Review

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Nanomaterials for cancer therapies

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Abstract: Cancer is one of the most deadly diseases in the world. In recent years, nanotechnology, as a unique technology, has been comprehensively applied in the therapy of cancer through diagnosis, imaging and theranostics. Additionally, with the emergence of advanced biomaterials which are capable of being applied in biomedical, research in cancer nanotechnology has made significant progress. Particularly, nanomaterials with dimensions below several hundred nanometers are intensively studied among these advanced biomaterials. In past decades, a number of organic and inorganic nanomaterials have emerged as novel tools for cancer diagnostics and therapeutics due to their unique characteristics, like their solubilization effect, drug protection, passive/active tumor targeting, controlled release of drugs which result in enhanced anticancer efficacy while reducing the side effects. In this review, we first provide a brief description of the key properties of nanomaterials, such as nanoparticle (NP) size, surface properties and tumor targeting. The major goal of this review is to summarize the achievements that have been made in the development of the application of nanomaterials for cancer therapies, along with a short description of their general characteristics and preparation of various kinds of nanoparticles.

Keywords: cancer therapies; inorganic nanoparticles; nanomaterials; organic nanoparticles.

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1 Introduction

In the past few centuries, cancer has been one of the most serious threats to human health. Cancer patients have a sort survival expectation and poor life quality [1]. Although significant progress has been made in medical technology for cancer therapies, the mortality from cancers is still higher than expected and cancer treatment requires further research. Current cancer therapies mainly include surgery, chemotherapy, and radiotherapy. While surgery on many occasions is unable to completely remove all cancer cells in the human body, both chemotherapy and radiotherapy have severe toxic side effects on normal cells and poor specificities for cancer cells. For instance, doxorubicin (DOX), one of the most common chemotherapeutic agents, can induce apoptosis of rapidly dividing cells, but it can also result in apoptosis of numerous normal cells dividing rapidly.

In recent years, there have been significant achievements in the application of nanotechnology, especially in photonics, material science, supramolecular assemblies and drug delivery. In particular, the medical application of nanotechnology, which was called nanomedicine, promoted the development of various kinds of nanoparticles (NPs), such as polymeric micelles, carbon nanotubes, liposomes, etc. [2, 3]. Great effort has been spent on the engineering of nanoparticulate carriers, which function as efficient diagnostic or therapeutic tools for cancer [4–6]. NPs can accumulate at the site of tumors through enhanced permeability and retention (EPR), decreasing the side effects of drugs and increasing treatment efficiency. Various organic and inorganic nanomaterials have emerged as novel tools for cancer diagnosis and therapy due to their unique characteristics.

In this review, we detail the recent achievements in the development of the application of nanomaterials for cancer therapies with an emphasis on synthetic processes, therapeutic agent delivery and tumor imaging, including inorganic nanomaterials, like carbon nanotubes, silica NPs, gold NPs, magnetic NPs and quantum dots, and emerging organic nanomaterials, such as polymeric micelles, liposomes, dendrimers, etc. (Figure 1 and Table 1).

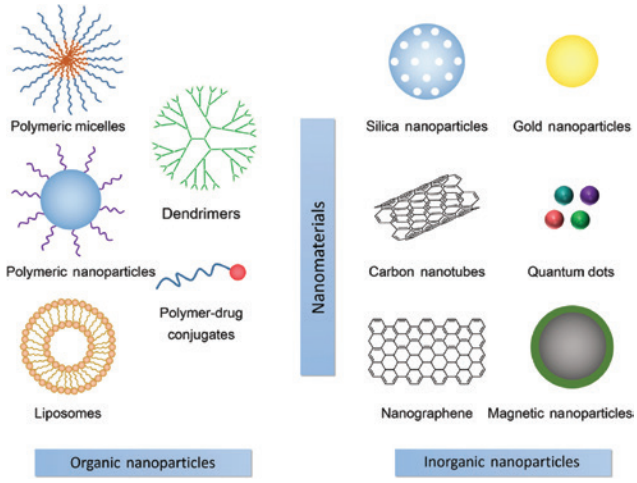

Figure 1: Representation of nanomaterials, including organic and inorganic nanoparticles, applied for cancer therapy.

2 Key properties of nanomaterials

2.1 Size

One of the advantages of nanomaterials is that their size is tunable. The size of NPs used in a drug delivery system should be large enough to prevent their rapid leakage into blood capillaries but small enough to escape capture by fixed macrophages that are lodged in the reticuloendothelial system (RES) [7]. Conventionally, systemically administered NPs should have diameters ranging from 10 to 200 nm, larger than 10 nm in diameter to avoid first-pass elimination through the kidneys while smaller than 200 nm to avoid sequestration by sinusoids in the spleen and fenestra of the liver, benefiting biodistribution and clearance/accumulation behavior [8]. Additionally, as the normal endothelium has an average effective pore size of 5 nm, particles smaller than that will rapidly extravasate across the endothelium [9]. The size of NPs has been shown to influence circulation half-life and tumor accumulation.

2.2 Surface characteristics

In addition to their size, the surface characteristics of NPs also play an important role in determining the life span and fate of nanomaterials during circulation. Surface characteristics can increase a NP's stability and prolong its circulation in the blood, which then increases passive accumulation in tumors via the EPR effect. Moreover, surface characteristics can dramatically influence the electrostatic and hydrophobic interactions between NPs (aggregation) and clearance by opsonization [10]. Nanomaterials should ideally have a hydrophilic surface to escape macrophage capture. PEGylation is one of the most preferred methods to significantly reduce the binding of plasma proteins, interaction with opsonins and clearance by the RES system, and it refers to the process of covering the NPs with polyethylene glycol (PEG) or its derivatives through grafting, entrapping, adsorbing, or covalently binding to the NP surface [11, 12].

2.3 Passive and active targeting of a tumor

NPs could passively target tumor sites through the EPR effect. Unlike the blood vessels found in most normal tissues, angiogenic tumor vessels usually have larger pore

Table 1: Examples of nanomaterials for cancer therapies and imaging.

Material	Type	Size	Main component	Main applications
Organic	Polymeric micelles	20–200 nm	Polymer	Therapeutic and imaging agent carrier
	Polymeric NPs	10–1000 nm	Polymer	Therapeutic and imaging agent carrier
	Liposomes	10–1000 nm	Lipid	Therapeutic and imaging agent carrier
	Dendrimers	1–15 nm	Poly (amidoamine)	Therapeutic and imaging agent carrier
	Polymer-drug conjugates	5–50 nm	Polymer	Drug carrier
Inorganic	Silica NPs	20–100 nm	Silica	Therapeutic and imaging agent carrier
	Carbon nanotubes	0.4–2 nm 1.4–100 nm[a]	Carbon	Therapeutic and imaging agent carrier; photodythermal therapy
	Nanographene	20–300 nm	Carbon	Drug carrier; photodythermal therapy
	Gold NPs	1–100 nm	Gold	Radiotherapy; imaging; drug carrier
	Magnetic NPs	10–50 nm	Iron oxide	Drug carrier; magnetic hyperthermia; MRI
	Quantum dots	2–100 nm	Metal compound	Fluorescence imaging; photodynamic therapy; drug carrier

[a]The diameter of carbon nanotubes varies from 0.4 to 2 nm for SWNTs and from 1.4 to 100 nm for MWNTs.

sizes between adjacent vascular endothelial cells, resulting in preferential tumor accumulation of NPs and then release a large amount of the loaded anticancer agents specifically into the extracellular tumor medium or tumor cells, thereby allowing for effective anticancer therapy with minimum side effects [13]. The EPR effect, applicable for almost all rapidly growing solid tumors, is now becoming a guiding principle in tumor-targeting nanomedicine design. The past decades have witnessed that EPR plays an important role in the delivery of nanomaterials to tumors. However, the EPR effect depends on a number of factors such as the surface characteristics of NPs, immunogenicity, tumor characteristics, which thus may result in many challenges in the optimization of passive targeting [14]. Therefore, a full understanding of the degree of these factors in the EPR effect would be worthwhile.

Passive targeting could facilitate the efficient localization of NPs in the tumor interstitium but cannot further promote cellular uptake by cancer cells, however, which can be achieved by actively targeting NPs functionalized with ligands such as antibodies, peptides, nucleic acid aptamers and small molecules (Table 2), to receptors or other surface membrane proteins overexpressed on target cells [15]. This strategy exploits the differences between malignant cells and normal cells. Specific interactions between the ligands on the surface of NPs and receptors expressed on the tumor cells facilitate NP internalization by triggering receptor-mediated endocytosis. Tumor-targeted nanomaterials are being employed for early tumor diagnosis and therapy, which could reduce or eliminate the delivery of potentially toxic agents to healthy tissues, resulting in increased diagnostic or therapeutic effectiveness and decreased potential side effects [16]. Furthermore, active targeting has shown great potential in overcoming a variety of obstacles such as bypassing the blood-brain barrier [17, 18] and multi-drug resistance (MDR) in tumors [19, 20].

Table 2: Targeting moieties for active tumor targeting.

