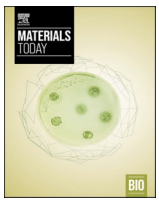
Materials Today Bio 32 (2025) 101607

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio



Bioinspired nanomedicines for the management of osteosarcoma: Recent progress and perspectives

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ARTICLE INFO

Keywords:
Bioinspired nanoparticle
Osteosarcoma
Targeting

ABSTRACT

Osteosarcoma (OS) is the most prevalent malignant primary bone tumor, predominantly affecting children and young adults between the ages of 11 and 20. OS presents huge challenges in treatment because of its aggressive nature and high metastatic potential. Chemotherapeutic drugs have attracted considerable interest for the treatment of OS, but they suffer from poor targeting, low bioavailability, severe side effects, and the multi-drug resistance acquired by the tumor. Therefore, it is imperative to develop novel therapeutic tactics that can improve OS outcomes while minimizing toxicity. Bioinspired nanoparticles, designed through exploiting or simulating the biological structures and processes, provide promising strategies for the treatment of OS. In this review, we elaborate on the biological properties and biomedical applications of state-of-the-art bioinspired nanoparticles, including cell membrane-based nanoparticles, exosome-based nanoparticles, protein template-based nanoparticles, and peptide template-based nanoparticles for the management of OS.

1. Introduction

Osteosarcoma (OS), is the most prevalent malignant primary bone tumor, accounting for 35 % of all orthotopic bone malignancies [1]. OS typically develops during the period of rapid bone growth, between the ages of 11 and 20, predominantly affecting children and young adults at a critical time in their development [2,3]. OS is characterized by a high tendency for local invasion and early metastasis, predominantly to the lungs, which poses major challenges for effective treatment and patient prognosis [4]. The five-year survival rate for OS patients treated with adjuvant chemotherapy in combination with surgery has plateaued at about 60 % [5]. Nonetheless, for patients with metastatic OS, the five-year survival rate drastically drops below 30 % in that surgery has a limited effect on the management of local tumors, with substantial morbidity and functional impairment in patients [2].

Several chemotherapeutic drugs, including doxorubicin (DOX) [6], methotrexate (MTX) [7], and cisplatin (CDDP) [8], have been recommended as the cornerstone of systemic treatment for tumors. However, these drugs suffer from poor targeting, limited bioavailability, and multi-drug resistance. Physiological barriers in bone, such as blood-marrow barrier, provide additional diffusion barriers to drug delivery, and the dense bone matrix contains abundant inorganic minerals, which also limit drug permeation and accumulation [9]. Furthermore, these chemotherapeutic drugs often lead to severe systemic toxicity, such as cardiotoxicity and nephrotoxicity [10,11]. In addition, there is no effective treatment for patients who suffer from the recurrence of OS after the use of the drugs [12].

Bioinspired nanoparticles, fabricated through employing or simulating biological structures and processes, have been studied for the treatment of various diseases [13]. Because the natural human system has been the result of millions of years of evolution in the way it does today, it has a precise mechanism to regulate its functions [14]. Bioinspired nanoparticles derived from nature can produce or achieve biological effects like the natural nanoparticles do, while only artificial materials are not able to fully realize these complex functions [15,16]. For drug delivery to treat OS, bioinspired nanoparticles can present the following merits: A. desirable biocompatibility; B. attractive tumor-specific drug accumulation; C. adequate drug loading efficiency.

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https://doi.org/10.1016/j.mtbio.2025.101607
Received 7 December 2024; Received in revised form 14 February 2025; Accepted 21 February 2025
Available online 5 March 2025

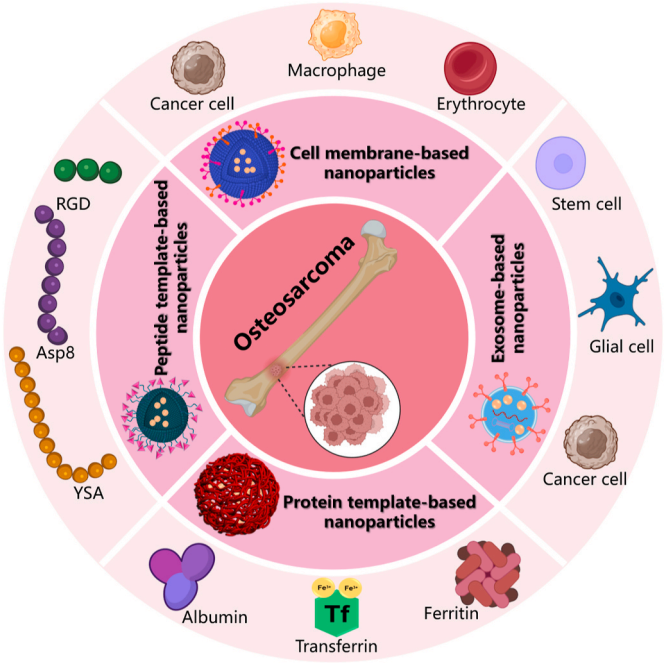

Fig. 1. Schematic illustration of bioinspired nanomedicines employed for the management of osteosarcoma. The focus of bioinspired nanoparticles employed in osteosarcoma treatment is primarily on the following: cell membranes from cancer cell, macrophage, and erythrocyte; exosomes from stem cell, glial cell, and cancer cells; proteins such as albumin, transferrin, and ferritin, and peptides such as RGD, Asp8, and YSA. Created with BioRender.com.

