REVIEW ARTICLE

# Research Progress of Nanomaterials in Chemotherapy of Osteosarcoma

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Osteosarcoma (OS) is a common malignant bone tumor that occurs mostly in children and adolescents. At present, surgery after chemotherapy or postoperative adjuvant chemotherapy is the main treatment plan. However, the efficacy of chemotherapeutic drugs is limited by the occurrence of chemotherapeutic resistance, toxicity to normal cells, poor pharmacokinetic performance, and drug delivery failure. The delivery of chemotherapy drugs to the bone to treat OS may fail for a variety of reasons, such as a lack of selectivity for OS cells, initial sudden release, short-term release, and the presence of biological barriers (such as the blood-bone marrow barrier). Nanomaterials are new materials with at least one dimension on the nanometer scale (1–100 nm) in three-dimensional space. These materials have the ability to penetrate biological barriers and can accumulate preferentially in tumor cells. Studies have shown that the effective combination of nanomaterials and traditional chemotherapy can significantly improve the therapeutic effect. Therefore, this article reviews the latest research progress on the use of nanomaterials in OS chemotherapy.

**Key words:** Antineoplastic Agents; Drug Delivery Systems; Nanostructures; Osteosarcoma; Targeted Therapy

## Introduction

Osteosarcoma (OS) is a malignant bone tumor that originates from mesenchymal tissues and usually occurs in the metaphysis of long bones, such as femurs and tibias.[1,2] OS is more common in children, adolescents and the elderly.[3] It is mainly a secondary condition caused by Paget's disease or other bone lesions.[4,5] Due to the introduction of chemotherapy and advances in surgical techniques, the overall survival rate of patients with OS has significantly improved from 20% to approximately 70%.[6,7] When there is local recurrence of invasion and metastasis to respiratory organs, the 5-year survival rate is often less than 20%, which is also one of the factors accounting for the poor prognosis and high mortality associated with this condition.[8,9]

The conventional treatment for OS is comprehensive, that is, surgical treatment combined with chemotherapy. Chemotherapy has become a crucial type of clinical treatment for OS.[10,11] However, there are many reasons that chemotherapy drug delivery in conventional chemotherapy may fail, such as the poor pharmacokinetic performance of powerful anticancer drugs such as cisplatin (CDDP), doxorubicin (DOX) and paclitaxel (PTX); toxic effects on normal cells; and a lack of sensitivity and selectivity to OS cells. In addition to the low rate of encapsulation of drugs by the vehicle, it is difficult for the drug to reach the tumor site through biological barriers (such as the blood-bone marrow barrier), which ultimately reduces the efficacy of chemotherapy.[12–16] In addition, the efficacy of chemotherapy is affected by multidrug resistance (MDR), which may lead to the recurrence or progression of OS to a certain extent.[17–20] Therefore, improving conventional chemotherapy is an important way to improve the survival rate of patients with OS.

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In recent years, nanomaterials have been widely used in drug delivery research due to their good biocompatibility, biodegradability, and responsive release, making them suitable carriers for overcoming the pharmacokinetic limitations of conventional chemotherapeutics.[21–24] Nanomaterial-based chemotherapy, photodynamic therapy, photothermal therapy, immunotherapy, nucleic acid therapy, targeted therapy, antiangiogenic therapy and acoustic dynamic therapy have been used for cancer treatment.[25–27] A variety of nanomaterials from man-made and natural sources, such as polymer nanoparticles, carbon-based nanomaterials, mesoporous silica nanoparticles, metal nanomaterials, extracellular vesicles and quantum dots, are involved in these therapies.[22,28] Endogenous nanomaterials can effectively compensate for the side effects and treatment failure caused by exogenous nanomaterials due to the interaction of nanoproteins and the induction of adverse immune reactions.[29] Targeted delivery is also one of the advantages of nanomaterials for cancer treatment. These materials can protect drugs from degradation, increase the half-life of drugs, deliver drugs to specific tumor cells and reduce the toxicity of drugs to normal cells by active or passive targeting. In active targeting, tumor cells are targeted by coupling small molecules, antibodies and other ligands, whereas the enhanced permeability and retention (EPR) effect of nanomaterials is a type of passive targeting.[30–37] With the advent of nanomaterials, the disadvantages of conventional chemotherapy and other existing therapies can be effectively remedied. Therefore, exploring new methods for the delivery of chemotherapeutic drugs based on nanomaterials can provide new ideas and targets for overcoming the deficiencies of conventional chemotherapy in OS.

Nanomaterials can be divided into two types: organic and inorganic (Figure 1). The most researched organic nanomaterials to date mainly include lipids, polymers and carbon-based materials. Inorganic nanomaterials mainly include mesoporous silica, calcium-based materials and metal materials. Typical nanomaterials share several common characteristics: (1) enhanced permeation and retention effects; (2) reduced toxicity of chemotherapeutic drugs; (3) controlled drug release; (4) high surface-to-volume ratio; and (5) ease of surface modification.[22] However, nanomaterials also have their own unique properties due to differences in composition and structure. Organic nanomaterials have been shown to have high biocompatibility and biodegradability for chemotherapeutic drug delivery. Among them, liposomes can encapsulate both hydrophilic and hydrophobic drugs, polymers have high drug encapsulation rates, and carbon-based materials have high drug loading capacity and unique optical properties. Among inorganic nanomaterials, mesoporous silica has the advantage of a large pore size, and calcium-based materials have high hardness and promote bone regeneration. Metal materials are divided into metal oxides and pure metal particles. Metal oxides can induce the production of reactive oxygen species in tumor cells, and pure metal nanoparticles have excellent optical and electrical characteristics. Since it is usually difficult for a single type of nanomaterial to have multiple functions, composite nanomaterials composed of different types of materials have greater development potential.[38]

## Organic Nanomaterials

### *Lipids*

Lipid nanoparticles (LN) have good biocompatibility and high drug encapsulation efficiency and can deliver lipophilic and hydrophilic drugs. Compared with conventional chemotherapy,

