. Due to a strong absorbance of CNTs, SWCNTs were also developed as photoacoustic imaging agents. Photoacoustic imaging is a sensitive imaging method that converts light into ultrasound by photoacoustic effect for the detection of tumors in deep tissues with fine spatial resolution. A highly sensitive photoacoustic imaging agent was developed by incorporation of indocyanine green (ICG) dye onto the surface of SWCNT/PL-PEG-RGD complex covalently [120]. After intravenous injection of ICG-SWCNT/PL-PEG-RGD, brain tumors in a human tumor xenograft model (U87MG) in nude mice were detected by photoacoustic imaging. Addition of ICG dye increased tumor specific photoacoustic signals by threefolds compared with the signal in the tumor of the mice that received SWCNT/PL-PEG-RGD without the ICG dye.

Although PL-PEG demonstrated satisfied dispersion of SWCNTs, the preparation procedures always require a long sonication time, which is proven significantly damaging to SWCNTs that causes low quantum yield and lowers imaging sensitivity [121]. A unique 'exchange' method was developed with less harm to SWCNTs and an order of magnitude higher quantum yield than direct sonication SWCNT modification [122]. In this aspect, an intrinsic near-infrared photoluminescence SWCNT has been developed for imaging of tumor vessels using whole body imaging [122]. Almost no autofluorescence background was observed, while a strong fluorescent signal was observed in the tumor, suggesting the great potential of using SWCNTs as biological fluorescent imaging agents. More recently, the NIR-II imaging has been successfully applied in hind limb imaging [123, 124], brain imaging, and endocarditis [125] in live animals. In addition, by changing the surface modification agents, SWCNTs are reported suitable for many imaging techniques not only as aforementioned but also for magnetic resonance imaging, ultrasound imaging, single-photon emission computed tomography (SPECT), Raman imaging and multimodalities imaging. All of these studies demonstrated that SWCNTs have the potential for further development of nanoparticle imaging and therapy agents for image-guided cancer therapy.

Because of their large surface area (2600 m^2/g) and unique shape, CNTs have the capacity to load drug molecules via different strategies. Small drug molecules such as paclitaxel, camptothecin, cisplatin, gemcitabine, methotrexate, and DOX [126] are loaded onto SWCNT by either chemically conjugated onto the well-dispersed SWCNTs or non-covalently attached onto the surface of SWCNT through π–π stack between aromatic drug molecules and SWCNT [127–129].

Targeted SWCNT/drug complex can recognize cancer biomarkers and enter into cells, subsequently triggering mechanisms for drug release or interacting with an external laser light to ablate cancer cells [118]. In addition, SWCNT has also been reported as a gene delivery vehicle to deliver DNA, small interfering RNA and micro-RNA to generate a therapeutic response in cancer cells. In comparison with other gene delivery systems, SWCNTs have a higher efficiency in penetrating cell membranes and therefore delivering genes into cells more effectively due to their unique shape and surface properties. For example, SWCNTs carrying siRNAs showed a good effect in the treatment of melanoma in a mouse tumor model by silence of Braf expression, an important signal molecule in the MAPK pathway for regulating cell growth and proliferation [130]. Polyethyleimine (PEI) functionalized SWCNTs that protected siRNA stability in vitro and in vivo demonstrated antitumor effect after SWCNT/siRNA complex treatment [130]. SWCNT has been an attractive nanoparticle system for PTT mediated cancer therapy. Success of NIR-II/MRI-guided PTT has been shown in tumor growth inhibition of primary tumor and cancer cells in lymph nodes. After administration of well-dispersed SWCNTs, primary tumor and metastasis tumor were identified by fluorescent imaging and MRI. PTT was then carried out and eliminated the primary tumor as well as cancer cells in lymph node [131]. The survival rates in treated mouse groups were significantly prolonged compared to the mice received control treatments [131]. By combination with chemotherapy, gene therapy or photodynamic therapy (PDT), SWCNTs have been designed as an effective agent for the generation of the synergistic antitumor effect. Albumin-bound paclitaxel was loaded to Evans blue molecule dispersed SWCNT mediated by the interaction of Evans blue molecule with albumin [118] (Fig. 8.5). The final complex, SWCNT/EB/Albumin/PTX, has dual functions of chemotherapy and photothermal therapy. A stronger tumor growth inhibition was demonstrated in the MDA-MB-435 breast tumor-bearing mice that received the combination treatment compared to chemotherapy or PTT alone. Additionally, photodynamic therapy is another noninvasive phototherapy approach that has been used in clinic. The multifunctional and PTT and PDT multimodal therapeutic approaches have been developed to enhance the treatment response in tumors. Various photosensitizers were chosen for functionalization of SWCNTs. For example, Ru(II) modified SWCNT was constructed for PTT and PDT combined therapy [118]. A greater cervical cancer tumor ablation effect was observed compared with PDT or PTT alone, highlighting the potential of using SWCNT carrying photosensitizers for the combination therapy. In summary, because of their large surface areas and specific surface properties, SWCNT is one of the promising nanoparticle systems for the development of theranostic agents. Through surface engineering, SWCNTs can be easily modified with diagnosis and therapy agents. So far, radioisotopes, dyes, magnetic nanoparticles, chemotherapy drugs, DNAs or RNAs, and photosensitizes all have been used to develop theranostic SWCNTs. Although promising results on theranostic applications have been achieved so far in experimental animal tumor models, future clinical applications of SWCNTs will still be challenging due to the concerns of biodegradability and the in vivo safety [132]. Currently, the mechanisms of clearance and long-term