Table 1
Characteristics of bioinspired nanoparticles.

Type	Advantages	Limitations
Cell membranes	High yield Long circulation Tumor-homing effect Immune evasion	High cost Potential toxicity Low loading capacity
Exosomes	Long circulation Tumor-homing effect Immune evasion Immune modulation	Cumbersome extracted steps Composition variability Limited in vivo non-invasive method Poor stability
Proteins	Specific targeting Easy functionalization Scalable production	Potential toxicity Limited stability in physiological conditions
Peptides	Specific targeting Easy functionalization Low immunogenicity Low cost	Insufficient for personalized medicine Structural instability

It allows for non-invasive conventional routes of administration and maximizes the use of drugs [17]. Therefore, bioinspired nanoparticles can achieve the next generation of therapeutics for the management of OS.

The most widely employed bioinspired materials in nanotechnology include cell membranes, exosomes, proteins, and peptides. This review aims to offer an overview of the biological features of the bioinspired nanoparticles and their applications in OS management. The organization and scope of the present review are shown in Fig. 1.

2. The biological properties of bioinspired nanoparticles

Simulating nature is an attractive tactic for designing novel nanoparticles in OS treatment. These nanoparticles have chemical and structural properties that mimic those of biological agents, enabling them to replicate the key function of natural materials [13]. Herein, we outline the biological features of the most widely employed bioinspired nanoparticles, including cell membrane-based nanoparticles, exosome-based nanoparticles, protein template-based nanoparticles, and peptide template-based nanoparticles. Table 1 summarizes the advantages and limitations of different bioinspired nanoparticles. Especially, we focus on their ability to achieve targeted drug delivery, drug loading efficiency, and biocompatibility.

2.1. Cell membrane-based nanoparticles

It is common knowledge that cell membranes possess excellent biocompatibility, enveloping a variety of proteins with crucial biological functions within their phospholipid bilayer [18]. Since the early 1980s, cells have been exploited as vehicles for drug delivery to improve retention and targeting efficiency. To date, diverse cell membrane-coated nanoparticles have been designed, and widely employed to enhance the delivery efficiency of drug delivery systems [19]. By hypotonic treatment and ultrasound extrusion, different nanoparticles can be coated with various types of cell membranes [20]. Cell membrane-coated nanoparticles present the characteristics of both the cell membrane and the nanoparticle and are a recent research hotspot in active-targeting drug delivery systems [13,21]. For instance, VEGF-modified red blood cell membrane-camouflaged nanoshells are able to evade recognition by the immune system, and platelet membrane-coating can confer tumor-targeting capabilities to the nanoparticles [22,23].

Cancer cells have many unique characteristics, including unlimited replicative potential, immune evasion, and homing capabilities endowed by specific surface membrane proteins [24–26]. Therefore, cancer cell-camouflaged nanoparticles can target and adhere to tumor tissues, thereby enhancing drug delivery efficiency and potentiating tumor-killing efficacy [27]. Moreover, cancer cells can be readily acquired by in vitro cell culture. Inspired by the intrinsic immune evasion and homing targeting properties of cancer cells, a variety of cancer cell membrane-coated nanoparticles have been developed for tumor-targeted treatment [15]. For instance, polymeric nanoparticles coated with the membrane of brain metastatic breast cancer cells have been employed for the diagnostic treatment of breast cancer brain metastases, where the VEGF receptor on the cancer membrane facilitates the attachment of the nanoparticles to endothelial cells and the following permeation of the BBB [28]. Hybrid membrane-coated methyl-triazeno-imidazole-carboxamide (MTIC)-loaded self-assembled micelles were also used for the treatment of brain tumors [21]. The results showed that the bioinspired hybrid membrane mUMH (HMC3 membrane: macrophage membrane: U87MG membrane = 1:1:2) could target-deliver MTIC to glioblastoma multiforme (GBM) tissues and presented desirable effects in GBM treatment.