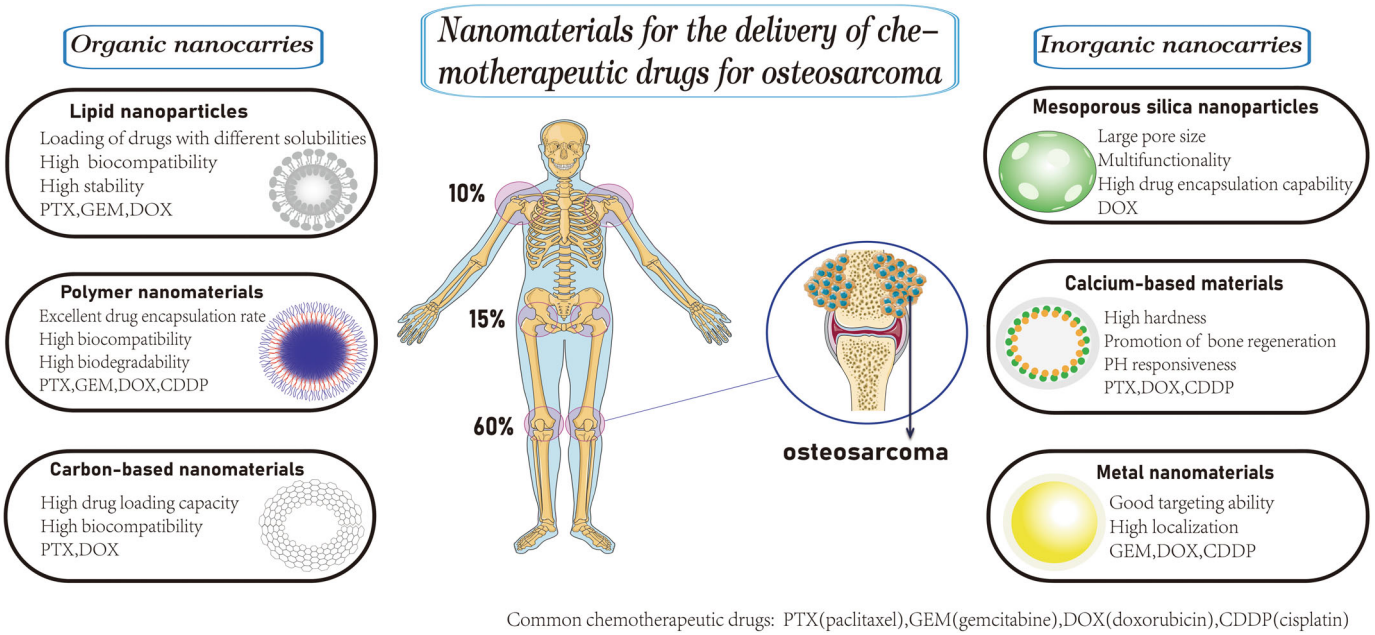


**FIGURE 1** Different categories of nanomaterials for delivering common chemotherapy drugs for OS.

the use of LN as a carrier enhances the uptake of chemotherapeutic drugs by OS cells, thus reducing the minimum effective drug concentration and making it easier to overcome drug resistance.[39,40] Liposomes were the first generation of lipid nanoparticles to be produced and one of the first nanoscale drug delivery vehicles. Excitingly, many liposome-based chemotherapeutic agents have been approved for clinical use by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). Examples include PEGylated liposomal DOX (PLD) (brand names: US: Doxil® and Lipodox® (generic Doxil), Europe: Caelyx®), non-PEGylated liposomal DOX (Myocet®), vincristine sulfate liposome injection (Marq), vincristine sulfate liposome injection (Marqibo®) and irinotecan (IRI) nanoliposome (Onivyde™).[41] These clinically approved liposome formulations effectively reduce the blood and cardiac toxicity caused by free chemotherapeutic agents in the body and improve the biosafety of chemotherapeutic agents. With the improvement of preparation technology, new types of lipid nanoparticles, such as solid lipid nanoparticles (SLNs), lipid polymer hybrid nanoparticles (LPNs) and lipid core nanocapsules (LNCs), have been gradually developed and are expected to overcome the drawbacks of liposome technology.

*Liposomes*

Liposomes are spherical lipid vesicles with a bilayer structure composed mainly of natural or synthetic phospholipids. First discovered in lecithin liquid crystals, they have the ability to encapsulate solutes and release them selectively, an ability that forms the basis of the liposomal chemotherapeutic drug delivery system.[42] Different preparation methods can be used to prepare liposomes with different sizes and numbers of layers, and the resulting liposomes can be classified into multilayer vesicles (MLVs), large unilayer vesicles (LUVs) and small unilayer vesicles (SUVs). MLVs are usually prepared using the thin-film hydrophoresis method, which is very easy but suffers from a poor drug encapsulation rate.[43] To improve the drug encapsulation rate, LUVs have been developed. However, LUVs are large, and liposomes that are too large may be recognized and cleared by macrophages in the reticuloendothelial system, which in turn reduces the effective concentration and circulation time of drugs in the body.[44] SUVs can be prepared from MLVs and LUVs using ultrasound.[45] Due to the hydrophilic and hydrophobic nature of phospholipids, liposomes are also considered multifunctional drug carriers that can encapsulate both hydrophilic and hydrophobic drugs to achieve the synergistic effect of multiple chemotherapeutic drugs against cancer.[46] Hydrophilic chemotherapeutic drugs (e.g., gemcitabine, GEM) are encapsulated in the core part of the liposome, and hydrophobic chemotherapeutic drugs (e.g., clofazimine, CLF) are located in the lipid bilayer, a loading method that largely enhances the encapsulation rate of the carrier for chemotherapeutic drugs (more than 90% for GEM and more than 80% for CLF).[47] In addition, liposomes have a negatively charged hydrophilic surface layer, which can effectively inhibit phagocytosis of the drug-carrying system by macrophages during drug delivery, thus prolonging the circulation time of the chemotherapeutic drugs *in vivo* and improving the therapeutic effect of drugs in OS.[48,49] However, when liposomes enter the bloodstream, they can interact with plasma proteins, which can lead to deformation of the nanoparticles and leakage of the chemotherapeutic drugs.[50] To reduce the interaction of liposomes with plasma proteins, polyethylene glycol (PEG) is loaded onto the liposome surface. These PEG groups can induce liposome-cell membrane interactions and deliver encapsulated chemotherapeutic drugs to the cytoplasm for action.[47] Despite the many advantages of the PEG moiety, OS cells may have reduced uptake of liposomes with PEG due to the spatial site resistance of the PEG moiety. This can be overcome by modifications that confer liposome targeting ability. Wu *et al.* designed liposomes decorated with alendronate (ALN) and low-molecular-weight heparin (LMWH) for the delivery of DOX. ALN is used as a target ligand and selectively accumulates in bones, while DOX and LMWH can synergistically improve the antimetastatic efficiency. The combination of ALN and LMWH can significantly inhibit tumor progression.[51] Some studies have developed cationic nanoliposomes functionalized with the YSA peptide and PEG for the simultaneous delivery of DOX and siRNA. The YSA peptide is a ligand for the EphA2 receptor on the surface of OS cells, and siRNA targets JIP1 in OS cells.[52] The above studies were conducted by actively targeting bone or OS cells, thus improving the efficiency of the chemotherapeutic drug delivery system, but more studies are currently focused on diseases such as liver cancer and breast cancer, and active targeting strategies applied to OS still need more attention and development.[53,54] In addition to the above methods of active targeting, passive targeting can also be employed to take advantage of the properties of the OS anatomy for chemotherapeutic drug delivery to accumulate drugs specifically at the OS cell site. Such passive targeting relies on EPR effects, that is, the property that nanosized molecules such as liposomes tend to aggregate in tumor tissues with abundant blood vessels, wide vessel wall gaps, and poor structural integrity compared to normal tissues.[55] Passive targeting lays a good foundation for active targeting. The proposed targeting provides many advantages for liposome delivery of chemotherapeutic agents, but their internalization pathways and ultimate sites of action are still unknown, and this is a needed direction for future research. In addition to the above pathways, we can also design liposomes that respond to specific stimuli for chemotherapeutic drug release. pH sensitivity and temperature sensitivity are two common approaches, and factors such as redox sensitivity, enzyme sensitivity and magnetism can also be investigated for controlled chemotherapeutic drug release.[56.57]

*Other Systems Based on Lipids*

To overcome the shortcomings of liposomes, a new generation of lipid nanoparticles has been developed, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers

(NLCs) and lipid polymer hybrid nanoparticles (LPNs).[58,59] Among them, NLCs can compensate for the burst release of chemotherapeutic drugs by SLNs, but unfortunately, there are fewer existing studies on the loading of chemotherapeutic drugs by SLNs and NLCs for OS. LPNs are the latest development in the field and have the properties of both liposomes and polymeric nanoparticles. Liposomes provide high bioavailability and compatibility, while the polymer core provides stability and controlled release, effectively overcoming the drawbacks of liposomes that are unstable in fluidic environments.[60] Wang *et al.* developed lipid core nanocapsules (LNCs) loaded with ifosfamide to induce apoptosis in OS cells by increasing the expression levels of caspase-3 and caspase-9 in MG-63 OS cells. OS cells take up LNCs *via* endocytosis, which may lead to accelerated destruction of acidic endolysosomal vesicles and subsequent release of the drug into the cytoplasm.[61] Duan *et al.* used LPNs to deliver both paclitaxel (PTX) and etoposide (ETP) for the combined treatment of OS. Both PTX and ETP were stably loaded in the hydrophobic PLGA core and lipid structure. In addition, a protective lipid layer formed by 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol) improves the encapsulation efficiency, and polyethylene glycol (PEG) is responsible for stabilizing the hybrid nanoparticles.[62] In particular, functionalized modification of LPNs with different moieties or ligands (e.g., folic acid, transferrin) can confer the ability to actively target OS cells to increase the uptake and absorption of nanoparticles containing chemotherapeutic agents by OS cells.[63,64] In addition to nonspecific targeting ligands, which are common to various tumor cells, specific targeting ligands on LPNs can be designed for OS cells. Researchers have developed LPNs with CD133 ligands for drug-targeted delivery to CD133+ OS stem cells in hopes of curing OS 51 at the root.[65] Interestingly, differentiated cancer cells can be transformed into OS stem cells. Therefore, a study has again addressed this phenomenon by adding CL4, which targets EGFR+ CD133- OS cells, to achieve dual targeting of CD133- and CD133+ OS cells.[66] This design has many advantages, but it also has some drawbacks, especially since hematopoietic stem cells also have CD133 receptors, so targeting OS stem cells may be potentially toxic to hematopoietic stem cells as well. Many scholars now believe that lipid nanoparticles, which do not have proteins in their bilayer phospholipid structure, are not immunogenic in principle and are a safe drug-carrying nanomaterial. However, the size and shape of lipid nanoparticles are very similar to those of the pathogenic microorganisms targeted by the innate immune system, which means that lipid nanoparticles can activate the complement system and have the potential to cause adverse reactions in OS patients; thus, relevant personnel are needed to investigate specific methods to prevent these adverse reactions.[67]

### *Polymers*

In recent years, polymeric nanoparticles (PNPs) have received more attention for the targeted delivery of chemotherapeutic agents for OS. Natural polymers such as chitosan, hyaluronic acid, alginate, and dextrin have shown good biocompatibility and biodegradability, thus increasing the therapeutic effect with minimal side effects.[68–70] Synthetic polymers include nanoparticles based on poly(anhydride), poly(3-hydroxybutyrate-3-hydroxyvaleric acid) (PHBV) and poly(lactic acid) (PLA).[71] In addition, polymer micelles are a new generation of polymer nanocarriers.