Targeting moieties	Targets	Type of cancer
FA	FA receptor	MCF-7, MGC803 and KB cells; ovarian cancer
Tf	Tf receptor	A549, PANC-1, BT-549, and MDA-MB-435 cells
HA	CD44 receptor	SCC7, MDAMB-231, HCT116, and MCF-7 cells
RGD peptide	Integrin $\alpha_v\beta_3$	U87MG cells; RCC
NGR motif peptide	CD13	MCF-7 cells; RCC
Aptamer	PSMA	LNCaP cells
	Nucleolin	C6 glioma cells

FA, Folic acid; Tf, transferrin; HA, hyaluronic acid; RCC, renal cell carcinoma; PSMA, prostate-specific membrane antigen.

3 Organic nanomaterials for cancer therapies

Because of the excellent properties, such as biological compatibility and degradability, natural or synthetic polymer-formed organic-based nanomaterials have been extensively used in the field of cancer therapies. They can roughly be divided into five types, i.e. polymeric micelles, polymeric NPs, liposomes, dendrimers and polymer-drug conjugates.

3.1 Polymeric micelles

3.1.1 General characteristics and synthetic aspects

Polymeric micelles (PMs), prepared from certain amphiphilic co-polymers, are spherical, nano-sized colloidal particles with a hydrophilic shell and a hydrophobic core [21–24] (Figure 2). PEG is the most used in constructing the hydrophilic shell, which can help to stabilize the carriers and protect them from degradation by reducing unspecific interactions *in vivo* [25, 26]. To construct the hydrophobic core, several natural or synthetic polymers have been frequently taken into consideration, including polysaccharides, poly(ε-caprolactone) (PCL), poly(lactide) (PLA) and poly(lactic-co-glycolic acid) (PLGA). The hydrophobicity of the hydrophobic core provides a perfect medium to entrap hydrophobic drugs, helping to solve their poor water solubility. Except for the ability of solubilization of hydrophobic drugs, the small size with narrow distribution also makes polymeric micelles ideal nano-drug delivery systems, as it could avoid rapid renal excretion, helping to realize a long circulation time [27, 28].

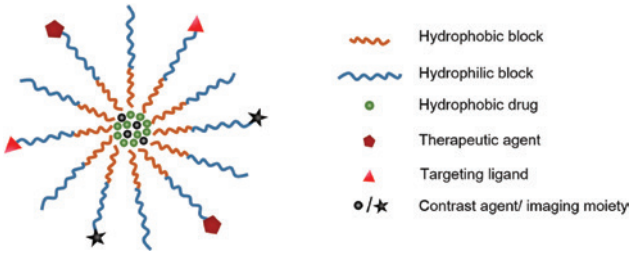

Figure 2: Schematic of optimized polymeric micelle for anticancer therapy, bearing targeting ligands, contrast agents or imaging moieties and therapeutic drugs.

In the preparation of polymeric micelles, we need to compose a desirable amphiphilic block copolymer, and then a conversion of micelle at a critical micelle concentration (CMC) through several techniques including the dialysis method, the oil-in-water (o/w) emulsion method, the solvent evaporation method, the nano-precipitation method and the solid dispersion method [29, 30]. In the dialysis method, polymer and hydrophobic drugs are first dissolved in organic solvent, then the addition of small amounts of water and stirring is followed to form a water-miscible organic solvent. Finally, a dialysis bag is used for dialysis against excess water for several hours to remove the organic solvent [31]. As to the solid dispersion method, similar to the dialysis method, polymer and hydrophobic drugs are dissolved in organic solvent first. Then, a solid polymer matrix could be obtained by evaporating the organic solvent under reduced pressure [32]. In addition, except for physical entrapment, drug loading can also be completed by chemical conjugation.

3.1.2 Polymeric micelles for drug delivery

As they could load and deliver drugs to the desired function site, improving the pharmacokinetic of the loaded drug and decrease non-specific toxicity, polymeric micelles have been extensively explored as drug carriers in the past decades. In a recent study, in order to increase the drug-loading content, Liang et al. [33] used different p-conjugated moieties, including 7-carboxymethoxy coumarin, cinnamic acid and chrysin, to modify the terminal hydroxyl groups of PCL segments in mPEG-PCL micelles, as DOX could be loaded on the micelles through the evocation of the p-p stacking interaction. The results showed that the modification could improve the mPEG-PCL's ability of crystallization; therefore, the drug-loading content increased significantly from 12.9% to 25.5%. As cRGD peptide could inhibit cancer metastasis, Makino et al. [34] prepared cRGD-conjugated polymeric micelles to impede the development of lymph node metastasis. Besides, an anticancer drug (1,2-diaminocylohexane) platinum(II) was entrapped into the micelles to further inhibit the metastasis progress. The results showed that the micelles could effectively inhibit lymph node metastasis by inhibition of the spreading of cancer cells.

Because the natural pH gradient exists in the tumor microenvironment and intracellular endo/lysosome, pH-sensitive degradable micelles are recently emerging as a promising platform for antitumor drug delivery [35, 36]. Recently, intracellularly acid-switchable micelles were prepared by Wang et al. [37] for accomplishing combinational therapy against drug-resistant tumors. The micelles were composed of a pH-sensitive diblock polymer, a photosensitizer and DOX. The results revealed that the activated micelles can induce notable reactive oxygen species (ROS) generation under near-infrared (NIR) laser irradiation for photodynamic therapies (PDT) and promoting tumor penetration of the chemotherapeutics. Furthermore, the micelles can cause significant temperature elevation via NIR laser illumination for PA imaging and photothermal therapies (PTT).

In our previous work, the pH-sensitive mixed micelles were prepared for cytosolic delivery of DOX [24]. The mixed micelles were composed of two block polymers, DSPE-PEG and pH-responsive poly(histidine)-PEG. The results showed that the micelles possessed a pH-dependent drug release property. Furthermore, while modified with nucleosome-specific monoclonal antibody, the micelles showed greatly enhanced endocytosis efficiency and antitumor efficacy. Similarly, we prepared other pH-sensitive micelles to protect and introduce the penetrating peptide (TAT) [38]. The micelles were composed of two block polymers, one was DOX-TAT and the other one was LHRH-PEG-PHIS-DOX, in which LHRH was an active targeting moiety, and PHIS was a pH-sensitive bond. Once they arrive at the tumor microenvironment, the micelles could respond to tumor extracellular pH_e and dissociate and release DOX-TAT, which could overcome multidrug resistance and transport directly into cancer cells. The *in vitro* and *in vivo* results demonstrated that this kind of micelles showed the highest anticancer efficacy compared with the control group.

3.2 Polymeric nanoparticles

3.2.1 General characteristics and synthetic aspects

Polymeric NPs, one of the hotspot issues in the field of nanomedicine, present superior pharmacokinetic properties, including drug load and drug stability, compared to polymeric micelles. Composed of polymer matrix, NPs provide the media for the drugs absorption, dissolution, entrapment and encapsulation [39–41]. They could improve the therapeutic effect of anticancer treatment through passive targeting via the EPR effect.

Several methods are used for the synthesis of polymeric NPs, including emulsification and solvent evaporation/extraction [42], nanoprecipitation (solvent-displacement) [43, 44], supercritical antisolvent method [45], and salting out [46, 47]. Emulsification and solvent evaporation/extraction was the most used method to

synthesize polymeric NPs. In this method, the polymer organic solution (oil phase) is first added into stabilizer-contained water to form the oil-in-water emulsion. Then, the organic solvent could be evaporated either under reduced pressure or by continuous stirring at room temperature. Evaporation of the organic solvent is followed by precipitation of the polymer as nanospheres of a few hundred nanometers in diameter. In 2014, a new method named electrospray nanoprecipitation was reported by Luo et al. [48] to prepare polymeric NPs, which combines agitated solvent displacement with electrospray. Compared with the agitated solvent displacement or the electrospray method, this combined technique could obtain polymeric NPs with a dramatically lower diameter range.

3.2.2 Polymeric nanoparticles for drug and gene delivery

Because of the superb characteristics, like biodegradability, biocompatibility and prolonged circulation, the polymeric NP-based delivery system for anticancer drugs has received extensive attention. In addition, polymeric NPs could deliver a great number of drugs for cancer therapies, including anticancer drugs, genes and proteins. Moreover, polymeric NPs may significantly reduce the adverse effects due to an alteration of the body distribution.

PEGylated PLGA NPs were employed by Danhier et al. [49] as a vehicle for the delivery of paclitaxel (PTX). Compared to Taxol, the polymeric NPs showed a threefold higher cytotoxicity on HeLa cells, resulting in remarkable inhibition of tumor growth. Polymeric NPs can be also used as a gene vector for extending brain tumor survival. Gene therapies have most often been performed using viral carriers. However, viruses pose significant safety risks due to their inherent toxicity, immunogenicity and tumorigenicity. In a recent study, polymeric NPs were introduced to deliver genes to extend *in vivo* brain tumor survival [50]. Two rat glioma cell lines, 9L and F98, were used to evaluate the efficacy of such NP formulations, and it was discovered that these treated animals displayed an enhanced survival rate compared to commercial reagent Lipofectamine 2000.