Macrophage membrane-coated nanoparticles not only present immune evasion characteristics and prolonged circulation time, but also exhibit chemotaxis towards inflammatory environments, exerting tumor homing targeting abilities through inflammation-related receptors [29]. Huang et al. [30] coated polymeric nanoparticles based on aggregation-induced emission (AIE) photothermal agent with macrophage membranes stimulated by mycobacteria for the theranostics of tuberculosis. Under 1064 nm NIR-IIb laser excitation, the nanoparticles, which carried specific receptors for tuberculosis mycobacteria, could target both tuberculous granulomas and internal mycobacteria, enabling high-resolution *in-situ* imaging in a tuberculosis mouse model. Under 1064 nm laser irradiation, the nanoparticles produced photothermal effects, eradicated target mycobacteria, reduced pathological damage and excessive inflammation in the lungs, and convincingly demonstrated good tuberculosis treatment effects. The NIR-IIb-responsive bioinspired nanoparticles have the potential for the theranostics of tuberculosis.

Cell membranes derived from a single kind of cell line can only be

employed for homing targeting of a single type of tumor cells. Hybrid membranes, which are the result of the integration of two different cell membranes, have been developed in order to further broaden the scope of targetability. The merit of hybrid membranes lies in their ability to integrate the targeting features of both cell types. PTX-loaded PLGA nanoparticles were coated with hybrid cell membranes, human OS cell line 143B and mice monocyte-macrophage cell line RAW264.7, denoted as PLGA@[143B-RAW] NPs [31]. By utilizing the homing targeting ability of tumor cell membranes, PLGA@[143B-RAW] NPs presented higher cytotoxicity against OS cells, compared with unmodified PLGA NPs. Meanwhile, macrophage membranes enhanced the chemotactic activity of nanoparticles towards inflammatory sites, leading to a greater preference for inflammatory sites [32,33]. Although the hybrid membrane modification obviously improved the drug accumulation in tumor tissues, the biodistribution of the hybrid membrane-coated nanoparticles in the spleen and liver appeared to be remarkably higher than that in tumor tissues, warranting further investigation [1].

Because cell membranes are derived from the human body, most cell membrane-coated nanoparticles possess biocompatibility, biodegradability, and non-immunogenicity. Nonetheless, the potential toxicity of the components of the cell and their secretions should not be overlooked. For instance, hemoglobin in the blood could lead to the death of neurons, and the secretions of blood platelets could also be neurotoxic [34]. Accordingly, the potential risks associated with nanoparticles coated with cell membranes should also be considered. Additionally, the drug loading capacity of the cell membrane-coated nanoparticles is often relatively low, because of the complexity of the nanoparticles. Above all, cell membrane-coated nanoparticles can provide a promising direction for active tumor targeting, but further in-depth investigation is needed.

2.2. Exosome-based nanoparticles

Exosomes are phospholipid bilayer membrane-containing vesicles, secreted by living cells, with a size range of 30–150 nm [35]. Exosomes are derived from intracellular multi-vesicles and released into the extracellular microenvironment via exocytosis. Exosomes typically load an array of genetic information molecules, e.g. DNA, RNA, lipids, and cytoplasmic proteins, and they facilitate the transfer of these regulatory molecules with genetic information from donor cells to recipient cells, playing a crucial role in various biological processes [36]. Because of widespread distribution in vivo, nanoscale size, and the ability to precisely target specific sites in the body, exosomes have been deemed as ideal candidates for drug delivery vehicles, biomarkers, and biofluid biopsies [37,38].

Exosomes, as the vehicles for intercellular communication, are capable of specifically recognizing target cells and possess innate targeting capabilities, as numerous studies have confirmed [39,40]. The ability of exosomes to interact with specific cell types makes them an ideal targeted delivery system for active pharmaceutical ingredients in the management of various diseases [41]. For instance, neuroblastoma-derived exosomes have been found to carry membrane glycolipid groups on their surface, which could bind to aggregates of amyloid-β peptide in the neuron. This offers a targeted therapeutic approach to Alzheimer's disease. Wang et al. [42] prepared a doxorubicin-loaded oligopeptide-modified exosome (Pep2-Exos-DOX) for the treatment of glioblastoma. The exosomes were derived from the mouse microglial cell line BV2. The results exhibited that DOX was highly concentrated in glioblastoma. In vivo pharmacodynamic study demonstrated that Pep2-Exos-DOX exhibited remarkable remission of glioblastoma in mice and desirable biocompatibility. Exosomes can not only deliver small molecules to target cells, but transport biomacromolecules, such as nucleic acids and proteins. Yuan and co-workers [43] successfully loaded brain derived neurotrophic factor (BDNF) into Raw 264.7 macrophage exosomes for treatment against brain inflammation. The exosomes facilitate drug penetration across the blood-brain barrier, carrying more BDNF to the sites of brain lesions, thereby enhancing the therapeutic effect.

A variety of cell types, including tumor cells, hematopoietic cells, and mesenchymal stem cells (MSCs), can secrete exosomes. For the large-scale production of exosomes, MSCs are the ideal candidates because of their multi-functionality, stability, and ease of expansion [44]. Utilizing exosomes from human MSCs, Chen et al. [45] designed engineered MSCs-exosomes modified with angiopep-2 brain tumor-targeting peptide. Small interfering RNA of GPX4, the key protein in the ferroptosis defense axis was loaded into the engineered exosomes, which successfully improved the anti-cancer efficacy of ferroptosis therapy for glioma.