#### *Natural Polymers*

Natural polymers have been widely used in the delivery of chemotherapeutic drugs because of their high biodegradability and low toxicity. Because natural polymers originate from nature, they are very diverse, including polysaccharides such as chitosan (CS), hyaluronic acid, and dextrin and proteins such as keratin, gelatin, and soy. CS is the most widely used natural polymer. The amine group located on its backbone gives chitosan its cationic properties, allowing it to interact with anionic components such as nucleic acids and cell surface macromolecules, resulting in rapid cellular uptake.[72,73] However, the study of CS as a cationic nanopolymer is still limited by its insolubility in water and most organic solvents under physiological pH conditions. To broaden the application range of CS, N-trimethyl chitosan (TMC) was developed to maintain good water solubility and adjustable biodegradability over a wide pH range.[74] The presence of the primary hydroxyl and amine groups on the CS backbone allows functionalized modification of CS to other carriers, which increases its overall value.[75] For example, the drug loading rate of nanocarriers can be improved for chemotherapeutic drugs. Yang *et al.* designed pH-responsive mesoporous ZSM-5/CS core-shell nanodiscs loaded with DOX. The interaction of the mesoporous structure of ZSM-5 zeolite and CS functional groups resulted in high drug loading performance. zSM-5/CS/DOX nanosheets were effective in releasing DOX after endocytosis by OS cells and inducing OS cell apoptosis.[76] The high positive charge on CS endows it with mucosal adsorption properties, which enhances the *in vivo* residence time of the agent in the gastrointestinal tract and effectively improves the bioavailability of chemotherapeutic drugs.[72,73] In addition, the accumulation of other nanocarriers using chitosan functional modification in the heart is significantly less, which can effectively reduce the cardiotoxicity of chemotherapeutic drugs and increase the deposition of chemotherapeutic drugs in the effective site.[76] In contrast to CS, hyaluronic acid (HA) is a linear glycosaminoglycan with a negative charge at physiological pH. HA helps to reverse the surface charge of nanoparticles, avoiding nonspecific uptake by the body caused by the positive charge and thus prolonging the circulation time of nanoparticles in the body.[77] HA also has bioadhesive properties and can bind to a variety of cell receptors. Notably, the CD44 receptor, which is highly expressed on OS cells, can specifically bind to HA, thus effectively blocking the proliferation and metastasis of OS cells.[78] Xu *et al.* synthesized organic–inorganic hybrid nanoparticles consisting of an HA-PEG polymer shell and a nanohydroxyapatite (nHA) core for

loading the chemotherapeutic adjuvant zoledronic acid. HA can target OS cells in the organism, and nHA improves the drug loading rate, thus reducing the rapid elimination of chemotherapeutic drugs by the kidney.[79] Although HA can specifically bind OS cells, it still causes cytotoxicity at high doses. To address this issue, a self-stabilized hyaluronic acid nanoparticle has been synthesized that can be used to deliver chemotherapeutic agents such as DOX and CDDP, effectively alleviating the adverse effects caused by high doses.[80] In addition, since the molecular weight of HA may be related to the immune response, low-molecular-weight HA is more likely to induce an immune response in the body, so attention should be given to the validation of its biosafety when HA is undergoing clinical translation and development. Keratin is a cysteine-rich structural protein, and keratin-based nanoparticles have higher stability and lower solubility than other protein-based natural polymers. There are unique tripeptide sequences on the keratin backbone, such as the Arg-Gly-Asp (RGD) and Leu-Asp-Val (LDV) sequences, which can bind to the highly expressed vitronectin integrin receptor of OS cells and have the potential to target OS cells. The poor water solubility of paclitaxel (PTX) can also be addressed by functionalized keratin-based nanoparticles. Recent studies have found that simultaneous delivery of PTX and the photosensitizer Chlorin-e6 using keratin-based nanoparticles is very effective against drug-resistant Saos-2/DX580 OS cells that tend to overexpress p-glycoprotein.[81] Natural protein polymers, which are relatively inexpensive and readily available, have attracted the attention of researchers in recent years, but unfortunately, no keratin-based nanoformulations are currently available for clinical use. Despite the many advantages of natural polymers as drug carriers over free drugs, the use of natural polymers remains challenging because of their wide molecular weight distribution and batch-to-batch variability, which represents a difficulty in ensuring that each batch of carriers produces the same efficacy and has controlled side effects.

*Synthetic or Hybrid Polymer Systems*

Although most natural polymers have the advantages of a high encapsulation rate and improved efficacy, they still have disadvantages such as a low drug loading rate, minor hepatotoxic effects and insolubility under physiological pH conditions.[82] One of the primary issues that needs to be addressed is its extremely low drug loading capacity for chemotherapeutic drugs, which largely affects the research and clinical applications of synthetic polymers. Encapsulation of chemotherapeutic drugs into the core of polymer-based nanoparticles is currently the conventional method for drug encapsulation. Drugs loaded using conventional encapsulation methods typically account for a low percentage of active ingredients on a mass basis due to the limitations of the high percentage of inactive agents inherent in synthetic polymer-based nanoparticles themselves. However, this does not mean that there is no way to solve the problem. If the active drug is incorporated as a repeating unit of the synthetic polymer-based nanocarrier during the preparation process, in principle, the drug loading capacity can be greatly enhanced.[83] Heyder *et al.* chemically modified gemcitabine (GEM) with a hydrolyzable linker and incorporated it as a repeating unit in a poly(anhydride ester) backbone. Each poly-GEM chain could incorporate an average of 26 GEM molecules, corresponding to a drug loading capacity of up to 58% w/w.[84] Polymers using a poly(anhydride ester) backbone can undergo that not only hydrolysis reactions release the chemotherapeutic drug completely but also complete biodegradation within the body itself. Targeted drug delivery systems are one of the most important tools to focus chemotherapeutic drugs on OS cell areas to reduce side effects. Currently, most targeted polymeric nanoparticles are actively targeted to the surface of OS cells, which is still a limitation for the efficacy of nucleus-acting chemotherapeutic agents such as DOX.[85] Several studies have modified poly(3-hydroxybutyrate-3-hydroxyvaleric acid) (PHBV) particles with nuclear targeting peptides to target the nuclear membrane of Saos-2 OS cells. The loaded DOX was released at the nuclear membrane and, after penetrating the nuclear membrane, induced apoptosis by promoting DNA cleavage and massive production of hydrogen peroxide.[86] Hydrogels are a network of water-soluble polymers that are able to respond to external stimuli (e.g., temperature, pH, and sound) with a volumetric phase change that enables stimulus-responsive drug delivery. The local release of chemotherapeutic drugs can be remotely controlled by embedding nanoparticles into the hydrogel and giving additional signals (e.g., magnetic field or light).[87] For example, if magnetic nanoparticles (MNPs) are wrapped in the shell of a stimulus-responsive hydrogel and then incorporated into gelatin, then the release of the resulting agent is dependent on the magnetic field.[88] In addition, reducing the initial burst of drug release is essential for controlled chemotherapeutic drug release. It was found that incorporating drug-loaded nanoparticles that can prolong the drug release rate into hydrogels containing silk fibroin (SF) can achieve pH-controlled sustainable drug release and make the drug delivery system safer in the bloodstream.[89] Site-specific targeted delivery of chemotherapeutic agents can be achieved by developing hydrogels modified with targeting ligands capable of binding specifically to OS cell sites. One study used sarcoma-targeting peptide-modified disulfide-bonded peptide nanogels to deliver shikonin (SHK), which can actively target and inhibit 143B OS cell proliferation and lung metastasis by inducing RIP1- and RIP3-dependent apoptosis.[90] Moreover, the high concentration of glutathione in the microenvironment of OS cells can break disulfide bonds in nanocarriers to release chemotherapeutic drugs, allowing drug release to be simultaneously regulated by passive targeting.[91] Although hydrogel-associated nanoparticles have great potential to improve the efficiency of chemotherapeutic drug delivery, they still face challenges in clinical translation. This is because hydrogels are prone to premature gelation within syringe needles at lower polymer concentrations and narrower gel temperatures, posing

the risk of syringe clogging. Notably, the presence of other entities should be removed during the preparation of synthetic or conjugated polymers to prevent toxic biological effects. Therefore, it is very important to choose the proper preparation route and purification steps during the preparation process.