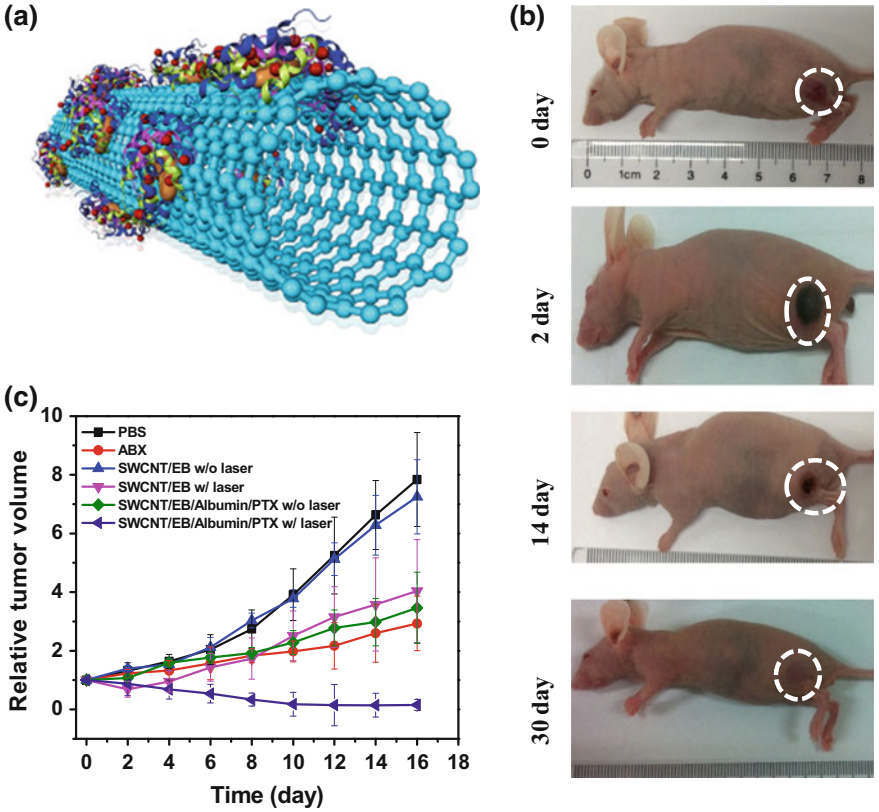

Fig. 8.5 A novel single-walled carbon nanotube (SWCNT) functionalization agent facilitated in vivo combined therapy. **a** The design of chemotherapy/PTT combined SWCNT. Paclitaxel (PTX) was encapsulated into albumin and bound with Evens Blue (EB) dispersed SWCNT. **b**, **c**. Antitumor effect of Evans blue functionalized SWCNT. Adapted with permission from [118] with permission from the Royal Society of Chemistry

systemic toxicity are largely unknown. Further preclinical studies will provide information on the feasibility of SWCNTs for human use as theranostic anti-cancer agents.