Although exosomes could be deserved as a promising tool for the diagnosis and treatment of cancer, there are several limitations. Firstly, exosomes obtained in vitro may be different in size from those derived by patients in vivo. Accordingly, there is a need to develop a novel non-invasive method to obtain exosomes in vivo, e.g. from vaginal secretions, faeces, or saliva [39]. Furthermore, the storage conditions for exosomes are very stringent, with exosomes typically stored in phosphate-buffered saline at −80 °C [44]. However, the physiological functions of exosomes can be affected by low temperatures. Finally, endogenous exosomes often present desirable biocompatibility, excellent stability, low immunogenicity, and negligible toxicity. Of note, exosomal composition varies considerably between different cell sources. Additionally, the multitude of mechanisms underlying exosome-mediated intercellular communication remain largely unknown. These knowledge gaps raise potential safety concerns regarding exosome applications. Thereby, further in-depth investigations are required to address these critical issues.

2.3. Protein template-based nanoparticles

Nanoparticles based on protein templates, such as albumin, transferrin, and insulin, have attracted widespread attention in drug delivery, owing to the biocompatibility, biodegradability, and precise targeting of these proteins [46]. Protein template-based nanoparticles could be categorized into diverse types: protein-drug conjugates, engineered active therapeutic proteins, and combined complicated platforms based on protein motifs [47]. These nanoparticles can be tailored into personalized functional nanoparticles based on protein modifications, realizing precise targeting and meanwhile minimizing off-target effects [48,49].

Albumin is a water-soluble and stable protein with low toxicity and easy modification for functionalization, making it suitable as a drug delivery carrier. Wang and co-workers [50] prepared paclitaxel (PTX)-loaded bovine serum albumin (BSA)-based nanoparticles, which underwent a condensation reaction with o-phthalaldehyde (OPA) to obtain an injectable in-situ gel. The in-situ gel was injected around the tumor in 4T1-tumor-bearing mice or C26-tumor-bearing mice. Compared with the free PTX solution group, the in-situ gel remarkedly improved the anti-tumor effect and prolonged the survival time of the mice.

Another widely used protein for drug delivery is transferrin. Transferrin facilitates the transport of iron ions into cells via transferrin receptors on the cell surface, thereby maintaining normal cellular physiological functions. The expression of transferrin receptors in tumor cells is several times higher than in normal tissues, because of the increased iron requirements for rapid nucleic acid replication in tumor cells [51]. Accordingly, the overexpression of transferrin receptors in tumors has the potential to serve as a tumor target, which has received considerable attention in recent years. Transferrin-doxorubicin conjugates (Tf-DOX) were designed for specific targeted therapy of prostate cancer [52]. After intravenous injection of Tf-DOX into 22RV1-tumor--bearing nude mice, ex vivo tissue imaging results showed that Tf-DOX accumulated negligibly in normal tissues, while it was enriched in tumor tissues. Moreover, distinct DOX fluorescence was observed both

Table 2
Summary of representative bioinspired nanoparticles in primary osteosarcoma treatment.

Type	Bioinspired nanoparticles	Cargo	Animal models	Refs
Cell membranes	143B cell membrane-coated silica nanoparticles	Indocyanine green	143B tumor xenograft BALB/c-nu mice	[73]
	WELL5 cell membrane-coated nanoparticles	Methotrexate; Floxuridine	WELL5 tumor xenograft BALB/c-nu mice	[74]
	HOS cell membrane-coated PLGA nanoparticles	IR780	HOS tumor xenograft BALB/c-nu mice	[75]
	VEGF-modified RBC membrane-coated nanoparticles	Doxorubicin; Zoledronic acid; Ca(II)	Saos-2 tumor xenograft BALB/c-nu mice	[22]
	RGD peptide-modified macrophage membrane-coated nanoparticles	pMETTL14; RS09	MNNG/HOS tumor xenograft BALB/c-nu mice	[76]
Exosomes	RGD-modified OS cell-derived exosomes	lncRNA MEG3	MNNG/HOS tumor xenograft BALB/c-nu mice	[80]
	RGD-modified engineered exosomes	siRad18	143B tumor xenograft BALB/c-nu mice	[82]
	BMSCs-derived exosomes	Doxorubicin	MG63 tumor xenograft BALB/c-nu mice	[83]
	BMSCs-derived exosomes	Doxorubicin	143B tumor xenograft BALB/c-nu mice	[84]
Proteins	Transferrin-modified cationic liposomes	p53 expression plasmid	HOSM-1 tumor xenograft BALB/c-nu mice	[85]
	Human 53BP1 protein-based nanoparticles	Fluorescent streptavidin	N/A	[86]
	Hydroxyapatite-binding HSA nanoclusters	Alendronate sodium; Doxorubicin	HOS/MNNG tumor xenograft BALB/c-nu mice	[87]
	Lectin-conjugated pH-responsive MSNs	Doxorubicin	N/A	[88]
Peptides	RGD-modified micelles	Doxorubicin	N/A	[89]
	RGD-conjugated Bi_2S_3@MSN	Doxorubicin	UMR-106 tumor xenograft BALB/c-nu mice	[90]
	RGD and mitochondrial dual-targeting nanoparticles	AIBI	MNNG/HOS tumor xenograft BALB/c-nu mice	[91]
	PT peptide-modified semiconductor polymer nanoparticles	N/A	143B tumor xenograft BALB/c-nu mice	[92]
	OS targeting peptide-modified nanodiscs	Cy7	HOS tumor xenograft nude mice	[94]