*Polymer Micelles*

Self-assembly of amphiphilic block copolymers in water allows the formation of thermodynamically stable polymer micelles (PMs). The amphiphilic polymer in the structure gives PM the ability to deliver hydrophobic drugs such as arsenic and the chemotherapeutic adjuvant curcumin (Cur), thus significantly improving the efficacy of hydrophobic drugs.[92,93] For PM with a shell-core structure, the hydrophobic core can be loaded with hydrophobic chemotherapeutic drugs, and the external hydrophilic corona can impart overall hydrophilicity to the nanocarrier and provide greater stability between the hydrophobic core and the external environment. PEG is the most versatile corona-forming polymer block used to effectively shield the hydrophobic core and prevent chemotherapeutic drug-carrying PM from being recognized by the reticuloendothelial system (RES) and carried to the liver and spleen for clearance.[94] In addition, we can tailor polymeric micellar nanocarriers with different surface charges and sizes to better meet the loading requirements of different kinds of chemotherapeutic drugs by varying the number of monomers in each polymer chain and adjusting the mass ratio of functionalized glucose-derived polycarbonate and near-infrared (NIR)-labeled nonionic polymers.[95] PMs synthesized using different block copolymer assemblies have their own unique chemotherapeutic drug delivery properties. For example, sulfur dioxide ($SO_2$) polymeric prodrug nanoparticles can self-assemble into micelles in water and release $SO_2$ in a reduced intracellular environment, which induces oxidative stress from oxidative damage in OS cells by elevating the reactive oxygen species (ROS) levels in K7 OS cells, thereby synergizing with chemotherapeutic drugs against cancer.[96] Although PM for the delivery of chemotherapeutic drugs already offers many advantages, its clinical application is limited by the early release of the drug and incomplete release from the target site. Therefore, stimulation sensitivity has been introduced into PM systems to improve nanocarrier-mediated targeted drug release and delivery by effectively releasing the drug from the micellar core, thereby enhancing therapeutic efficacy. UV light, reducibility, acidity, temperature, pH and ionic strength are among the various stimuli that have been explored.[97] Chen *et al.* used UV-sensitive amide bonds attached to PEG to form polymeric micelles to deliver DOX. After enrichment to the OS region by the EPR effect, the amide bonds were broken by UV irradiation, and the target PEG was shed, which in turn induced DOX uptake by OS cells.[98] Li *et al.* encapsulated DOX and PTX in a PEGylated poly(α- lipoic acid) copolymer (NP-TX-DOX), resulting in the synthesis of a dual-reactive PM with reducing and acidic properties. NP-PTX-DOX could be effectively internalized by K7 OS cells to release the drug, showing synergistic therapeutic effects. In a mouse OS model, NP-PTX-DOX exhibited better biodistribution and tumor growth inhibition than the control group[99] (Figure 2). Notably the abovementioned properties of PM, combined with the results of current experimental studies, can inhibit the multidrug resistance of OS cells to chemotherapy drugs, which is very exciting information. There is a considerable amount of preclinical research on PM-loaded chemotherapeutic agents, and stability and the need for specific characterization are the two most important barriers to the translation of PM to the clinic. The manufacturing, quality characteristics, stability, pharmacokinetics and pharmacodynamics of PM should be appropriately validated for faster clinical application.

***Carbon-Based Materials***

Carbon-based nanomaterials, such as graphene oxide (GO), mesoporous carbon particles and carbonaceous systems, have been widely used in many fields due to their high biocompatibility, large surface area and unique optical properties compared to metallic materials. Graphene-based nanomaterials have been extensively investigated for chemotherapeutic drug delivery and, due to their unique physicochemical properties, can host both chemotherapeutic drug delivery and bioimaging for OS therapeutic diagnostic applications.[100] The large surface area and conjugated structure of GO promote strong π-π stacking between drugs, which increases the loading of chemotherapeutic drugs. Huang *et al.* constructed a high-drug-loading NP consisting of GO, PEG, folic acid (FA) and a photosensitizer indocyanine green (IGG) conjugate. GO exhibits a photothermal effect upon 808 nm NIR radiation, FA is a targeting agent, and this carrier can exert a chemophotodynamic effect in OS.[101] Further innovation based on graphene nanomaterials resulted in graphene-related polymers, which have the advantages of both graphene and polymers.[102] Such nanocarriers often have multiple functional groups, such as hydroxyl (–OH), carboxylic acid (–COOH) and amine ($–NH_2$), which further improve the loading efficiency (LE) of the carrier for chemotherapeutic drugs.[103] The side effects of the chemotherapeutic drug DOX, which include cardiotoxicity and drug resistance, can be addressed by using magnetic nanoparticles to target chemotherapeutic drug transport into OS tissue under the action of an external magnetic field.[104] Niu *et al.* designed an $Fe_3O_4$-functionalized graphene-dendrimer system as a magnetic nanocarrier for dual delivery of DOX and the chemotherapeutic adjuvant melatonin (MLT). This system has the advantages of many functional groups, pH response and high drug loading. The MLT-loaded nanocarriers can be taken up by OS cells through endocytosis. Notably, MLT can reduce the cardiotoxicity and drug resistance of DOX.[103] For chemotherapeutic drugs with low lipophilicity, improving the overall lipophilicity is one way to promote drug efficacy. Borhan *et al.* synthesized a lipophilic and magnetic carbon dot-graphene composite for the