Hypoxia is a condition found in various intractable diseases including cancer. Thus, a hypoxia-responsive polymeric NP (HR-NPs) was prepared by Thambi et al. [51] for the tumor-targeting delivery of DOX. The HR-NPs were synthesized by carboxymethyl dextran conjugated with 2-nitroimidazole derivative, while DOX was entrapped into the NPs. Compared to normoxic cells, the DOX-loaded HR-NPs revealed higher cytotoxicity against hypoxic cells. As confirmed by microscopic observation, under hypoxic conditions, HR-NPs could promote cellular uptake of DOX, resulting in great antitumor efficacy *in vivo*.

3.2.3 Polymeric nanoparticles for imaging

Polymeric NPs loaded with imaging agents, namely, gadolinium complexes and magnetic NPs have been extensively explored to image cancer by magnetic resonance imaging (MRI). Typically, imaging agents were encapsulated into the core of the polymeric NPs. For instance, Li et al. [52] developed a novel folate-conjugated PEGylated PLGA-based NP for liver cancer therapeutics; sorafenib and magnetic NP were co-encapsulated into the NP. The results revealed that the polymeric NP possessed good imaging property. Furthermore, this NP formulation displayed great inhibition of tumor cell growth.

Recently, in order to realize combined diagnostic and therapeutic functions, Li et al. [53] prepared a theranostic NP, which was synthesized by the integration of a gadolinium-based MRI agent and an active gemcitabine metabolite through supramolecular self-assembly synthesis. The anticancer drug gemcitabine-5′-monophosphate was entrapped in such a NP for coordination with Gd(III). Thetheranostic NPs showed a strong T1 contrast signal for *in vivo* MRI of tumors and increased retention time. Moreover, the results showed that such a NP formulation could greatly inhibit the growth of MDA-MB-231 tumor *in vivo*.

3.3 Liposomes

3.3.1 General characteristics and synthetic aspects

Liposomes are self-assembling NPs with closed membrane structures. They are formed by dispersion of phospholipids featured with hydrophobic anionic/cationic long-chain tails and hydrophilic heads (Figure 3). Their specific structures enable water-soluble drugs to be entrapped in their aqueous core, while lipophilic drugs in the lipid bilayer(s) [54, 55]. In addition, liposomes can effectively load various bioactive molecules, including enzymes and nucleic acids [56, 57]. They have been proven to be beneficial for therapeutic compound stabilization, cellular and tissue uptake of therapeutic compounds and bio-distribution of compounds to target sites *in vivo* [58–60].

Liposomes can be created from cholesterol and natural nontoxic phospholipids. Typically, liposomes can be synthesized in a solution containing the desired drug by hydration of the phospholipid mixture. After vortexing,

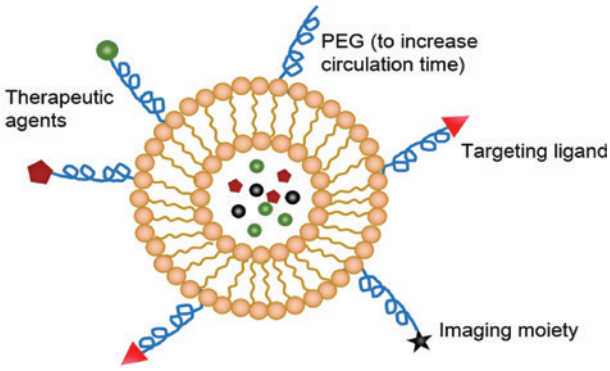

Figure 3: Schematic of liposomes used in cancer therapy. Liposomes are composed of lipids with PEG to increase their circulation time. They can be functionalized with therapeutic agents, targeting ligands, and imaging moieties or contrast agents.

unilamellar liposomes are extruded under high pressure, which can be further purified by column chromatography or ultracentrifugation. Jaafar-Maalej et al. [61] reported a new method to prepare liposome via the ethanol-injection technique and a membrane contactor module, which was specifically designed for colloidal system preparation. This method promoted pharmaceutical agents to be entrapped into liposomes.

3.3.2 Liposomes for drug delivery

In the past decades, liposomes have been extensively explored as an anticancer drug delivery system. They could be used to stabilize therapeutic agents, promote targeted site accumulation and endocytosis of these agents *in vivo*. At present, several liposomal anticancer drugs have been successfully applied into the clinic or clinical test stages [62–64]. For instance, Doxil, a PEGylated liposomal DOX, has been approved by the US Food and Drug Administration (FDA) for cancer therapy, as it could improve the plasma pharmacokinetics and tissue distribution.

In a recent study, $H_7K(R_2)_2$-modified pH-responsive liposomes were prepared by Zhao et al. [65] for the tumor-targeting delivery of DOX. $H_7K(R_2)_2$ referred to a targeting ligand but can respond to the mild acidic pH in the glioma microenvironment, acting as a cell-penetrating peptide (CPP). The *in vitro* results confirmed this kind of pH-triggered specific-targeting effect, while *in vivo* results showed a liposomal formulation could greatly improve the antiangiogenic activity.

In another similar work, Chiang et al. [66] introduced pH-responsive polymer-liposomes for the extracellular matrix (ECM)-targeting delivery of anticancer drugs. The results indicated that such ECM-targeting liposomes showed rapid drug-releasing profiles in acidic conditions. Because the ECM-targeting liposomes accumulated preferentially in the tumor site, the ECM-targeting liposomes showed exceptional anticancer activity *in vivo* and lower hepatic and renal toxicity.

3.3.3 Liposomes for imaging

Except for drug delivery, liposomes can also be functionalized with imaging contrast agents, providing combined diagnostic and therapeutic functions. Recently, a theranostic liposomal drug delivery system was prepared by Ren et al. [67] to realize a real-time image of bio-distribution by MRI and accomplish chemotherapy through the carried anticancer drug. Compared to commercial MRI contrast agent Omniscan®, this liposome showed a 36-fold higher T1 relaxation rate; moreover, its circulation time could reach 300 min *in vivo*. Besides, both hydrophobic and hydrophilic chemotherapeutic drugs could be loaded in such a liposome, resulting in synergetic therapy without noticeable toxicity.

Park et al. [68] prepared hyaluronic acid derivative-coated liposomes for tumor-targeting delivery of DOX and MRI contrast agent (Magnevist). Under HA and CD44 receptor interaction, the cellular uptake of DOX greatly increased compared to plain liposome. Furthermore, such a liposome appeared to be a promising tumor-targeting MRI probe for cancer diagnosis, which was confirmed by the *in vivo* contrast-enhancing effects.

3.4 Dendrimers

3.4.1 General characteristics and synthetic aspects

Dendrimers, as perfect monodisperse macromolecules, are characterized with a highly branched 3D architecture [5, 69–71]. They could load drugs and gene molecules through simple electrostatic interactions, encapsulations and covalent conjugations. Dendrimers possess empty internal cavities and an extremely higher density of surface functional group (-NH_2 or -COOH), which makes them become attractive carriers for anticancer therapeutics. Moreover, due to the relatively small size, dendritic carriers (1–15 nm), can be cleared from the blood through the kidneys, which can decrease their toxicity *in vivo*.

Dendrimers can be prepared by the divergent and convergent synthesis approaches. In the divergent approach,

the synthesis begins with the preparation of the core of the dendrimer, then the arms are attached to the core by adding building blocks in a step-by-step manner [72]. Most commercially available dendrimers are produced by the divergent approach. The convergent approach involves preassembly of the complete wedge-shaped branching units, which are coupled to the central core moiety in the final step [73]. This strategy can provide the best structural control by necessitating the synthesis of branches of various requisite sizes [74].

3.4.2 Dendrimers for drug and gene delivery

In recent years, dendrimers have been extensively introduced to act as drug carriers, and a variety of drugs can be entrapped or covalently conjugated to the dendrimers. Among all the dendrimers, polyamidoamine (PAMAM) was the most widely investigated dendrimer as its surface contains a great number of amine groups, which could be used to conjugate various functional moieties. Liu et al. [75] combined liposomes and dendrimers (PAMAM, G4.0) into hybrid nano-systems for the encapsulation of PTX to treat ovarian cancer. Compared with free PTX, the anticancer efficiency of PTX was greatly enhanced (37-fold higher) as it loaded in such a nano-formulation. Moreover, the anticancer effect could be improved by the combined function of PTX and the dendrimer.

A folate-PEGylated PAMAM dendrimer was prepared by Cheng et al. [76] for the delivery of DOX and enhanced tumor selectivity. DOX was covalently attached to PAMAM through an acid-labile linker. The results revealed that such a dendrimer formulation showed what was evidently pH-dependent drug release pattern. In addition, the cellular uptake of DOX was greatly improved, which was confirmed by fluorescence microscopy and flow cytometry. In 2014, Liu et al. [77] for the first time, prepared the G5 PAMAM dendrimer-based targeting nano-delivery system for the delivery of Hsp27 dsiRNA. Besides, a dual targeting peptide was used to decorate the dendrimer for simultaneously promoted cancer cell targeting. The results showed that this kind of nano-system could promote cancer cell targeting, resulting in enhanced gene silencing and anticancer efficacy.