8.2.5 Polymeric Materials

Polymeric nanoparticles are the most commonly used nanoparticle drug carriers [133]. It has similar structures to lipid vesicles but different properties. Initially, polymeric materials are designed for drug delivery due to their biocompatibility, biodegradability, stability, and low toxicity. The polymeric drug formulation

significantly improved the drug solubility and stability with increased drug loading efficiency [134]. Polymeric materials have also been developed to carry imaging agents by encapsulation of different fluorescent dyes, magnetic nanoparticles, and radioisotopes. Recently, polymer nanoparticles have been produced as theranostic systems for further development of image-guided cancer therapy, targeted drug delivery as well as monitoring the therapeutic responses.

Polymeric nanomaterials can be structurally defined as solid nanoparticles, micelles, and dendrimers with diameters that are usually smaller than 300 nm [133]. Typically, polymeric nanoparticles are synthesized by assembling amphiphilic block copolymers, forming spheroidal architectures. A polymeric nanoparticle contains a hydrophilic shell and a hydrophobic inner core, where hydrophobic drugs can be encapsulated during the self-assembly process [134–136]. Interestingly, by adjusting the hydrophobic/hydrophilic ratio, chemical property or linkage of each polymer bock, it is now possible to generate specific stimuli-responsive polymeric nanoparticles, such as pH, enzyme, light, and temperature [135–137]. Under certain circumstances, designed polymeric nanoparticles will be active for imaging or releasing drugs, achieving a controlled theranostic function. In addition, polymeric nanoparticles can be easily functionalized with targeting moieties to improve specificity and delivery efficiency, because of their large surface and abundant surface functional groups. So far, a handful of successful polymeric nanoparticles on drug delivery and theranostic applications have been reported in the literatures. In this section, we will overview these state-of-the-art polymeric nanoparticles from tradition drug carriers to multifunctional polymer assemblies.

In the 1980s, a serial of polymeric drug delivery systems was reported by Speiser et al. Antitumor drugs were absorbed or loaded to polyalkylcyanoacrylate nanoparticles. Drug release mechanisms, distribution, and toxicity were also uncovered in vivo [138–140]. Since those reports brought attentions to polymeric nanoparticles, increasing efforts have been given to their biomedical applications. Although polymeric nanoparticles as delivery candidates for drugs, functional genes, and proteins were achieved, in most cases, clinical translation of polymeric nanoparticles was limited by a low drug loading efficiency (<5%) due to the fast drug aggregation kinetics in the hydrophilic core of polymeric nanoparicles [141]. Recently, a simply method for preparation of polymeric nanoparticles with over 50% drug loading was developed [141]. In this newly developed nanoparticle production protocol, two camptothecin (CPT) was covalently modified and formed a CPT dimer via carbonate linkage, which could be triggered by a reducing agent. The fast drug aggregation kinetics was then inhibited, resulting in small drug aggregates that could be used as cores for improving drug loading after interacting with amphiphilic polymers [141]. Polymeric nanoparticles are also widely used to improve drugs' solubility and reduce their side effects. For example, paclitaxel was encapsulated into poly (lactic-co-glycolic acid) (PLGA) nanoparticles. A small size (<200 nm) polymeric nanoparticle formation with homogeneous negatively charged anticancer drugs was produced and demonstrated stronger antitumor effect compared to conventional paclitaxel therapy [142–144]. Furthermore, hyaluronic

acid (HA) nanoparticle was developed with the capability of encapsulation of more than 30% (w/w) camptothecin [53]. Similarly, DOX could also be loaded into HA nanoparticles with a high loading efficiency [145, 146]. Resulting polymeric nanodrug showed nice aqueous solubility, physiological stability, and the ability of targeting cancer cells. Excellent antitumor efficiency was observed in vitro and in vivo [53]. It is well known that HA binds to CD44 that is a cellular receptor highly expressed in aggressive tumor cell populations with cancer-stem cell-like properties. Therefore, HA-based nanoparticles are also CD44 targeted drug delivery carriers that are able to target delivery of therapeutic agents into aggressive and invasive tumor cells [34, 135].