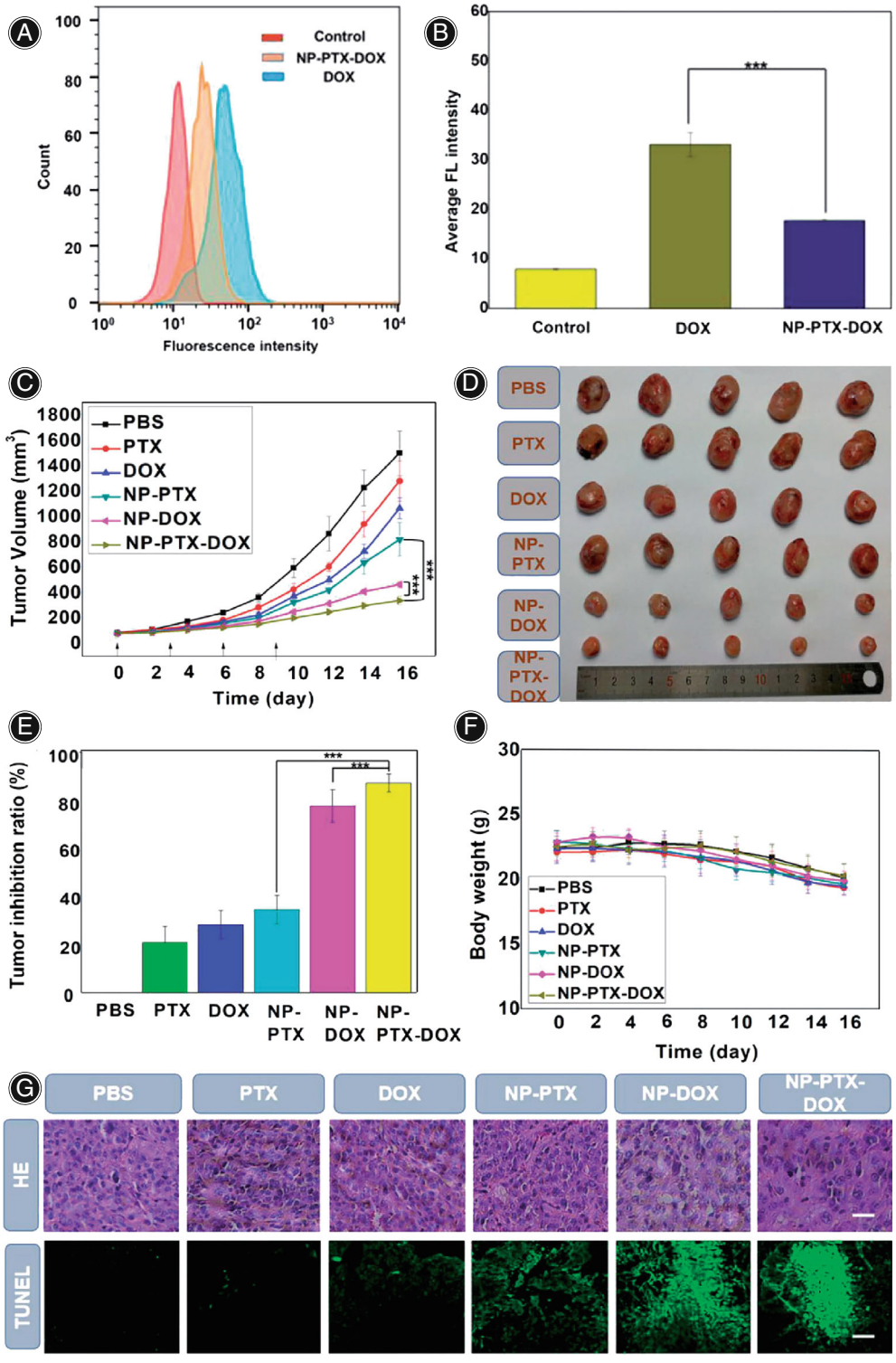


**FIGURE 2** Codelivery of doxorubicin and paclitaxel by reduction/pH dual-responsive nanocarriers for OS therapy. (a) Cellular internalization of DOX and NP-PTX-DOX incubated with K7 cells for 2 h at 37°C determined by flow cytometry. (b) Mean fluorescence intensity of K7 cells treated with DOX and NP-PTX-DOX for 2 h determined by flow cytometry. ***$p < 0.001$. Data are shown as the mean ± SD (n = 3). (c) Mean tumor volumes of K7 tumor-bearing mice after intravenous injection of PBS, free PTX, free DOX, NP-PTX, NP-DOX and NP-PTX-DOX on days 0, 3, 6 and 9 (2 mg·kg$^{-1}$ DOX, 4 mg·kg$^{-1}$ PTX). Data are shown as the mean ± SD (n = 5). (d) Images of the excised tumors from the mice treated as described in (c) on day 16. (e) Tumor inhibition ratios of the treated groups on day 16. (f) Change in body weights of K7 tumor-bearing mice during treatment. (g) H&E staining and TUNEL analyses of K7 tumors from the mice treated as described in (c) on day 16. ***$p < 0.001$. Scale bar = 100 μm. Reprinted with permission from Reference 99.

delivery of mitoxantrone by a rapid cooling-assisted sol–gel method, which effectively improved the lipophilicity of the chemotherapeutic drug, resulting in a 47% increase in MG-63 OS cell death after 24 h of treatment.[105] Mesoporous carbon nanoparticles have excellent biocompatibility and additional supramolecular π- (or pi-) stacking. This result in the unique advantage of loading fewer hydrophilic and aromatic chemotherapeutic drugs, thus providing superior loading capacity. However, under liquid conditions, mesoporous carbon can easily leak. To avoid this, reactive polymers can

be coated on its surface to close the pore entrance. For example, mesoporous carbon matrix systems with tert-butoxycarbonyl (BOC) molecules as the capping end have three times the drug loading capacity of mesoporous silica.[106] As the drug loading increases, the problem of biocompatibility arises. To solve this problem, it is necessary to find a balance between the concentration and drug loading of carbon-based nanomaterial drug delivery systems. Despite the significant advantages of carbon-based nanomaterials for loading aromatic chemotherapeutic agents with low lipophilicity, low hydrophilicity, and high side effects, there are still some challenges in their preparation. Since the structure of carbon-based nanomaterials is usually inhomogeneous, which hinders the establishment of standard preparation and functionalization methods, further exploration is needed in terms of preparation methods and evaluation of efficacy experiments for OS cells.

## Inorganic Nanomaterials

### *Mesoporous Silica*

Mesoporous silica nanoparticles (MSNs) have the advantages of an ordered porous structure, good biocompatibility, a large pore size, a high surface area, and an adjustable particle size. Moreover, it is easy to modify the surface to achieve functions such as targeting and responsiveness.[107] MSNs are used to treat malignant tumors such as OS and for diagnosis, resulting in a therapeutic diagnostic platform that combines diagnosis and cotreatment. Zhou *et al.* synthesized metal manganese-doped ALN-targeted modified gold-core mesoporous silica nanoparticles for DOX delivery, integrating bone-targeted chemistry-chemodynamic combination therapy and CT/MR imaging into one platform. Diagnostically, the accumulation of $Mn^{2+}$ and gold nanoparticles (AuNPs) in tumors facilitates imaging; therapeutically, their entry into OS cells is followed by redox reactions with high concentrations of glutathione (GSH) and Mn-O frameworks. On the one hand, this promotes the biodegradation of materials, and on the other hand, the generated $Mn^{2+}$ can convert $H_2O_2$ into toxic ·OH through a Fenton-like reaction.[108] In addition, the porous structure of MSNs can store large amounts of chemotherapeutic drugs and can accumulate in the tumor tissue for passive targeting. Yao *et al.* found that MSN-coated bismuth sulfide nanoparticles covalently bound to RGD peptide delivered DOX with a better encapsulation efficiency (99.85%) and enabled photothermal therapy combined with chemotherapy to enhance the eradication of OS cells through the mitochondrial apoptosis pathway. Among them, $Bi_2S_3$ provides NIR responsiveness for CT imaging and RGD peptide for targeting OS cells.[109] Considering that excessive UV radiation may cause some damage to the human body, the use of a siliconized porphyrin cap to block MSNs can make them responsive to visible light.[110] MSNs can perform various functions through surface modification, which will greatly expand their application. An MSN nanodevice containing a pH-responsive polyacrylic acid shell and the targeted lectin concanavalin A was used for efficient chemotherapeutic drug delivery. It was internalized twice as much in human OS cells as in human preosteoblasts and showed an 8-fold increase in antitumor effect compared to free drugs.[111] However, most MSN particles were discontinued before clinical studies. Thus, there is a need not only for long-term establishment of various pharmacological and toxicological studies for humans but also for the exploration of reproducible pathways for synthesizing nanomaterials and reducing errors between batches to ensure stability.

### *Calcium-based Materials*

*Calcium Phosphate Material*

Hydroxyapatite (HAp) is the most widely used bone tissue nanocarrier among calcium phosphate nanomaterials, and it has high biocompatibility and good biodegradability because calcium phosphate is an inorganic mineral within human bones and teeth. For drug delivery, it fulfills many important requirements for efficient delivery systems, namely, the ability to incorporate drugs or biomolecules on physically or covalently bound internal and external surfaces and the ability to retain such biomolecules until the particles reach the target site and dissolve, as well as its inherent biodegradability (calcium and phosphate ions).[112,113] Liu *et al.* used HAp, bovine serum albumin (BSA) and PTX to form a ternary delivery system, which has sustained release properties of PTX and calcium ions ($Ca^{2+}$) and low cytotoxicity. *In vitro* and *in vivo* experiments have shown that it can block the G2/M cycle to inhibit tumor metastasis and the proliferation and invasion of 143B OS cells.[114] To optimize the potential of HAp, trace elements such as zinc, iron, potassium, and sodium can be mixed into the ternary drug delivery system. Sarda *et al.* explored the interaction between the drug and nanocrystalline apatite (HA) and the drug and iron-doped superparamagnetic apatite (FeHA) and found that FeHA has a stronger adsorption affinity for drugs, while HA can release drugs rapidly; both complexes have good biocompatibility.[115] Studies have shown that the incorporation of mesoporous zinc into HAp can adjust its physicochemical properties, and the massive accumulation of zinc in tumor cells can induce cell apoptosis. For example, researchers covalently bonded methotrexate (MTX) and F127 on the surface of mesoporous ZnHAP to form MTX-F127@ZnHAP nanoparticles. The nanoparticles are mainly internalized by cells through clathrin-mediated endocytosis. If the clathrin-mediated pathway is hindered, caveolae-mediated endocytosis can be used as an alternative pathway for nanoparticle uptake.[116] In addition, functional modification can endow HAp with properties such as targeting and colloidal stability. Wu *et al.* found that loading the inhibitor JQ1 used to deliver the bromodomain to HAp allows delayed release of JQ1 and multifold increases in efficacy, but the loading rate is low.[117] Another study used 3-aminopropyltriethoxysilane to modify mesoporous HAp and achieved good antioxidant activity.[118] Regarding other calcium phosphate materials, researchers

have synthesized Ca-polyP coacervates from $Ca^{2+}$ and inorganic polymer polyphosphates (polyP) at neutral pH. Hydrophobic drugs such as dexamethasone can be added to form a core-shell structure that can increase osteogenic activity.[119] To overcome the initial burst and short-term release of calcium phosphate, polymers such as alginate can be added to control the drug release rate.[120] For the development of OS treatment, research on calcium phosphate nanomaterials should consider the material's own properties, focusing on the efficiency of drug delivery, pH sensitivity and the promotion of bone defect repair.