3.4.3 Dendrimers for imaging

The unique morphology of dendrimers makes them a promising candidate for diagnostic applications. For example, in order to realize *in vitro* and *in vivo* computed tomography (CT) imaging of cancer cells, Wang et al. [78] introduced an acetylated dendrimer to entrap gold NPs. After treatment with such dendrimers, SPC-A1 cells can be detected by micro-CT images under X-ray. Moreover, the *in vivo* results also confirmed that the synthesized dendrimers' administration could be imaged, whether intratumor or intraperitoneum.

In 2013, multifunctional dendrimer-based gold NPs (AuNPs), as a dual-modality contrast agent, were prepared by Li et al. [79] for *in vitro* and *in vivo* CT/MRI of breast cancer cells. In this study, gadolinium chelate (DOTA-NHS) and PEG monomethyl ether-modified G5 PAMAM dendrimers were used as templates to synthesize AuNPs, then the remaining dendrimer terminal amine groups were chelated and acetylated by Gd(III). The results showed that MCF-7 cells and the xenograft tumor model after treatment with such a contrast agent could be effectively imaged by CT or MR imaging. Recently, radionuclide (131)I-labeled dendrimers were prepared by Zhu et al. [80] for targeted single-photon emission computed tomography (SPECT) imaging and radiotherapy of tumors. In this study, G5-NH_2 were first modified with 3-(4′-hydroxyphenyl)propionic acid-OSu (HPAO) and PEGylated folic acid (FA), and then the remaining dendrimer terminal amine groups were acetylated by radioactive iodine-131 [(131)I]. The results showed that such a dendrimer platform possessed good stability and high radiochemical purity for *in vivo* targeting SPECT imaging and radiotherapy on the FA receptor-overexpressing xenografted tumor model.

3.5 Polymer-drug conjugates

3.5.1 General characteristics

Polymer-drug conjugates are synthesized through conjugating drugs to water-soluble polymers, which contain a water-soluble polymer, an agent and/or a biodegradable linkage [81–83]. They could increase the tumor-targeting ability via the EPR effect and enable endocytic capture at the cellular level, which could promote lysosomotropic drug delivery. In addition, in spite of the development of multi-drug resistance, distinct cell uptake mechanisms make polymer-drug conjugates less sensitive to efflux pumps. To date, drug conjugates are the most successful nanomedicine therapeutics that are applied in clinical cancer treatment [82, 84–86]. Although many other devices achieved great progress, polymer-drug conjugates are still favored due to their distinct advantages.

3.5.2 Polymer-drug conjugates for drug delivery

Polymer-drug conjugates are drug delivery systems. Drug(s) can covalently attach to the functional groups of the polymer directly or through a spacer. They have been an excellent platform for drug delivery. Tu et al. [87] prepared a stimuli-responsive polymer-drug conjugate for improving cancer-targeting ability and anticancer efficacy. In this study, this polymer-drug conjugate consisted of a PEG, a matrix metalloproteinase 2 (MMP2)-sensitive peptide linker, a TAT and DOX. The polymer-drug conjugate possessed multifunctional properties, including an MMP2-mediated tumor-targeting ability and P-gp inhibition ability, resulting in enhanced cell endocytosis and followed by improved antitumor efficacy.

In our previous research, we prepared a pH-response charge convertible polymer-drug conjugate for the delivery of antitumor drugs [88]. In this polymer-drug conjugate, poly(β-L-malic acid) (PMLA) was used as a water-soluble polymer and was modified by polyethylenimine (PEI), a fragment antibody (HAb18 $F(ab')_2$), charge convertible group (2,3-dimethylmaleic anhydride) and DOX, which were covalently attached to the polymer. The *in vitro* results showed a significantly enhanced endocytosis, which was caused by receptor-mediated endocytosis and strong positive charge, resulting in increasing antitumor efficacy.

Owing to the complex molecular basis, single therapeutic agents could not effectively sustain cancer therapies. The majority of cancers are being treated by a combination of drugs [89]. Therefore, polymer-drug conjugate-based combination therapy would be an exciting therapy, which could achieve simultaneous delivery, providing synergetic drug effects [81]. In order to achieve combination therapies, DOX and mitomycin C (Mit C)-conjugated HPMA copolymer-based polymer-drug conjugate was prepared by Kostková et al. [90]. In this polymer-drug conjugate, DOX and Mit C, two drugs that have different action mechanisms, were conjugated to the polymer through a pH-sensitive hydrazone bond. Both *in vitro* and *in vivo* results showed a significant synergetic antitumor activity on EL-4 cells. In another similar work, a polymer-drug conjugate co-delivery of oxaliplatin and demethylcantharidin (DMC) was synthesized by Wang et al. [91]. The results revealed that this polymer-drug conjugate, which could be activated in two modes against cancer cells, resulting in higher cytotoxicity against SKOV-3 cells compared to free drugs used alone, which was mainly caused by the synergistic effect between oxaliplatin and DMC.

4 Inorganic nanoparticles for cancer therapies

Besides organic NPs used in the field of cancer therapies, various inorganic materials with interesting structures as well as unique chemical and physical properties have also been explored as NPs for cancer therapies.

4.1 Silica nanoparticles

4.1.1 General characteristics and synthetic aspects

As a major component of sand, silica is known for its compatibility in biological systems. A large variety of silica-based nanostructures have been synthesized in the past few decades and used in different applications [92]. The particle size, shape, porosity and surface chemistry of silica NPs can be successfully controlled during the synthesis process. It has been found that silica-based NPs with a special nanostructure can be used to encapsulate various antitumor agents for cancer therapies [93–98].

Two major types of silica-based NPs have been successfully synthesized and studied. One is solid silica NPs (SiNPs) and the other is mesoporous silica NPs (MSNs). In recent years, functionalized SiNPs have been widely used as drug delivery carriers and optical imaging contrast agents. When used as optical contrast agents, SiNPs show remarkable properties, including biocompatibility, photophysical stability and favorable colloidal properties. Besides, the particle surface of silica can be modified with a series of functional groups such as aptamers and antibodies [99, 100]. MSNs also holds many special properties such as stable and rigid frameworks, high surface areas, large pore volumes, tunable pore sizes and have shown great promise as drug delivery vehicles during the past several decades [101–104].

There are two main methods that are widely used to synthesize SiNPs, including the Stöber method and the reverse microemulsion method [105, 106]. The Stöber method mainly involves two processes, the controlled hydrolysis and condensation of a silica precursor. Tetraethoxysilane (TEOS) in ethanol and water was used in the Stöber method, and ammonia was used as a catalyst. The size of the particles can be controlled by adjusting the synthesis conditions. For the reverse microemulsion method, the synthesis process involves the ammonia-catalyzed polymerization of TEOS in water-in-oil or a reverse-phase microemulsion. The micelles of the microemulsion act as "nanoreactors", where the particle growth is carried

out. The final size of SiNPs is controlled by the water-to-organic solvent ratio. MSNs are usually prepared by the modified Stöber method, which relies on the cooperative self-assembly of supramolecular surfactant assemblies, acting as structure-directing agents and oligomeric silica species. The synthesis process can be conducted in either acidic or basic conditions.

4.1.2 Silica nanoparticles for drug and gene delivery

MSNs have been extensively used for drug and gene delivery due to their unique mesopores and nanochannels, which can render a high payload of the drug and easy stimuli-controllable release [101, 102]. For example, in order to overcome drug resistance in breast cancer, a multifunctional MSN carrier was prepared by Meng et al. [107] to co-deliver DOX and siRNA, which could target the P-glycoprotein (Pgp) drug exporter. This kind of delivery system showed a synergetic inhibition of tumor growth *in vivo*, providing a promising platform for multiple drug delivery and overcoming DOX resistance. In a recent work, Ngamcherdtrakul et al. [108] reported a PEI-PEG-coated and anti-HER2 monoclonal antibody (trastuzumab)-coupled MSNs for the targeting delivery of siRNA to breast cancer. The results showed that the synthetic antibody-NPs could induce cell apoptosis in HER2-positive breast cancer but not in HER2-negative ($HER2^-$) cells *in vitro*. More importantly, this synthetic antibody-NPs showed no noticeable systemic toxicity.

In our previous research, a SiO_2@AuNP sequential drug delivery system was introduced to deliver three kinds of different drugs, including bio-drugs (monoclonal antibody), siRNA and a combination of chemotherapeutics with a synergetic effect [109]. Such a multifunctional NP system could target the colon cancer cell (colo-205) under mAb guidance, followed by endocytosis, endosome escape and sequential drug release. The siRNA released by the glutathione exchange was used to inhibit the Bcl-2 protein, while the sequential release of hydroxycamptothecine (HCPT) and DOX played a role in synergetic antitumor efficacy. The *in vitro* and *in vivo* results showed significantly increasing antitumor efficacy without noticeable systemic toxicity, providing a promising platform for multiple drug delivery and controllable sequential drug release.