To effectively treat highly heterogeneous human tumors, efforts have been focused on the combination therapeutic approaches to overcome drug resistance. For example, cyclopamine (CPA) was loaded into polymeric micelle particles (M-CPA) to enhance radiation sensitivity of pancreatic cancer [147]. Combined M-CPA and Caesium-137 treatment showed enhanced toxicity to pancreatic cells. Another example is that DNA topoisomerase I inhibitor treated cancer cells become more sensitive to DNA topoisomerase II inhibitors [148]. Synergistic antitumor effect by combining therapeutic agents targeting different key pathways in tumor cells has, therefore, attracted great attentions. Although the combination of chemotherapy drugs is routinely used in cancer patients, the production of a synergistic antitumor effect has been limited by different pharmacokinetic, distribution, and clearance of different drugs following administrations. The advantage of co-delivery of multiple therapeutic agents using a single nanoparticle should ensure the therapeutic effect of different drugs occurring in the same tumor cells at the same time. A recently report demonstrated promising combined tumor therapy effects [148]. DNA topoisomerase I (CPT) and II (DOX) inhibitors were conjugated onto hyaluronic acid at an optimized ratio and then allowed assembling into HA-drug nanoparticles. A very low dose of the polymer drug complex (in equivalent to 2 mg/kg of CPT and 1.05 mg/kg of DOX) was able to inhibit tumor growth significantly with negligible side effects to normal organs, suggesting a great translational potential of HA polymeric nanoparticles. Besides the promising drug loading and delivery capacities, polymeric nanoparticles are ideal carriers for imaging contrast agents such as radioisotopes, fluorescent dyes, and magnetic reagents [14, 149]. The above-described HA nanoparticle drug carriers can also be converted into theranostic nanoparticles by conjugation with NIR dyes, radioisotopes, or encapsulation with ultrafine magnetic oxide nanoparticles [150].

A cyclodextrin polymer based nanoparticle, IT-101 (or CRLX101), modified with DOTA for ^{64}Cu coupling was conjugated with camptothecin, resulting in theranostic nanoparticles around 40 nm in diameter. It has a good water solubility and long circulation time (t1/2:13.3 h) in vivo. PET imaging in a Neuro2A tumor-bearing mouse model [151] revealed that the nanoparticle drug delivery by the passive targeting led to the accumulation of 11% injected dose per cm^3 in tumors at 24 h post injection, confirming the possibility of using polymeric nanoparticles for image-guided drug delivery assessment. Fluorescent dye labeled polymeric nanoparticles was developed as theranostic agents with optical imaging

ability [152–155]. By modification of designed fluorescent dyes, polymeric nanoparticles with tunable fluorescent emission wavelength can be prepared, facilitating optical imaging, or real-time imaging. Additionally, a fluorescent polymer, pDA-PEG, was prepared by conjugation of synthesized copolymer that is fluorescent at second near-infrared window with phospholipids–polyethylene glyco [156]. An ultrafast NIR-II window imaging of mouse hind limb was obtained immediately after intravenous injection of pDA-PEG, allowing visualization of blood flow moving inside the femoral artery. Because each imaging modality has different advantages and limitations, a multimodality polymeric imaging agent that is able to offer complementary information in a single matrix has become a new trend. Currently, polymeric multimodality imaging agents are also reported by several research groups, including SPECT/MRI, PET/CT, PET/fluorescent, fluorescent/MRI [157], and photoacoustic/fluorescent imaging [158] for potential clinical applications. Furthermore, γ-ray emitters, ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{64}Cu, and ^{111}In, all can be used for labeling of polymeric nanoparticles for imaging nanoparticle drug accumulation in tumors. In this aspect, ^{111}In labeled PPEGMA-b-PESPMA block copolymer has been shown to detect MDA-MB-468 breast cancer xenograft in nude mice by PET/optical imaging [159]. Long circulation and passive tumor accumulation behavior was observed following in vivo administration of those nanoparticles. A major concern for the application of radioactive agent as theranostic agents is that high therapeutic dose and repeated administrations of the theranostic nanoparticles will be required for effective cancer therapy in cancer patients. The use of radioactive therapeutics as imaging agents may cause systemic side effects and damages. It is unlikely that radioisotopes with short half lives (<4–6 h) can be effective imaging agents for monitoring drug delivery since it will take over 24 h to reach the maximal intratumoral accumulation of the nanoparticle drugs. However, such a long half-life radioactive agent limits the clinical use in cancer patients.