*Calcium Carbonate Material*

Calcium carbonate ($CaCO_3$) particles have the advantages of high hardness, porous internal structure, large specific surface area, high pH sensitivity, and low degradability, making them excellent candidates for drug delivery carriers.[121] Li *et al.* developed a $CaCO_3$-core cross-linked methoxypoly(ethylene glycol)-block poly(I-glutamic acid) highly drug-loaded hybrid nanomaterial (CaNP/DOX), which can deliver hydrophilic and hydrophobic drugs for intracellular drug delivery in OS chemotherapy. CaNP/DOX is a sphere with an average diameter of 150.3 ± 8.6 nm and an average hydrodynamic radius of 103.0 ± 7.5 nm. The small size and uniform shape result in a prolonged circulation time *in vivo*, while the better pH sensitivity allows uniform distribution in OS cells[122] (Figure 3). Fu *et al.* extracted biogenic aragonite nanoparticles (ANPs) with $CaCO_3$ as the main component from the shell of a hairy ark for the delivery of DOX. In an orthotopic model of rat OS prepared by injecting UMR-106 cells into the tibial cavity, two types of DOX-ANPs, each carrying 1.5 and 2 mg equivalents of DOX/kg, exhibited similar anticancer effects and showed lower toxicity than free DOX alone.[123] Zhao *et al.* used $CaCO_3$ NPs doped with selenium (Se) to deliver CDDP and found that selenium protected normal tissues by reducing the side effects of CDDP and that the optimal codelivery ratio of CDDP to selenium was 1:1 (mol/mol).[124] It is important to note that although these materials are considered nontoxic, it is always important to control the concentration of particles used to avoid adverse effects. When using biological fluids (e.g., cell culture media, plasma), more factors regarding particle stability should be considered to avoid particle aggregation. Therefore, they should be characterized not only in aqueous solutions but also in biological fluids.[125]

***Metal Materials***

Metal nanomaterials can be divided into metal compounds, such as oxides, or pure metal particles, such as gold, silver, and platinum, which can be used to inhibit bacterial infection and tumor growth.[126]

*Metal Oxides*

Due to its good superparamagnetic activity, iron oxide is often used for magnetically mediated targeted chemotherapeutic drug delivery and bioimaging. Superparamagnetic iron oxide nanoparticles can be guided to the OS tissue region by a stepped external magnetic field, and the subsequent alternating magnetic fields can induce the release of chemotherapeutic drugs.[127] To stabilize iron oxide nanoparticles, they are usually modified with a biocompatible coating during preparation. Wu *et al.* synthesized superparamagnetic iron oxide nanoparticles (SPIONs) coated with a silicate interlayer and a carbon shell. The double-layer coating improved their colloidal stability and targeting ability. In addition, ferrofluid effectively reduced the viability of OS and glioblastoma cells *in vitro* with minimal effect on the primary cell line.[128] Iron oxide nanoparticles loaded with chemotherapeutic drugs can also effectively inhibit the metastatic migration of OS cells. Moreover, if additional ionizing radiation is applied during the treatment, it can enhance the macrophagocytosis of DOX-loaded iron oxide nanoparticles by MG-63 OS cells and distribute them in the perinuclear region, thus enhancing the cytotoxic effect of the drug on OS cells.[129] Iron oxide nanocages offer significant advantages in the delivery of highly charged drugs (e.g., riluzole), extending the half-life of the drug *in vivo* and enhancing the control of OS cells.[130] Some metallic materials that can induce ROS production in tumor cells have also received considerable attention because of their anticancer potential. Zinc oxide nanoparticles (ZnO NPs) are typical examples of such metallic materials that can enter OS cells *via* the VPS34/Dynamin 2-dependent endocytic pathway and initiate mitochondrial autophagy-$Zn^{2+}$-reactive oxygen species-mitophagy axis (mitophagy-$Zn^{2+}$-reactive oxygen species-mitophagy axis)-mediated apoptosis.[131,132] In the preparation of ZnO NPs, nanocarriers with diverse properties can be obtained using different preparation methods and raw materials to suit various therapeutic situations. ZnO NPs synthesized by acoustic waves have higher tumor selectivity and cytotoxicity.[133] To obtain more stable and safer ZnO NPs, researchers produced CA-ZnO NPs with a stable hexagonal Woz structure using cassia flower extract. These materials have been shown to reduce OS cell viability and matrix metalloproteinase (MMP) content and promote MG-63 OS cell apoptosis with significant effects.[134] In addition, for cerium oxide and tungsten oxide nanoparticles, a large number of electron–hole pairs are generated due to the reduction in the upwelling degree. This not only leads to the appearance of ROS but also allows interaction with oxygen and hydroxide ions, generating a large number of reactive radicals, such as superoxide anion radicals and hydroxyl radicals of holes. These radicals can oxidize and reduce macromolecules such as nucleic acids, lipids, and proteins, thus triggering severe oxidation reactions that cause cellular damage.[135–137] Nanoparticles such as titanium dioxide ($TiO_2$), iridium oxide ($IrO_2$), and terbium oxide are biocompatible and easily excreted by the human body. In addition, new bioluminescent $TiO_2$NPs and BSA-modified $IrO_2$NPs also show a high loading capacity for DOX.[138,139] Nevertheless, the current technology of fluorescently labeled $TiO_2$NPs is limited by challenges such as low fluorescence yield, nonspecificity and high cost.