4.1.3 Silica nanoparticles for imaging

In recent years, SiNPs loading fluorescent dye agents have achieved extensive interest in cancer imaging due to their brightness and photostability. Recently, a multifunctional theranostic magnetic MSN was prepared by Chen et al. [110] to achieve magnetic-enhanced tumor-targeting MRI. In order to realize reduction-triggered intracellular drug release, β-cyclodextrin (β-CD), acting as the gatekeeper, was anchored on the surface of MSN. The results showed that such MSN can realize active targeting of cancer cells and enhanced MRI *in vivo* under an external magnetic field, resulting in significantly increased antitumor efficacy without obvious systemic toxicity.

Iron oxide NPs seem to be promising diagnostic or therapeutic agents for cancer treatment. However, their *in vivo* application was hindered by the severely biological aggregation. Therefore, Hurley et al. [111] synthesized mesoporous silica-coated iron oxide NPs to prevent the aggregation. The results suggested that magnetic NPs coated with MSNs could avoid lower heating and imaging performance, which will be caused by aggregation. In another work, Chen et al. [112] developed a type of functionalized MSNs, coated with fluorescence-conjugated cyclodextrin, for pH-trigged drug delivery and imaging. *In vitro* results showed that drug release behavior can be controlled by the pH-responsive gatekeeper (cyclodextrin), which shall open the pores when facing acid environment. Moreover, such DOX-loaded functional MSNs showed greatly improved antitumor activity on both HepG2 and HeLa cells.

4.2 Carbon Nanomaterials

In recent years, carbon-based nanomaterials, namely carbon nanotubes (CNTs), fullerenes and graphene, have been developed as nanocarriers for drug delivery and as contrast probes for biomedical imaging. The carbon nanomaterials possess superb biocompatibility, sufficient surface-to-volume ratio, good thermal conductivity and rigid structural properties for post-chemical modification. They could deliver antitumor drugs and gene into cancer cells efficiently, in which the therapeutic molecules shall be safely carried, and then display enhanced antitumor efficiency [113, 114].

4.3 Carbon nanotubes

4.3.1 General characteristics and synthetic aspects

CNTs, which were first reported by Iijima in 1991, are made up of thin sheets of benzene ring carbons and rolled up into the shape of a seamless tubular structure [115]. Two

categories of carbon nanotubes have been discovered, one is the single-walled carbon nanotubes (SWNTs) and the other is the multi-walled carbon nanotubes (MWNTs) [116]. Because of their unique properties in electrics, thermotics, optics, mechanics and biology, CNTs have largely been used in cancer therapies. In recent years, almost everywhere, in relation to cancer treatment, CNTs can be applied, including drug and gene delivery, photodynamic therapies and thermal therapies.

Many methods to synthesize CNTs have been reported over the past several years. The main synthesis techniques for CNT construction are of three types, including arc discharge, laser ablation and chemical vapor deposition [117–119]. All methods involve using a source of carbon and energy to form CNTs. Arc discharge is the most reported method for the synthesis of CNTs as it is very easy. In this method, carbon electrodes act as a source of carbon; a potential difference of about 20 V acts as a source of energy. In the laser ablation method, the carbon electrodes are used as a carbon source while laser pulses provide the energy source. Chemical vapor deposition is the most widely used method for the large-scale production of CNTs. In this method, hydrocarbons like CH_4, acetylene, or carbon monoxide are utilized as a carbon source, and high temperature was used to provide sufficient energy for the decomposition of the hydrocarbons to form CNTs.

4.3.2 Carbon nanotubes for drug delivery

Because of tunable surface modifications and excellent physicochemical properties, CNTs have been extensively explored as drug carriers, and a variety of related research has been reported in the past several years [120, 121]. Liu et al. [122] reported SWNT-based drug delivery for the inhibition of tumor growth *in vivo*. PTX was conjugated to the branched PEG chains on SWNTs through a cleavable ester bond. Compared to clinical Taxol, such a SWNT-based formulation showed higher efficacy in inhibiting tumor growth, which was caused by prolonged blood circulation and much higher PTX accumulation at the tumor site through the EPR effect.

Recently, Al Faraj et al. [123] developed CD44 antibody-conjugated SWCNTs for targeting delivery of combining drugs to breast cancer and cancer stem cells (CSCs). The SWCNTs were modified with PEG for improved pharmacokinetics; combining PTX and salinomycin drugs as the conjugated carriers through a hydrazine bond, providing pH-dependent drug release. Compared with treatment using individual drug-conjugated nanocarriers or free drugs, this combined treatment showed considerably enhanced therapeutic efficacy against both breast cancer and CSCs, which was confirmed by bioluminescence and MRI. Zhang et al. [124] used modified SWCNTs for tumor-targeting delivery and controlled release of DOX. This system displayed superb stability under physiological conditions, while at acidic pH and conditions such as tumor microenvironment and intracellular endosomes and lysosomes, the DOX were quickly released and entered the cell nucleus, resulting in cell apoptosis. The results demonstrated that this nanoscale drug system possesses higher selectivity and effectiveness than that of the free drug.

4.3.3 Carbon nanotubes for imaging

As one of the darkest materials, CNTs could exhibit excellent absorbance in the NIR region; thus, they could be utilized as imaging contrast agents, making them achieve extensive attention in the field of cancer imaging. Recently, Al Faraj et al. [125] used CD44 antibody-conjugated SWCNTs as novel multimodality nanoprobes to realize specific targeting and imaging of breast CSC. MRI, single-photon emission CT, and NIR fluorescence imaging noninvasive imaging moieties were used to monitor the biodistribution and preferential homing of such SWCNTs toward the tumor site. The results showed that anti-CD44 SWCNT specifically target CD44-overexpressed cancer cells, and an enhanced colocalization was observed.

Similarly, in order to realize the targeted photoacoustic imaging of gastric cancer, Wang et al. [126] developed RGD-conjugated silica-coated gold nanorods, which were attached to the surface of MWNTs. The results revealed that these kinds of probes possessed excellent water solubility and low non-specific toxicity; moreover, they can target gastric cancer cells and obtain strong *in vivo* photoacoustic imaging.

Wu et al. [127] developed prostate stem cell antigen (PSCA) antibody-conjugated MWNTs [CNT-PEI(FITC)-mAb] for drug delivery and targeted ultrasound imaging. The results showed that such a MWNT-based formulation could realize specific targeting of PSCA-overexpressed cancer cells. In addition, CNT-PEI(FITC)-mAb showed high promise to be used as a targeted ultrasound contrast agent, which was confirmed *in vitro* and *in vivo* ultrasound imaging. Furthermore, the *in vivo* anticancer efficacy testing demonstrated that CNT-PEI(FITC)-mAb could realize targeted delivery of anticancer drugs to the tumor and inhibit the growth of tumor cells.

4.3.4 Carbon nanotubes for photothermal therapies

In the past several years, a variety of researches have demonstrated that CNTs possessed great potential to be applied for photothermal ablation of cancer cells due to their strong optical absorption in the NIR region [128–134]. Recently, manganese oxide (MnO)-coated CNTs were prepared by Wang et al. [129] to act as dual-modality lymph imaging agents for photothermal treatment of lung cancer metastasis. MnO-coated CNTs further covered by PEG was explored as a lymphatic theranostic agent to realize diagnosis and treat metastatic lymph nodes. The results showed that the desired regional lymph nodes were clearly imaged by T1-weighted MR of MnO and dark dye imaging of MWNTs. Furthermore, under the guidance of dual-modality imaging, metastatic lymph nodes could be killed by NIR irradiation as well.

In order to improve and optimize the antitumor efficacy, Zhang et al. [133] prepared Ru(II) complex-functionalized SWCNTs for PTT and PDT. Ru(II) complexes were covalently loaded on the SWCNTs by π-π interactions, and they could be efficiently released under the photothermal effect. Under two-photon laser irradiation, Ru(II) complexes can produce singlet oxygen species; thus, it could be used as a two-photon PDT agent. Compared to single therapy, such Ru(II) complex-functionalized SWCNTs possessed greater anticancer efficacy due to the combination of PTT and two-photon PDT, which was also confirmed by *in vivo* experiments. In 2011, Zhou et al. [134] reported a novel SWNT-based drug delivery system, which could realize mitochondria targeting for cancer PTT. This kind of SWNTs can efficiently convert 980-nm laser energy into heat and selectively destroy the targeting mitochondria, resulting in mitochondrial depolarization, caspase 3 activation, and cytochrome c release. The results revealed that the SWNTs + laser process could afford excellent efficacy in inhibiting tumor growth in the breast cancer model; moreover, in some cases, they could induce complete tumor regression.

4.4 Nanographene

4.4.1 General characteristics and synthetic aspects

Graphene, with a two-dimensional (2D) honeycomb structure composed of an atom-thick monolayer of carbon atoms, was first separated from graphite in 2004, and it is believed to be the basic structure (unit) for the composition of other graphitic materials [135–137]. Recently, graphene and its derivatives such as graphene oxide (GO) and reduced graphene (rGO) have attracted tremendous interest in biomedicine owing to their special physical, chemical and optical properties [138–143]. During the past 10 years, their application in disease treatment based on various mechanisms has been widely explored, and extensive studies have been performed to develop graphene-based NPs for cancer therapies.