Another well-studied example is using bacteriochlorophyll-lipid as building blocks for optical imaging and metal chelating. By using filling in perfluorocarbon gas, a polymeric nanoparticle, named porphyrin microbubbles (pMB), with high photoacoustic and fluorescent imaging capabilities, was developed. The gas-encapsulated nanoparticle was able to be used as an ultrasound imaging agent. After ultrasound simulation, pMB was converted into porphyrin nanoparticles (pNP) with a good stability. A high level of intratumoral accumulation of pNPs after applying ultrasound was visualized by both photoacoustic and NIR imaging, suggesting the potential of using pMB for efficient drug delivery.

Encouraged by the excellent tumor targeting ability, imaging agents, as well as therapeutic drugs, were engineered into polymeric nanoparticles for simultaneous tumor imaging and therapeutic applications. A copper sulfide (CuS) encapsulated Cy5.5-conjugated hyaluronic acid nanoparticle (HANP) was developed for fluorescent/photoacoustic imaging guided tumor photothermal therapy [135] (Fig. 8.6). In this system, HANPs were delivered into tumors via the EPR effect as well as active CD44 targeting, which allowed HANPs to be delivered and bound to tumor cells more efficiently. Moreover, CuS with strong optical absorbance is an

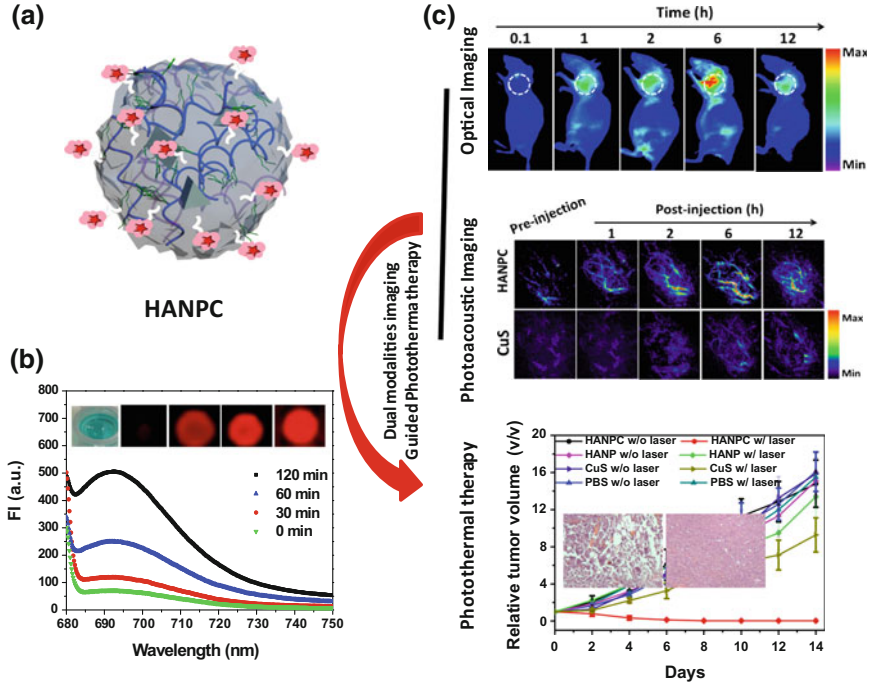

Fig. 8.6 Development of an activatable polymeric nanoparticle for image-guided tumor PTT. **a** Design of activatable hyaluronic acid nanoparticles (HANP) for photoacoustic/fluorescent image-guided PTT. **b** Fluorescent recovery of CuS encapsulated HANP utilizing high enzymatic activities in tumor. **c** Image-guided effective tumor ablation effects. Adapted with permission from Ref. [135]. Copyright © 2015 American Chemical Society

excellent photoacoustic agent. Effective quench of Cy5.5 fluorescent signals could be recovered after degradation of HANPs by hyaluronidase, resulting in NIR fluorescence signals for optical imaging of drug delivery. In the view of that CuS was able to convert proper light energy into heat, HA-based nanopolymer HANPC, and was capable of simultaneous imaging of tumor and ablation of tumor cells effectively. Aside from nice physiological stability and cancer cells targeting ability, HANPC demonstrated significant tumor ablation property by photothermal therapy with the guidance of optical and photoacoustic imaging. Therefore, results of this study support the possibility of using the polymeric nanoplatform for theranostic applications.