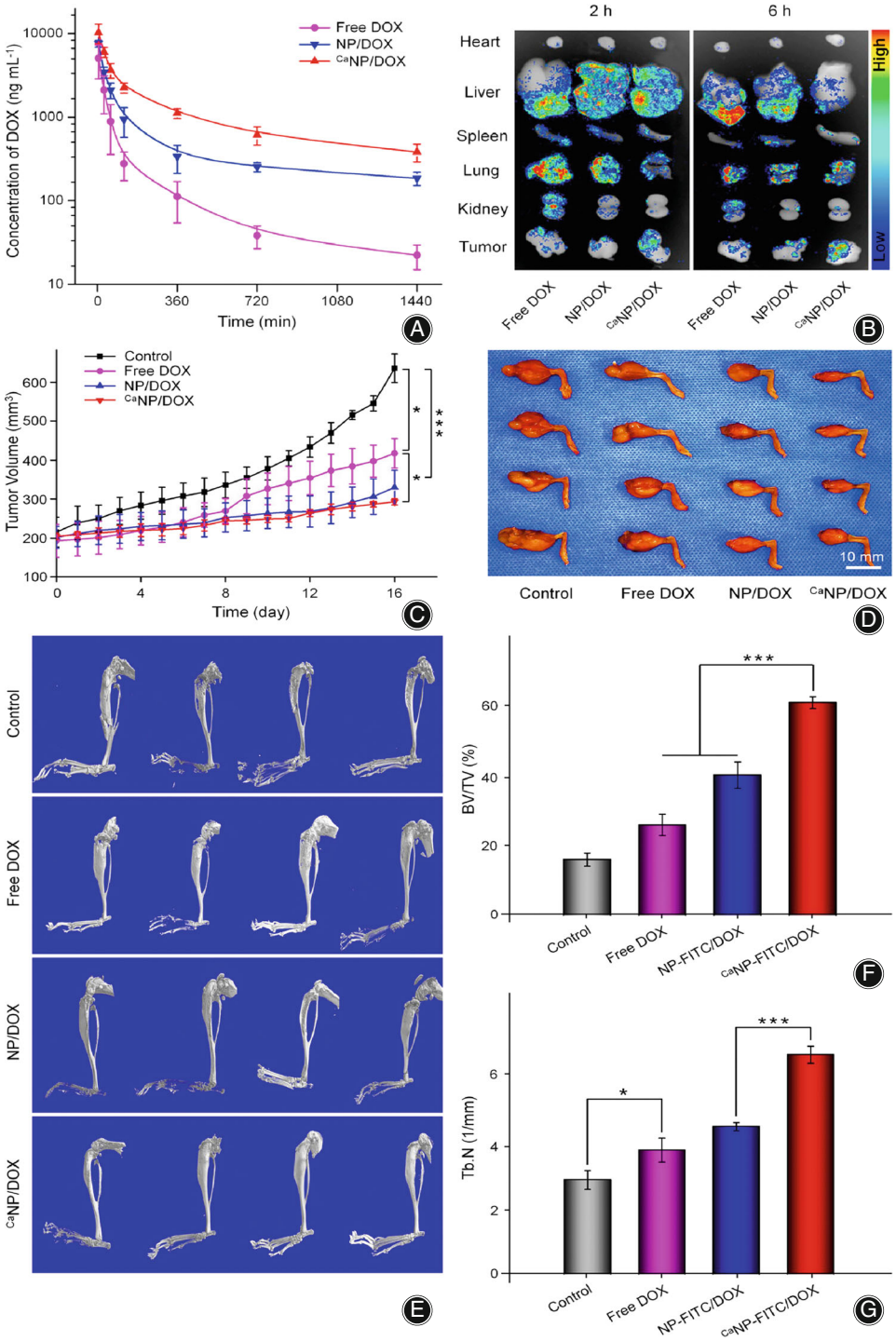


**FIGURE 3** Calcium-mineralized polypeptide nanoparticle for intracellular drug delivery in OS chemotherapy. (a) *In vivo* DOX pharmacokinetics after i.v. injection of free DOX, NP/DOX, or CaNP/DOX into Sprague–Dawley rats. (b) DOX fluorescence images representing the tissue distribution of DOX. Data are presented as the mean ± SD (n = 3; *$p < 0.05$, ***$p < 0.001$). (c) Tumor region volumes and (d) photographs of tibial primary OS tumors. (e) 3D reconstructed image of the tibia performed using micro-CT of 143B OS-bearing BALB/c mice after treatment with PBS, free DOX, NP/DOX, or CaNP/DOX. (f) Bone volume/total volume (BV/TV) and (g) trabecular number (Tb. N) in the regions of interest (ROI) of mice. Data are presented as the mean ± SD (n = 4; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). Reprinted with permission from Reference 122.

*Pure Metal Particles*

Pure metal nanoparticles constitute a unique class of chemotherapeutic drug delivery materials with strong optical and electrical characteristics. Moreover, the physicochemical properties of pure metal nanoparticles change with the composition, size and shape of nanoparticles, thus adapting to the delivery of various chemotherapeutic drugs.[140] Gold and silver nanoparticles are the most commonly used pure metal nanoparticles in OS chemotherapy. Gold nanoparticles (AuNPs) can be prepared by various chemical, physical and biological means, and their size and shape can be controlled by changing the preparation method, which in turn changes their properties and toxicity. AuNPs synthesized by bromelain can bind to four CDDP molecules. Bromelain can

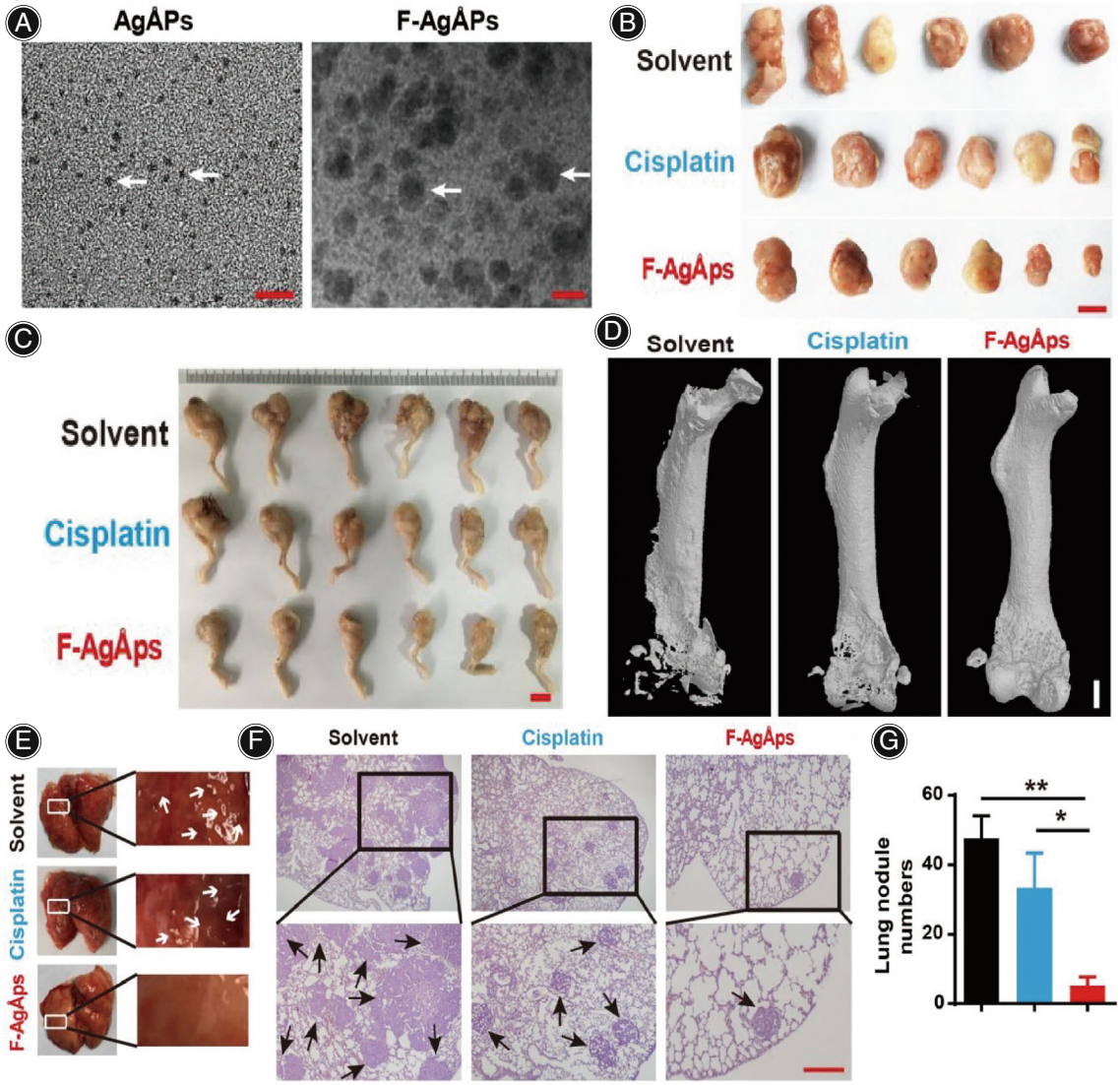


**FIGURE 4** Fructose-coated AgÅPs (F-AgÅPs) are used to inhibit the growth and metastasis of OS. (a) Morphologies of AgÅPs and F-AgÅPs under a transmission electron microscope. Scale bar: 10 nm. (b) Photographs of tumor samples from subcutaneous 143B xenograft mice in different treatment groups on day 21. Scale: 1 cm. N = 6 for each group. (c) Photographs of right hindlimb samples from orthotopic SJSA-1-bearing mice receiving different treatments for 21 days. Scale bar: 1 cm. (d) Representative μCT images of the mouse right hindlimb specimens in (c). Scale bar: 1 mm. (e) Gross view of lungs from the mice in (c). (f and g) Representative images of the H&E-stained lung sections (f) and quantification of the metastatic tumor nodule numbers (g). Scale bar: 200 μm. n = 3 per group. Data are shown as the mean ± SD. Reprinted with permission from Reference 148.