GO is an oxygenated derivative of graphene, which has the structure of a single-atom thick layer of graphene sheets and ranges from tens to several hundred nanometers according to the oxidizing conditions. It can be prepared using the Brodie, Staudenmaier, Hummers, and improved Hummers' methods [144–146]. With large amounts of epoxide, carboxylic acid and hydroxyl groups on its surface, GO has good dispersibility and biocompatibility. Meanwhile, GO can be bio-functionalized by the introduction of various functional groups to synthesize GO derivatives with different properties and functions. To obtain rGO, GO is treated by chemical-reducing, thermal-reducing, or UV-reducing processes [147].

4.4.2 Nanographene for drug delivery

Nanographene has properties suitable for the delivery of various molecules. With its two-dimensional structures, nanographene provides relatively high surface areas and capacity for non-covalent π-π stacking and hydrophobic interactions with various drug molecules. In particular, GO could provide a great number of residual carboxylic acid, epoxide groups and hydroxide on its surfaces. Thus, it can also load various agents via covalent conjugation, hydrogen bonding and electrostatic interaction [148–150].

Recently, Zheng et al. [151] prepared poly-L-lysine-functionalized rGO and conjugated with anti-HER2 antibody for efficiently targeting the delivery of DOX to the nucleus of cancer cells. The results showed that cellular uptake of this kind of nanocarriers into MCF7/HER2 cells was significantly higher than the nanocarriers without anti-HER2 antibody, resulting in improved antitumor efficacy. Tian et al. [152] developed a GO-based nanocarrier, which can achieve targeted delivery of anticancer drugs by conjugation of the folate and self-monitoring both *in vitro* and *in vivo* as a labeled fluorescein peptide. The results showed that the drug-loaded nanocarrier can specifically carry the drugs into the folate receptor high-expressed cancer cells. In addition, drug-induced cancer cell apoptosis could be visualized by confocal fluorescence imaging. Living imaging in tumor-bearing mice further demonstrated the dual function mentioned above.

In 2013, Miao et al. [153] synthesized new rGO nanosheets, coated by cholesteryl hyaluronic acid (CHA), for the delivery of anticancer drugs. Compared to rGO, CHA-coated rGO nanosheets could display enhanced colloidal stability and increased safety *in vivo*. *In vivo* experiments revealed that CHA-coated nanosheets showed higher tumor accumulation than nanosheets without CHA coating, therefore, resulting in significantly improved antitumor efficacy.

4.4.3 Nanographene for photothermal therapies

Apart from its nature of being an excellent drug carrier, due to high NIR absorbance, nanographene can also serve as a photothermal agent that could convert the absorbed light into heat, inducing hyperthermia to the cancer cells [154]. For example, a dual anticancer drug-loaded GO was prepared by Tran et al. [155] to achieve a dual-in-dual synergetic treatment against cancer cells. Poloxamer 188 was used to stabilize GO and generate heat to induce cancer cell apoptosis under NIR laser irradiation. Compared with chemotherapy or photothermal therapy used separately, the combined therapy displayed a synergetic effect, resulting in higher antitumor efficacy.

In order to improve tumor targeting and photothermal treatment, a dual-ligand (folate and cRGD) targeting nGO was developed by Jang et al. [156]. The results revealed that cellular uptake of dual-ligand targeting nGO was much higher than single targeting FA-nGO or cRGD-nGO. cRGD-FA-nGO also showed a greatly higher tumor accumulation, resulting in complete ablation of tumor cells by photothermal therapy. In 2015, Kim et al. [143] prepared novel rGO-based NPs, conjugated with PEG-g-poly(dimethylaminoethyl methacrylate) and hyaluronic acid, for targeting PTT and pH-sensitive bioimaging. The rGO-based NPs could respond to the tumor environment to generate photothermal heat, resulting in the suppression of tumor growth. Moreover, the malignant tumor could be completely healed, which was demonstrated by histopathological studies.

4.5 Gold nanoparticles

4.5.1 General characteristics and synthetic aspects

AuNPs are a kind of colloidal or clustered particles with diameters in the range of a few to several hundreds of nanometers. AuNPs are made up of an Au core and/or a surface coating. The size and shape of AuNPs can be easily controlled through changing the synthesis condition (Figure 4). AuNPs have received particular research attention, as they exhibit special properties in labeling, delivery, heating and sensing. Multi-disciplinary research performed over the past decade has demonstrated well the potential of AuNP applied in cancer therapies [157–159].

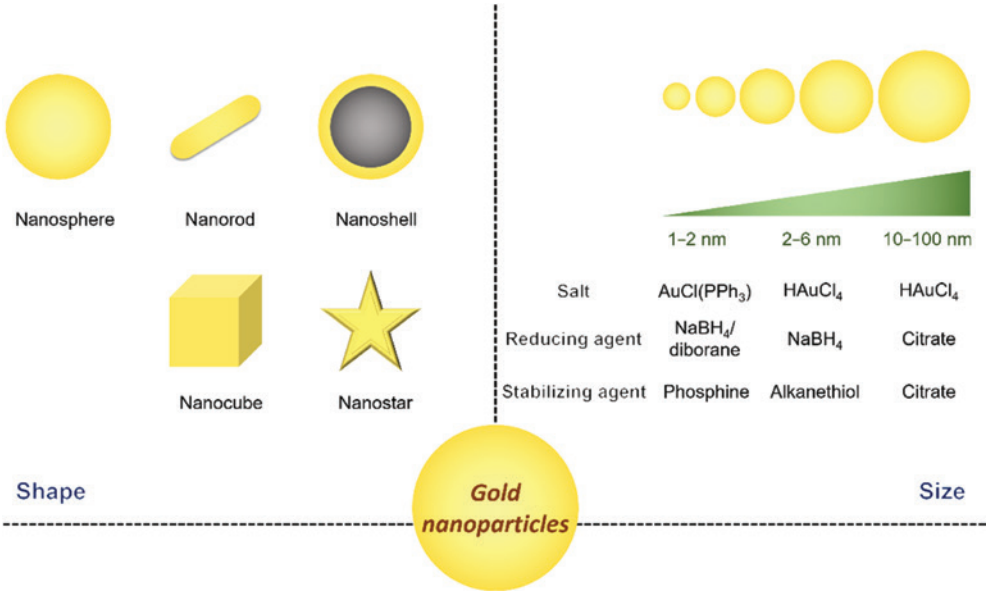

Figure 4: The synthetic versatility of AuNPs. Various shapes and sizes of AuNPs controlled through changing the synthetic condition.

A number of chemical and physical methods were used in the synthesis of AuNPs. Usually, AuNPs are prepared by reducing metal salt precursors in either organic or water solvents [160]. In addition, another widely used method is seed-mediated growth of AuNPs, which was grown from small seed particles of gold [161, 162]. Because of the high affinity between the thiol group and gold, thiol-modified ligands were the most widely used to bind to the surface of AuNPs by the Au-thiol bond.

4.5.2 Gold nanoparticles for cancer radiotherapies

AuNPs have emerged as novel radiosensitizers owing to their high X-ray absorption, synthetic versatility and unique chemical, electronic and optical properties. In the past several years, multi-disciplinary research has demonstrated the potential of AuNP-based radiosensitizers and identified possible mechanisms underlying the observed radiation enhancement effects of AuNPs.

Recently, a combination therapy was reported by introducing core/shell NPs containing AuNPs and DOX [163]. This nanomedicine could realize both radiotherapies and chemotherapies by EPR effect-mediated passive targeting to cancer cells. AuNPs acted as a radiosensitizer, and they were incorporated into vesicles, which were prepared by liposome containing DOX. As shown in the results, the combination therapies achieved the highest antitumor efficacy when compared with the divided therapies. In another work, [164] glucose-capped AuNPs (Glu-AuNPs) were introduced to improve tumor cell targeting and radio-sensitization. Compared with X-rays used alone, this nanoplatform displayed a 1.5- to 2.0-fold enhancement in growth inhibition under 2 Gy of orthovoltage irradiation.

CT contrast and radiosensitization usually increase with particle sizes of AuNPs, but there is a huge challenge to improve both by adjusting sizes under the requirements of *in vivo* application. Therefore, Dou et al. [165] found that AuNPs within 3–50 nm showed great size-dependent enhancements on CT imaging and radiotherapy (RT) [165]. They also demonstrated that about 13-nm-sized AuNPs could simultaneously possess excellent CT contrast ability and significant radioactive disruption. *In vivo* studies further indicated that this optimally sized AuNP improves real-time CT imaging and radiotherapeutic inhibition of tumors in living mice by effective accumulation at tumors with prolonged *in vivo* circulation times compared to clinically used small-molecule agents.

4.5.3 Gold nanoparticles for imaging

As detection methods are simple and convenient, AuNPs have been extensively explored for imaging of tumor cells. Compared with most organic dyes, AuNPs exhibit much higher absorption and scattering intensity. Therefore, AuNPs appear to be superb contrast agents for imaging [166].