AIBI: Azo initiator 2,2′-azobis[2-(2-imidazolin-2-yl) propane] dihydrochloride; BMSCs: Bone marrow mesenchymal stem cells; HSA: Human serum albumin; MSN: Mesoporous silica nanoparticles; N/A: Not applicable; PLGA: Poly(lactic acid-glycolic acid); RBC: Red blood cell; VEGF: Vascular endothelial growth factor receptor.

at tumor margins and deeper within the tumor, demonstrating Tf-DOX exhibited desirable tumor-targeting with little toxicity against normal tissues.

Protein-template-based nanoparticles usually possess an external surface and an internal core, allowing for drug loading either by adsorption to the external surface or incorporation into the internal core. Additionally, the protein template can be modified to improve drug loading efficiency. For instance, a hydrophilic albumin can be hydrophobic through modification, creating an amphipathic micelle for loading hydrophobic drugs. In addition, protein templates can be cationised for easy loading of nucleic acid drugs [53]. Once the protein-template-based nanoparticles enter target cells, they are enzymatically degraded by proteases, resulting in a controlled drug release [46,54].

Most protein templates used for drug delivery are endogenous, and as a result, have negligible in vivo toxicity. Nevertheless, the fabrication of protein template-based nanoparticles often needs the use of substantial amounts of harmful substances, such as cross-linking agents like glutaraldehyde, to increase the stability of the nanoparticles [55]. Consequently, removing all harmful substances from the preparation process and even developing novel less toxic fabrication methods are crucial issues, which need to be addressed urgently in the exploration of protein template-based nanoparticles.

2.4. Peptide template-based nanoparticles

Targeting peptides exhibit attractive specificity and affinity for cell surface targets. The merits of these peptides include excellent targeting efficacy, ease of synthesis, desirable biocompatibility, and negligible immunogenicity [56,57]. Targeting peptides-modified nanoparticles can obviously enhance targeting capabilities, and thus a variety of targeting peptides have been designed for targeted therapy [56].

YSA (YSAYPDSVPMMS), a 12-amino acid peptide, acts as a ligand for the ephrin type-A receptor 2 (EphA2), which is overexpressed in primary and metastatic OS cells [58]. Therefore, YSA has the potential to be a targeting peptide for OS. Haghiralsadat and co-workers [59] fabricated YSA peptide-modified nanoparticles for OS treatment via covalently binding YSA peptide to PEGylated liposomes. Furthermore, Saos-2 OS cells exhibited remarkably enhanced uptake of YSA peptide-modified nanoparticles, with an almost twofold increase in cytotoxicity. Therefore, YSA peptide is expected to be an excellent targeting peptide for OS-targeted nanoparticles.

STP (VATANST) can specifically bind to vimentin, which is overexpressed on the surface of tumor cells and related to tumor metastasis [60]. Liu et al. [61] fabricated DOX-loaded STP peptide-modified nanoparticles, denoted as STP-mNPs/DOX, for the targeted treatment of orthotopic colon cancer in mice. STP-mNPs/DOX presented specific binding with vimentin, which is overexpressed in the colon cancer cell line CT26. Accordingly, STP-mNPs/DOX could enhance the uptake of DOX by CT26 cells and improve the antitumor efficacy against CT26 cells. In an in-situ colon cancer model using Balb/C mice, STP-mNPs/DOX presented more potent remission of the tumor, compared with other formulations. Therefore, STP peptide can be employed to actively target vimentin-overexpressed cancer cells, such as OS [62].

Peptides containing adequate aspartic acid (Asp) showed a high affinity for bone tissue, owing to the electrostatic interaction between the carboxyl group of Asp and calcium ions of hydroxyapatite (HAp), a major component of bone [63]. Accordingly, Asp-rich peptides have bone-targeting properties and enhanced bone affinity depending on the number of exposed Asp residues [64]. The most commonly employed peptide sequence for bone-targeting is the d-Asp octapeptide (Asp8), consisting of eight Asp [65]. Recent studies exhibited that Asp8-modified nanoparticles can improve their affinity for bone tissue several-fold [66,67]. Zhang et al. [67] developed Asp8-modified dendritic platinum-copper nanoparticles, which could accumulate in bone tissue surrounding bone tumors and showed effective photothermal therapy (PTT). Asp-rich peptides are attractive as bone-targeting modification groups, and show little adverse effect, making them worthy of broader application for bone-targeting [68].