Polymeric micelles have also been used as MRI-guided cancer chemotherapeutic agents. Self-assembled pH-sensitive polymeric nanoparticle, TPTN, was produced using poly (lactic acid)-poly (ethylene glycol)-poly (L-lysine)-diethylenetriamine pentaacetic acid (PLA-PEG-PLL-DTPA) and pH-sensitive material, poly (L-histidine)-poly (ethylene glycol)-biotin (PLHPEG-biotin) [113]. After sorafenib and Gd loading, intratumoral TPTN delivery was evaluated by MRI to demonstrate

drug delivery into tumors. Breaking TPTN in tumor cells under low pH conditions led to drug release and resulted in tumor growth inhibition [113]. Recently, NIR fluorescent image-guided phototherapy was reported based on poly (ethylene glycol)-block-poly (ε-caprolactone) (PEG−PCL) [160]. Silicon naphthalocyanine (SiNc) was used to construct a polymeric nanoparticle that provided NIR fluorescent signals and phototherapeutic capabilities. The final product, SiNc-PNP, demonstrated good reactive oxygen generating ability and efficient photothermal property. After intravenous injection, tumor accumulation was observed 24 h post injection by optical imaging with a low body background. Phototherapy, composed of photothermal and photodynamic therapy, was conducted. Tumors were found effectively ablated without obvious toxicity to normal organs, suggesting that the reported polymeric nanoparticle is promising for precise treatment of tumor under fluorescent imaging guidance.

Overall, polymeric nanoparticles are excellent nanoparticle systems for the development of targeted theranostic agents, especially for those hydrophobic drug payloads. Fortunately, with the development of material chemistry, it is now possible to combine imaging and therapeutic capabilities in a single nanoparticle, allowing visualization of disease area by noninvasive imaging for evaluation of the delivery efficiencies and monitoring treatment responses. Due to their excellent biocompatibility, biodegradability, biostability, and easy surface chemistry, the polymeric nanoparticle is one of the most promising drug carriers for clinical translation. Nevertheless, several criteria have to be satisfied for an ideal polymeric nanoparticle drug carrier. For example, a polymeric imaging agent has to reach to the target fast enough with low imaging background. It has to be washed out body effectively without affecting next imaging. A long circulation time is necessary for drug delivery by polymeric nanoparticles for better tumor accumulation, which can be done through targeting ligand modification or the EPR effect. Collectively, novel polymeric designs with good tumor targeting ability, low immunogenicity, and controlled drug release are the future directions of the development of clinically translatable polymeric theranostic nanoparticles.

8.3 Prospects and Challenges

In this review, research advancements on the development of several nanoparticle systems for cancer theranostic applications were discussed. The ultimate goal of developing theranostic nanoplatform is to apply them to personalize cancer treatment through targeted and image-guided drug delivery, and assessment of tumor responses to the therapy by noninvasive imaging. We have discussed methods of surface modifications, functionalizations, and drug loading for different nanoparticle drug delivery systems. Imaging properties of various theranostic nanoparticles have also been presented in the review. By carrying different molecules, such as fluorescent dyes and radioisotopes, and the use of iron oxide or gold nanoparticles, intratumoral accumulation of theranostic nanoparticles could be detected using a