Recently, Zhou et al. [167] prepared a cisplatin prodrug-conjugated gold nanocluster for fluorescence imaging and targeted therapies of the breast cancer. The fabrication was composed of fluorescence gold nanoclusters (GNC) conjugated with a cisplatin prodrug and folic acid (FA-GNC-Pt). Fluorescence imaging *in vivo* using the 4T1 tumor-bearing nude mouse model showed that FA-GNC-Pt NPs selectively accumulated in the orthotopic 4T1 tumor and generated a strong fluorescence signal due to the tumor targeting effect of FA. Moreover, they demonstrated that FA-GNC-Pt NPs could significantly inhibit the growth and lung metastasis of the orthotopically implanted 4T1 breast tumors. In another study, an aptamer-AuNP bioconjugate was prepared by Kim et al. [168] for both CT imaging and therapies of prostate cancer. This bioconjugate could realize targeted molecular CT imaging through aptamer-receptor specific binding, achieving an over fourfold greater CT intensity compared with a non-targeted cell.

4.5.4 Gold nanoparticles for drug and gene delivery

Because of special properties, namely, biocompatibility, size diversity and efficient translocation, AuNPs have also been extensively used as drug or gene carriers [169]. In 2014, Kumar et al. [170] synthesized glutathione-stabilized AuNPs for the delivery of platinum (IV) to prostate cancer cells by construction. The results revealed that the nanocarriers, themselves, showed no toxicity; however, once functionalized with a targeting peptide and loaded with a drug, they showed very high cytotoxicity against tumor cells.

Targeting of G-protein-coupled receptors (GPCRs) like somatostatin-14 (SST-14) could have a potential interest in delivering anticancer agents to tumor cells. Therefore, Abdellatif et al. [171] developed AuNPs coated with somatostatin as a promising delivery system for targeting somatostatin receptors. A cellular uptake study on HCC-1806 cell lines showed that the number of AuNPs-SST per cell was significantly higher compared to citrate-AuNPs when quantified using inductively coupled plasma spectroscopy. Moreover, the binding of AuNPs-SST to cells could be suppressed by the addition of an antagonist, indicating

that the binding of AuNPs-SST to cells is due to receptor-specific binding. In order to achieve synergistic efficacy, Ren et al. [172] prepared NIR-radiation-responsive hollow AuNPs to sequentially co-deliver an microRNA inhibitor (miR-21i) and DOX. Compared to free DOX, this kind of nanoplatform showed a fourfold higher tumor accumulation, resulting in significantly improved antitumor efficacy.

4.6 Magnetic nanoparticles

4.6.1 General characteristics and synthetic aspects

Because of the unique physical properties such as magnetic targeting and MRI, magnetic NPs (MNPs) are an important class of nanomaterials, which could be utilized in the field of cancer therapies, including imaging of cancer cells, drug delivery and hyperthermia treatment [173–176] (Figure 5).

MNPs could be synthesized into various different compositions and phases, including iron oxides, pure metals, spinel-type ferromagnets and alloys. In recent years, a number of researches have been reported to synthesize MNPs, including several common methods, like thermal decomposition, co-precipitation, micelle synthesis and hydrothermal synthesis. MNPs prepared by these methods are of high quality [177, 178].

Co-precipitation provides a simple way to prepare iron oxides. During the hydrothermal and high-temperature reactions, iron salts in aqueous solutions and microemulsions were used. In high-temperature organic solvents, the thermal decomposition of iron pentacarbonyl and iron acetylacetonate is carried out. Surfactants can be used to synthesize monodisperse MNPs with a smaller size. For the microemulsion method, MNPs are prepared within micelles, in which the iron salt precursors are encapsulated and could control the nucleation and growth of the MNPs. For hydrothermal synthesis, a broad range of MNP nanostructure can be synthesized using these methods.

4.6.2 Magnetic nanoparticles for imaging and diagnostic applications

The most widely used application of MNPs is as MRI agents that can detect even the earliest stage disease, monitor tumor response to drug therapies and track cell

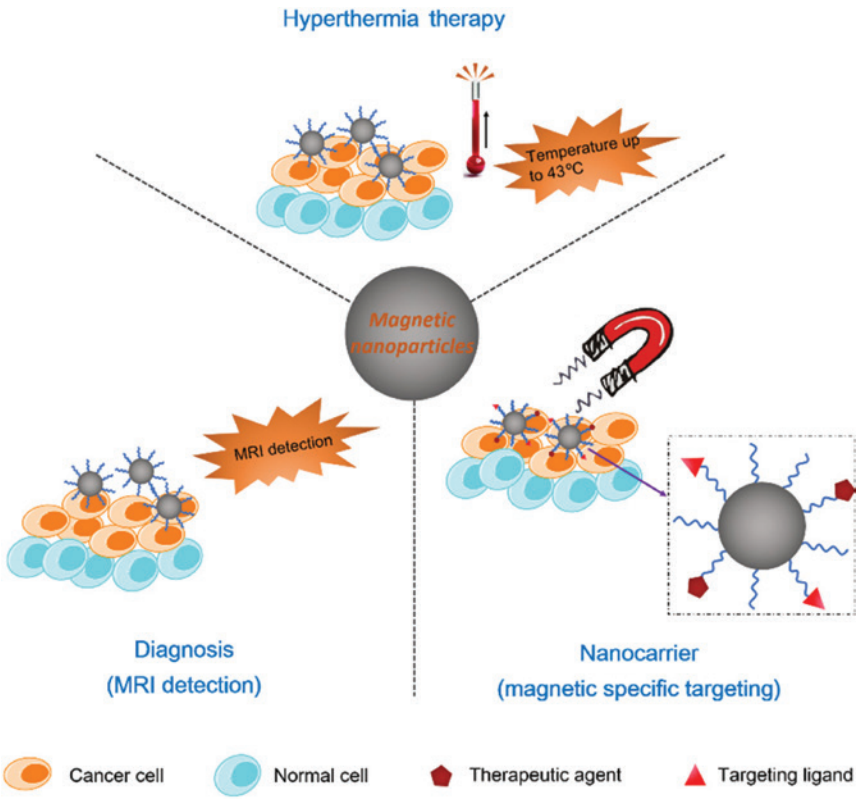

Figure 5: Example of magnetic nanoparticle for cancer therapy. Nanocarrier, diagnosis and hyperthermia therapy.

migration [179–182]. In a recent study, Bai et al. [183] developed a novel approach using a polymeric nanocapsule to engineer a triple-modal fluorescence/MR/SPECT imaging and magnetic targeting system, encapsulating hydrophobic superparamagnetic iron oxide NPs. When a static magnetic field was applied to the tumor for 1 h, up to ~3- and ~2.2-fold increase in tumor uptake at 1 and 24 h was achieved. Furthermore, the results indicated that the proposed system offered sufficient sensitivity to monitor its tumor uptake and magnetic targeting *in vivo*.

During the last decades, the development of early diagnostic methods for various tumors enabled an improvement in the treatment of cancer patients. This achievement, however, has not been achieved for pancreatic ductal adenocarcinoma (PDAC). Rosenberger et al. [184] developed targeted diagnostic magnetic NPs for the medical imaging of pancreatic cancer, which was prepared using recombinant human serum albumin (rHSA) and incorporated iron oxide (maghemite, γ-Fe_2O_3) NPs. Galectin-1 has been chosen as a target receptor as this protein is upregulated in pancreatic cancer and its precursor lesions but not in healthy pancreatic tissue nor in pancreatitis. Improved targeting and imaging properties were shown in mice using single-photon emission computed tomography-computer tomography (SPECT-CT), a handheld γ camera and MRI.

4.6.3 Magnetic nanoparticles for drug delivery

MNPs have been proven to be a very promising drug carrier, as they can be synthetized into various sizes and can be modified with different functional groups in order to load a number of molecules [185]. Usually, MNPs were coated with surfactants or polymers, such as PEG or dextran, to stabilize them and increase their biocompatibility. More importantly, MNPs can realize active targeting of cancer cells under an external magnetic field.

In a recent work, Farjadian et al. [186] prepared hydroxyl-modified magnetite NPs to deliver anticancer drug methotrexate (MTX). The modification resulted in the formation of highly hydrophilic NPs, which dispersed easily in water. The *in vitro* cell assays in the presence of free MTX and conjugated form showed an excellent anticancer effect of NPs with regard to soluble drugs. In a similar work, Hałupka-Bryl et al. [187] designed a novel MNP coated with PEG-b-poly(4-vinylbenzylphosphonate) to load DOX and realized targeting delivery. This formation displayed excellent relaxation properties under an external magnetic field. Thus, these kinds of MNPs seems to be good carriers to deliver magnetic anticancer drugs.

4.6.4 Magnetic nanoparticles for hyperthermia therapies

Under alternating magnetic fields, MNPs could be heated, and the heat produced can be directly employed for hyperthermia or indirectly used to induce drug release for killing cancer cells. Therefore, MNPs have been extensively explored as mediators of heat for hyperthermia therapies [188–192]. More importantly, magnetic hyperthermia appears to be a harmless approach to kill cancer cells, as it is based on the heat that is generated by the magnetic materials, themselves.

Hervault et al. [193] reported new magnetic nanocomposites (MNCs), which were composed of an iron oxide core and a thermo- and pH-responsive polymer shell. These novel MNCs could act as both a drug carrier and a hyperthermic agent. At a relatively low NP concentration, the MNCs were proven to preform as nano-heaters for hyperthermia therapies. In a previous work, Sadhukha et al. [194] prepared EGFR-targeted, inhalable SPIO NPs to realize targeting hyperthermia therapies in lung cancer. Because of the effect of EGFR, the tumor retention of SPIO NPs was greatly enhanced. Therefore, using these kinds of targeted SPIO NPs could contribute to significant inhibition of *in vivo* lung cancer growth by magnetic hyperthermia treatment.