Integrin αvβ3, an endothelial cell receptor, is overexpressed in both the tumor vasculature and tumor cells. The arginine-glycine-aspartic acid (RGD) sequence is a recognized targeting motif for integrin αvβ3, and it is common knowledge that RGD is a tumor-targeting peptide, with the merit of ease of synthesis and little toxicity [69,70]. RGD-modified nanoparticles have demonstrated excellent therapeutic efficacy in various tumor therapy strategies, including chemotherapy, phototherapy, and gene therapy [71]. Studies have revealed the RGD sequence targets integrins extremely specifically [71,72]. It has been reported that cRGDyk (cyclo(Arg-Gly-Asp-d-Tyr-Lys)) has a remarkably

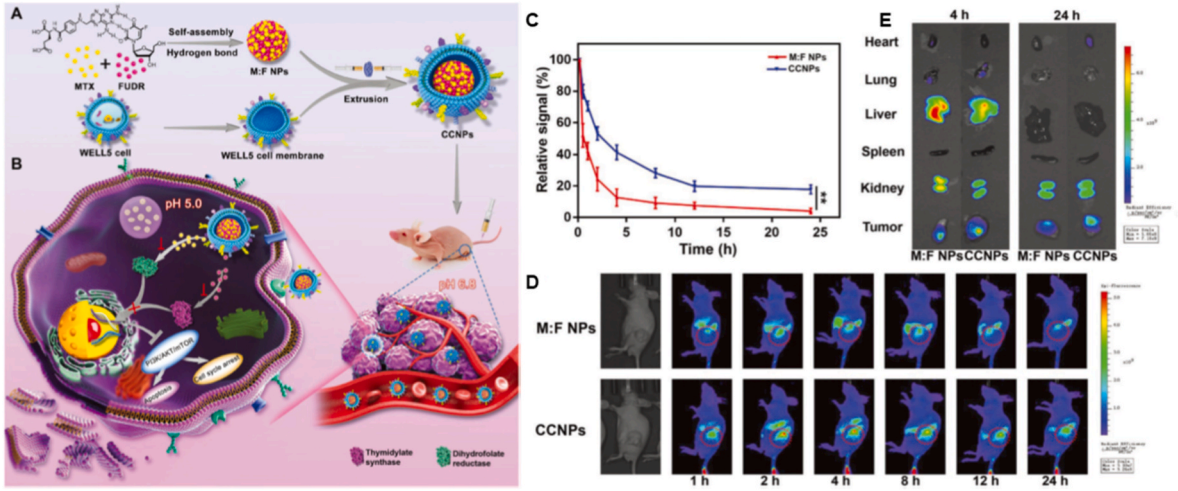

Fig. 2. Preparation of CCNPs and their use in targeted treatment of OS. (A) Schematic diagram of the preparation process of CCNPs. (B) Schematic diagram of the homologous targeting and synergistic therapeutic effects of CCNPs in OS. (C) Relative time-dependent plasma concentrations of Cy5.5-loaded M:F NPs and CCNPs after intravenous injection in rats. (D) Biodistribution of Cy5.5-loaded M:F NPs and CCNPs in OS-bearing mice as determined by in vivo fluorescence imaging. The red dashed area represented the tumor sites. (E) Ex vivo fluorescence images of main tissues and tumors at 4 h and 24 h after injection of Cy5.5-loaded M:F NPs and CCNPs [74]. Copyright 2022, John Wiley and Sons.