single or multimodal noninvasive imaging. Peptides, proteins, antibodies, and other small molecules are all suitable targeting ligands for conjugation onto the nanoparticles for improving tumor targeted drug delivery. Taking into consideration their small size and large surface area, nanomaterials have also been used for induction of antitumor therapeutic effects when loaded with chemotherapy drugs, antibodies, therapeutic genes, and/or photosensitizers. More interestingly, some nanomaterials with strong near-infrared absorbance can generate heat upon light irradiation for photothermal and photodynamic therapy. We have also discussed the advantages and limitations of each nanoparticle drug delivery carrier for the development and translation as theranostic agents for future clinical applications. It is believed that targeted cancer therapy in combination with image-guided drug delivery and monitoring tumor responses to therapy using the advanced theranostic nanoparticles offer a powerful and integrated cancer therapeutic approach for effective treatment of highly heterogeneous human cancers. The ability of noninvasive detection of tumor localization and accumulation of theranostic nanoparticles in tumors is extremely useful for image-guided cancer phototherapy. The therapy will be initiated precisely at the tumor site and the best time points by either laser irradiation or exogenous stimuli, resulting in an effective tumor ablation with minimum side effects. To obtain complementary tumor information in vivo, it may be necessary to combine more than one imaging modalities for visualization of interested tumors areas. For the development of theranostic nanoparticles, it is important to consider not only improving drug loading into nanoparticles, but also mechanisms of drug release. Various approaches, such as protease, pH, light, temperature, or reactive oxygen species (ROS) have been used to develop conditional activatable drug release nanoparticles. In addition to the efforts on incorporating diagnostic and therapeutic functions into single nanomaterial, nanoparticles particularly those containing two or more distinct components are also widely investigated. This type of nanomaterials, named hybrid nanoparticles, presents superior biomedical effects to that of single component due to the synergistic effect. Currently, carbon materials, magnetic nanoparticles, gold nanoparticles, and quantum dots are widely reported for the production of hybrid nanoparticles, providing improved theranostic property in a single platform. Although most reported nanoparticles or hybrid nanocomplex demonstrated exciting theranostic potentials in animal models, little were reported on the translation of these theranostic agents for human use. Collectively, it is still too early to predict the success of nanotechnology in cancer therapy and more investigations have to be conducted to answer some fundamental questions concerning the application of theranostic nanomaterials for clinical applications.

Until now, the most important issue is the potential toxicity of nanomaterials for biomedical applications in humans. Although the surface engineering is indeed helpful in improving physiological dispersion and stability of nanomaterials, only magnetic iron oxide nanoparticles have been approved by US FDA for clinical diagnostic radiology because most of the injected iron oxide nanoparticles can be endocytosed in the reticuloendothelial system and broken down in macrophages. The released iron can then be used as normal iron in red blood cells. However, the

potential long-term toxicity concern for many nanomaterials, particularly gold nanoparticle and carbon nanomaterials, is still the most important issue. More efforts are required to thoroughly investigate systemic toxicity, clearance, and distribution in not only rodent animals but also in bigger animals with different doses, injection routes, and intervals at different time periods. Most importantly, the effect of nanomaterials on the reproductive system has yet to be investigated seriously.

Besides the toxicity concern, the delivery efficiency is another major problem that has to be addressed before translating nanoparticles from bench to the clinic. First, the imaging efficiency of theranostic nanoparticles has to be considered since different imaging modalities have different specifications. For example, PET imaging is the most sensitive imaging modality with accurate quantification for data analysis but the resolution is relatively low. On the contrary, MRI imaging has excellent resolution but the sensitivity is not ideal. Optical imaging, which is less costly and nonradioactive, has high sensitivity and specificity, but tissue penetration depth and quantification remain concerns for clinic practice. At present, issues about how to take advantages of different imaging modalities in different theranostic nanoparticles have yet to be considered. In addition, the therapeutic efficiency is another factor that may hinder clinical applications of theranostic nanoparticles. Questions concerning how to effective delivery of nanoparticle drugs into a desired site rather than normal organs, and how to overcome tumor stromal barriers to deliver drug into tumor cells, remain to be answered by investigators in the cancer nanotechnology field.

It has to admit that nanoparticles can solve the traditional chemotherapy problems to some extent, such as the poor water solubility and the lack of a targeting ability of chemotherapy drugs. At the same time, nanoparticles bring new therapeutic approaches that allow attacking cancers using the combination of targeted and image-guided therapy. Although significant progresses have been made, numbers of issues remain to be addressed by multidisciplinary cooperation among biologist, chemist, engineers, and clinicians.

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