cooperate with CDDP to fight against tumors by prolonging blood circulation and enhancing neutrophil motility.[141] To obtain monodisperse AuNPs of different sizes, the concentration of pineapple protease, the reaction temperature and the incubation time can be adjusted during preparation.[142] To increase the stability of AuNPs, sodium citrate can be used for stabilization. Upon irradiation with visible light at 520 nm, the nanoparticles can maintain a narrow size distribution.[143] AuNPs have various shapes, such as spherical, rod and star shapes. Whereas the cytotoxicity of AuNPs for OS cells is shape and concentration dependent, star-shaped AuNPs are more cytotoxic than spherical and rod-shaped AuNPs and reduce the viability of 143B OS cells in a concentration-dependent manner.[144,145] AuNPs are characterized by easy synthesis, a high surface area-to-volume ratio and surface chemical functionalization. However, their anticancer effects are limited by renal clearance, the inherent heterogeneity of the immune system, and the tumor vascular system. To overcome these limitations, researchers often perform functional modifications of AuNPs, such as using

**TABLE 1 Examples of osteosarcoma-targeted strategies used in drug delivery nanomaterials**

| NP types | Target ligands | Targets | Cargos | References |
|---|---|---|---|---|
| Liposome | ALN | Skeleton | DOX | 51 |
| Liposome | siRNA | JIP1 | DOX, siRNA | 52 |
| Liposome | YSA | EphA2 | DOX, siRNA | 52 |
| Lipid-polymer NPs | FA | FR | DOX, EDL | 63 |
| Lipid-polymer NPs | CD133 aptamers | CD133+ OS cells | All-trans retinoic acid | 65 |
| Lipid-polymer NPs | CL4 | EGFR | Salinomycin | 66 |
| Natural polymer NPs | HA | CD44+ OS cells | Zoledronic acid | 79 |
| PHBV | Nuclear targeting peptide | Human OS cells (Saos-2) | DOX | 86 |
| Polypeptide nanogel | Sarcoma targeting peptide | Human OS cells (143B) | SHK | 90,91 |
| GO | FA | FR | MTH1, DOX | 101 |
| MSNs | ALN | Hydroxyapatite | DOX | 108 |
| MSNs | RGD | Tumor vasculature and tumor cells | DOX | 109 |

Abbreviations: ALN, alendronate; CL4, an RNA aptamer; DOX, doxorubicin; EDL, edelfosine; EGFR, epidermal growth factor receptor; FA, folic acid; FR, folate receptor; GO, graphene oxide; HA, hyaluronic acid; JIP1, JNK-interacting protein 1; MSNs, mesoporous silica nanoparticles; MTH1, MutT homolog 1 protein; NPs, nanoparticles; OS, osteosarcoma; PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate) particles; RGD, arginine-glycine-aspartic acid peptide; SHK, shikonin; YSA, a 12-amino acid peptide.

reduced glutathione (GSH) to modify AuNPs to deliver DOX or GEM. GSH confers low immunogenicity and high stability.[144] The application of silver nanoparticles (AgNPs) can induce mitochondria-dependent apoptosis mediated by ROS in addition to loading chemotherapeutic agents, which are prone to toxic effects on OS cells. Reduction of the precursor silver nitrate to AgNPs that favor tumor infiltration by using tannin-rich *Rhizophora apiculata* extracts or capping AgNPs with BSA can produce significant cytotoxic effects on MG-63 OS cell lines.[146,147] To obtain nanoparticles with small size, high tumor targeting efficiency, and favorable pharmacokinetics for tumor therapy, Hu *et al.* prepared fructose-coated spherical AgNPs ($9.38 \pm 4.11$ nm) using an evaporative condensation system. These materials were more effective than intravenous CDDP in inhibiting tumor growth, reducing osteoporosis and preventing lung metastasis in OS nude mice. By inhibiting pyruvate dehydrogenase kinase (PDK), the glucose metabolism of OS cells could be selectively converted from glycolysis to mitochondrial oxidation, thus inducing ROS-dependent OS cell apoptosis[148] (Figure 4). As mentioned above, pure metal nanoparticles show promise for the treatment of OS, but there are still some problems that cannot be ignored. Pure metal nanomaterials cause DNA damage and mutations that may cause irreversible damage to the body, which limits their clinical application. Although there are many individual studies showing that the shape, size, composition and ligand of AuNPs affect their biotoxicity, many conclusions are contradictory. Therefore, the issue of toxicity of AuNPs to organisms deserves our continued attention.

### *Conclusions and Future Perspectives*

The widespread use of chemotherapy has prolonged the survival period of OS patients to a certain extent. However, due to the immunogenicity, uncontrolled release of chemotherapeutic drugs, and possible drug resistance of tumor cells to such drugs in the later stage of treatment, the effect of chemotherapy is limited.[63] Nanomaterial drug delivery systems have been used in the clinic since the early 1990s, when the use of liposomes for drug delivery received clinical approval.[149] Early nanomaterial drug delivery systems had single functions, poor drug release control, and poor biocompatibility and stability of some nanomaterials.[150–152] The new generation of nanomaterials that have emerged in the past few decades not only overcome the shortcomings of the previous generation but also have many additional functions.[153–155] Currently, nanomaterial drug delivery systems have the advantages of good biocompatibility, high drug encapsulation efficiency, a high drug loading rate, controllable drug release, good pharmacokinetic properties, high selectivity and sensitivity to tumor cells, a long blood circulation time, good EPR effect and other characteristics that can compensate for the defects of conventional chemotherapy and improve the treatment effect and patient survival rate[32–36] (Table 1). For example, liposomes are spherical vesicles with a hydrophilic cavity that can encapsulate both hydrophilic and lipophilic drugs and can also effectively inhibit cellular uptake by macrophages to prolong the blood circulation time.[48,49] Notably, liposomes have potential instability issues, and liposome formulations currently lack effective sterilization techniques.[156] Carbon-based nanomaterials can exert various cytotoxic effects on tumor cells, such as ROS generation, DNA damage, and mitochondrial dysfunction.[157] However, there are still some *in vivo* side effects that need to be addressed, such as single-walled carbon nanotubes that may induce acute and chronic lung disease and damage the cardiovascular system.[158,159] Compared with other nanocarriers, MSNs have a unique mesoporous structure and high specific surface area, which contribute to their wide application in biocatalysis, biosensors, and disease diagnosis and treatment.[107] In addition, the large pore volume of MSNs effectively increased the drug loading of

OS chemotherapeutics. However, with increasing drug loading, the phenomenon of drug leakage also increased. To reduce the toxic and side effects of chemotherapeutic drugs on normal tissues and organs, methods of sealing the pore entrance of the material are urgently needed.[160,161] Researchers could consider using platelet membranes or lipids to coat nanocarriers and polydopamine coatings to narrow the pores.[162–164] Pure metal nanomaterials can overcome the disadvantage of the low mechanical properties of organic nanoparticles due to their excellent strength and stress absorption capacity.[165] Nevertheless, pure metal nanomaterials can cause DNA damage and mutagenesis and thus may be genotoxic and carcinogenic to humans, limiting their clinical applications.[166] To date, most studies have included only *in vitro* cytotoxicity analysis of nanomaterial drug delivery systems, and only a few have considered *in vivo* safety, which makes it difficult to meet the requirements for clinical translation.[167] Therefore, future studies should also focus on designing more comprehensive toxicity experiments *in vitro* and *in vivo*, such as macrophage and normal cell killing assays, hemolysis assays, normal tissue release assays, and toxicity evaluation in animal models, to improve the clinical translation of drug delivery.[168–170] In addition to chemotherapy, some unconventional therapies also require the participation of nanomaterials, such as hyperthermia, photodynamic therapy and gene therapy, to achieve highly effective anticancer effects.[171–174] Nanomaterials have become a medium for the combined treatment of chemotherapy and unconventional therapies, which provides feasible ideas for compensating for the shortcomings of different therapies. Nanomaterials are considered to have the potential to become a more promising therapeutic platform and play a role in promoting precision and personalized medicine. However, there is still much controversy regarding the method of administration and the degree of metabolism *in vivo*, the number of clinically approved nanomaterials has not increased substantially, and a large number of clinical trials are still needed to verify the effect in the future. Therefore, nanomaterials still have a long way to go in clinical transformation and application. Nanomaterials have now reached the stage of extensive research, and the next stage of development should be to establish a strict regulatory system for existing nanomaterial chemotherapy drug delivery systems and to verify their toxicity and safety in various aspects.

## Author Contributions

TY and ZC reviewed the literature and wrote the original draft. XC, CX and XG wrote the original draft and prepared the table. SW and JJ conceived the idea and revised the manuscript. All authors read and approved the final manuscript.

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