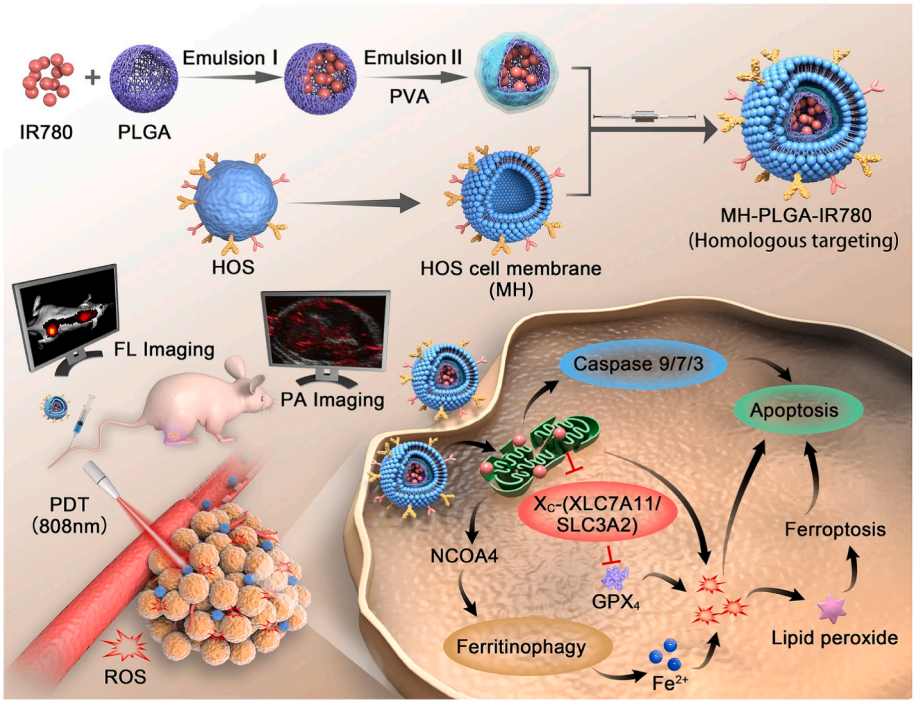

Fig. 3. Schematic diagram of the preparation process of MH-PLGA-IR780 NPs and homologous targeting for OS theranostics. IR780 was entrapped into PLGA nanoparticles through the double-emulsion method, and PLGA-IR780 NPs were coated by the HOS cell membrane. Utilizing homologous targeting, the nanoparticles could realize FL/PA imaging-guided synergistic treatment of apoptosis/ferroptosis/PDT against OS [75]. Reproduced under terms of the CC BY license. Copyright 2022, The Authors, published by BMC Press.

lower affinity for αvβ5 integrin, which is predominantly highly expressed in HCT-116 cells, compared with αvβ3 integrin. In contrast, cRGDfC (cyclo(Arg-Gly-Asp-d-Phe-Cys)) has a high targeting affinity for αvβ5 integrin. Thereby, when choosing RGD as a tumor-targeting ligand, it is necessary to carefully investigate the kinds of integrins highly expressed on the surface of tumor cells in order to enhance delivery efficiency.

Peptide-template-based nanoparticles not only exhibit excellent binding affinity to the targets, but also have desirable biocompatibility and little immunogenicity. In general, the nanoparticles do not cause an increase in levels of inflammatory cytokines, or lead to acute toxicity against main organs, including liver, kidneys, and brain. Thereby, the nanoparticles are suitable candidates for systemic administration in OS treatment, owing to their low toxicity and non-immunogenicity. The current major challenge in nanoparticles for treating OS is the vast histological heterogeneity and genomic instability associated with OS, which requires the development of more specific tumor-targeting peptides for personalized treatment of OS [1]. Additionally, further investigation is required to determine whether the targeting peptides can induce apoptosis and inhibit the proliferation of OS cells.