Recently, Espinosa et al. [195] reported that iron oxide NPs had the dual capacity to act as both magnetic and photothermal agents. In cancer cells, the laser excitation restores the optimal efficiency of magnetic hyperthermia, resulting in a remarkable heating efficiency in the DUAL mode (up to 15-fold amplification). In solid tumors *in vivo*, single-mode treatments (magnetic or laser hyperthermia) reduced tumor growth, while dual treatment resulted in complete tumor regression, caused by heat-induced tumoral cell apoptosis and massive denaturation of the collagen fibers, and a long-lasting thermal efficiency over repeated treatments.

4.7 Quantum dots

4.7.1 General characteristics and synthetic aspects

Within the particle size of 2–100 nm, quantum dots (QDs) possess excellent tunable optical and passive-targeting (EPR effect) properties [196–198]. Size, composition and shape of QDs can be strictly regulated by the reaction temperature and choice of surfactants and precursors to give a number of QDs with a distinctive set of optical properties. Compared with traditional organic dyes, most of the

QDs are semiconductor nanocrystals that could show better optical properties [199, 200]. They are featured with broad absorption and narrow emission spectra, and their emission maxima can be tuned between 450 and 850 nm through modulating their particle size. Recent developments in QD technology have already made a remarkable impact on cancer therapies.

The synthesis of QDs was first precipitated from a solution that contains metal ions (Cd, Ag, Pb, Hg, Zn, In) by adding into a hydroxide of S, Se, or Te [201]. In the preparation process of QDs, the size, shape, homogeneity and the surface structure need to be controlled, which are imperative for their unique properties mentioned above. Traditionally, trioctylphosphine oxide (TOPO) and trioctylphosphine (TOP) are used as coordinating solvents to stabilize the particles and protect from agglomeration.

4.7.2 Quantum dots for imaging

In the past decade, QDs have been explored as an excellent probe in cancer research due to the optical advantages [202–206]. Compared to conventional dyes, they are brighter, which means a very small number of QDs are sufficient to produce a signal, which is more photostable, affording for the acquisition of images after long periods of time and have a broader excitation spectrum. Furthermore, QDs could also be made to emit in the near-infrared window of the spectrum, where autofluorescence is considerably reduced and where no good dyes exist.

Rakovich et al. [207] prepared antibody-QD conjugate for detecting HER2 biomarker in breast and lung cancer cells. QD-based nanoprobes were applied for immunolabeling of breast and lung cancer cell lines via conjugating with single-domain anti-HER2 antibodies. The antibody-QD conjugates exhibited a superior staining efficiency in a panel of lung cancer cell lines with differential HER2 expression. In another study, Ye et al. [208] synthesized ZnO QDs for imaging and treating mouse tumors while showing no obvious toxicity on the body itself. ZnO QDs were synthesized and covered with polymer shells for the coordination with Gd^{3+} ions and adsorption of DOX to form ZnO-Gd-DOX QDs. This kind of QDs exhibited strong red fluorescence and possessed a high longitudinal relaxivity, superior to many other Gd^{3+}-based nanoplatforms. Thus, except for effective drug delivery, fluorescence labeling and magnetic resonance imaging could be acquired simultaneously in the tumor-bearing mice as well. Kong et al. [209] designed a kind of PbS QDs, which encapsulated ribonuclease-A (RNase-A) for ultrasensitive fluorescence *in vivo* imaging in the second NIR region of the spectrum. Confirmed by the quantum yield (Φ_f) measurement, this PbS-based QDs were proven to be one of the brightest emitters in the second NIR region. The high Φ_f (~17.3%) and peak emission at ~1300 nm contributed to deep optical penetration to muscle tissues and superb imaging contrast at an ultra-low dose.

4.7.3 Quantum dots for photodynamic therapies

In previous research, QDs have proven to be successfully applied in PDT, and they could act as either photo-sensitizers, themselves, or an activator for another photo-sensitizer by providing energy [210]. They can match any PDT photosensitizer via changing their size and composition and used as an energy supplier.

Morosini et al. [211] reported the preparation of CdTe(S)-based hydrophilic QDs used as photosensitizers in the PDT of cancer. This kind of QDs were conjugated with folic acid for active targeting, and they can emit in the NIR region. The results showed significant difference in photodynamic efficiency between KB (overexpression of FR-α) and HT-29 cells (lacking FR-α) when the folic acid-conjugated QDs were evaluated. Besides, an enhanced photocytotoxicity effect was achieved under optimal conditions, demonstrating that this kind of QDs could be applied in targeted PDT. In 2015, Martynenko et al. [212] reported an effective reagent for photodynamic therapies, which was based on chlorin e6-ZnSe/ZnS QDs. Compared with chlorin e6 molecules, as shown by the PDT test, the effect of the complexes on the Erlich acsite carcinoma cell culture showed a two-fold enhancement of the cancer cell photodynamic destruction.

4.7.4 Quantum dots for drug and gene delivery

Because of the appropriate particle size, QDs could also be designed for simultaneous drug delivery, particularly for antitumor drug or gene delivery [213–216]. For example, Li et al. [217] designed multifunctional QD-based complexes for the co-delivery of DOX and siRNA into multidrug resistance tumor cells and realized real-time tracking. The complexes were composed of two kinds of QDs, CdSe and ZnSe, which were modified with β-CD in order to couple L-Arg or L-His. The complexes then were used to simultaneously deliver DOX and siRNA, which could target the *MDR1* gene, thus, realizing the reverse of the multidrug resistance of HeLa cells. Compared with free DOX, after treatment with the complexes, the number of apoptotic HeLa cells was greatly increased. Besides, this kind of

system could be tracked by laser confocal microscopy due to the QDs' intrinsic fluorescence. In another study, Zhu et al. [215] synthesized a system based on QDs for the delivery of HIF-1α siRNA into tumor cells. In this novel system, CdTe QDs were used as the core and covered by a functional shell, which was composed of 2-deoxyglucose (DG)-PEG. Besides, the compound of lipoic acid, lysine and 9-poly-D-arginin were connected with 2-deoxyglucose (DG)-PEG through a hydrazone bond. Results obtained in both *in vitro* and *in vivo* experiments demonstrated that this kind of delivery system could highly improve the delivery efficacy of the siRNA into tumor cells.

5 Conclusions

Nanomedicine, as a promising tool for cancer therapy, has received tremendous attention and yielded a great number of medical benefits. Recently, various kinds of nanomaterials, which could exhibit better cellular uptake, tumor site specificity, and prolonged circulation time after surface modification, have been investigated for imaging, diagnosis and treatment of cancers. Additionally, on account of their high surface area/volume ratio, nanomaterials can load numerous therapeutic drugs, which are delivered to tumor tissues via the EPR effect after penetrating into the leaky tumor vasculatures. Owning to these advantages, nanomaterial-based therapeutics have exhibited comparable or even superior anticancer efficacy to commercial formations, while displaying reduced side effects, providing new strategies to fight against carcinomas.

In this review, a variety of nanomaterials were presented including polymeric NPs, liposomes, dendrimers, polymeric micelles, polymer-drug conjugates, silica NPs, carbon nanotubes, nanographene, magnetic NPs, AuNPs and quantum dots. The investigation of these nanomaterials through improving their structure and cellular targeting ability has provided a more efficacious therapeutic delivery. Most of these works have shown great potential to create life-altering nanomedicine therapies for clinical cancer therapy. There are already some novel nanomaterial-based formations approved for cancer therapies available commercially, such as Abraxane, Doxil, and Embosphere, etc.

Despite excellent advantages, the successful translation of nanomaterial-based therapeutics into clinical practice still has many concerns and challenges including biocompatibility, pharmacokinetics and *in vivo* targeting efficacy. The most important concern would be nanomaterial toxicity and potential health risks, as little is known about how they behave in humans. Of all the nanomaterials discussed in this review, liposomes are the most developed, are clinically approved and currently possess the greatest number of clinical trials with some formulations already available in the marketplace, while many other nanomaterial-based formulations, especially inorganic ones, have not received such approval and success. This is probably due to the biocompatibility of the other nanomaterials that have not been investigated for the same duration in comparison with liposomes. A variety of nanomaterials are not biodegradable and may be retained inside the body for long periods of time after administration. The development of biocompatible and biodegradable nanomaterials for cancer therapy could, thus, have a much higher clinical value.

Although nanomaterials still have a number of technical limitations on clinical translation, they provide us with a direction for cancer therapy. There is good reason to believe that, in the near future, clinically featured nanomaterials will be developed, which will be followed with well-designed clinical trials to demonstrate their practical usage in clinical settings.

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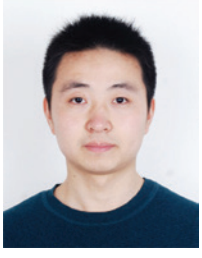

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