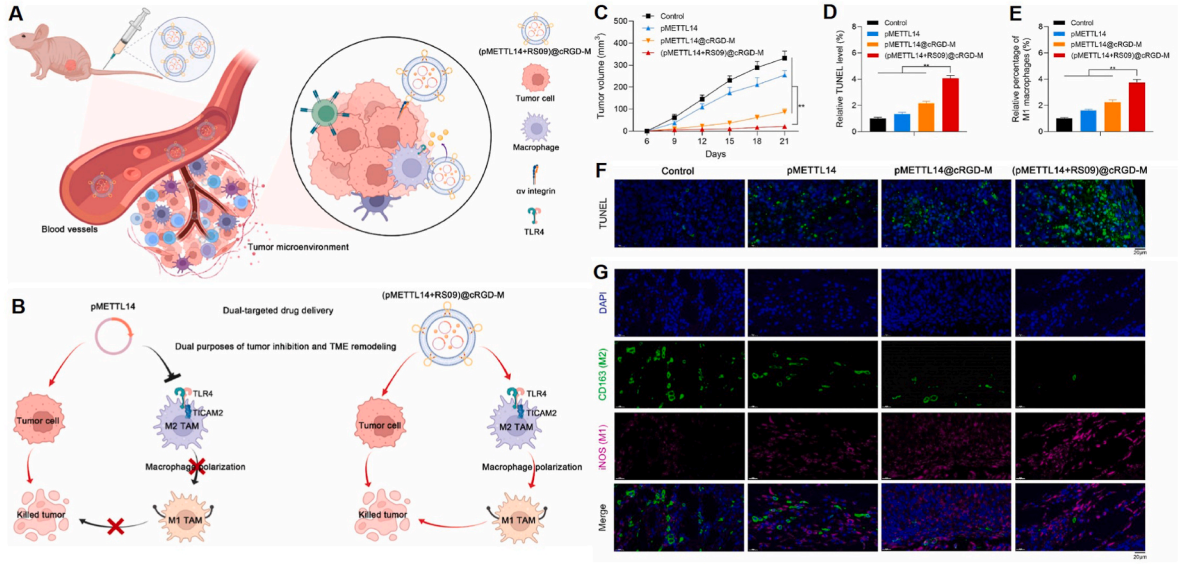

Fig. 4. Targeted OS therapy of (pMETTL14+RS09)@cRGD-M. (A) Schematic diagram of the targeting ability of (pMETTL14+RS09)@cRGD-M towards tumor and macrophages. (B) Schematic diagram of the therapeutic mechanism of (pMETTL14+RS09)@cRGD-M for OS treatment. (pMETTL14+RS09)@cRGD-M could simultaneously inhibit tumors and induce M1 polarization of macrophages. (C) In vivo anti-tumor therapy of (pMETTL14+RS09)@cRGD-M. The volumes of subcutaneously transplanted tumors in MNNG/HOS tumor xenograft BALB/c-nu mice were recorded. (D, F) TUNEL staining in tumor tissues (Scale bar: 20 μm). (E, G) The numbers of M1 (iNOS) and M2 macrophages (CD163) in tumor tissues through IF staining (Scale bar: 20 μm) [76]. Reproduced under terms of the CC BY license. Copyright 2023, The Authors, published by KeAi Chinese Roots Global Impact.

3. The applications of bioinspired nanoparticles for the management of osteosarcoma

3.1. Primary osteosarcoma

Herein, we will introduce the applications of diverse bioinspired nanoparticles for the management of primary osteosarcoma (Table 2). Cell membrane-based nanoparticles have been directly exploited as a drug delivery system for osteosarcoma. Zhang and co-workers [73] utilized cell membranes (CM) from the human osteosarcoma cell line 143B to coat silica nanoparticles (SLNs), and the nanoparticles entrapped indocyanine green (ICG), denoted as CM/SLN/ICG, which was able to target OS and treat OS through photothermal effects. Cell membranes from the human osteosarcoma cell line WELL5 also exhibited excellent tumor-homing effects. Fu et al. [74] fabricated floxuridine and methotrexate co-loaded nanoparticles coated by WELL5 OS cell membranes (CCNPs) for the treatment of OS (Fig. 2A and B). CCNPs facilitated drug uptake by WELL5 cells and were rich in the tumor target site, thereby enhancing the anti-cancer activity of the drugs (Fig. 2C–E).

Cell membranes from the human osteosarcoma cell line HOS can also endow nanoparticles with OS-homing effects. As a paradigm, Wang et al. [75] used HOS cell membranes to coat IR780-loaded PLGA nanoparticles (MH-PLGA-IR780 NPs) (Fig. 3). MH-PLGA-IR780 NPs significantly facilitated osteosarcoma cell endocytosis, increased drug accumulation in the tumor in vivo, and could further enhance the photodynamic therapy effect under near-infrared irradiation. Moreover, MH-PLGA-IR780 NPs possessed the tumor-homing effect and photoacoustic/fluorescence (PA/FL) dual-modal imaging capabilities. This facilitated real-time dynamic monitoring of nanoparticle distribution within tumor tissues and thus had a potential for clinical application in the management of OS. Wu et al. [22] prepared VEGF-modified red blood cell membrane to co-load zoledronic acid and doxorubicin (V-RZCD) for OS treatment. The results showed that V-RZCD could target the VEGF receptors overexpressed on the surface of OS cells, thereby remarkably inhibiting OS proliferation.

Recently, the polarization of macrophages has been proven to play a pivotal role in remodeling the tumor microenvironment, and hence macrophage membrane-camouflaged nanoparticles promise great potential for the treatment of tumors [21,30]. As a paradigm, cRGD peptide-modified macrophage membrane-clocked nanoparticles (cRGD-M) were fabricated for targeted OS therapy [76]. RS09, a Toll-like receptor 4 (TLR4) agonist, and the methyltransferase like 14 (METTL14) were co-delivered by the nanoparticles, denoted as pMETTL14+RS09@cRGD-M. The cRGD-modified nanoparticles improved tumor targeting and macrophage membranes enabled immune evasion, which facilitated more nanoparticles accumulation in tumor tissues (Fig. 4A). In the tumor microenvironment, the pMETTL14+RS09@cRGD-M released pMETTL14 and RS09. Subsequently, METTL14 could downregulate TICAM2 to inhibit TLR4 signaling, while RS09 could activate TLR4 to polarize immunosuppressive M2 macrophages into antitumor M1 macrophages (Fig. 4B). In vivo pharmacodynamic studies suggested that pMETTL14+RS09@cRGD-M presented more potent remission of OS in MNNG/HOS-tumor-bearing mice (Fig. 4C), and enhanced cell apoptosis in tumor tissues, compared with other groups (Fig. 4D and F). Furthermore, as exhibited in Fig. 4E and G, immunofluorescence analysis revealed that an increased population of M2 macrophages (characterized by high expression of CD163) and a decreased population of M1 macrophages (characterized by high expression of iNOS), confirming tumor-associated macrophages (TAMs) repolarization. Accordingly, pMETTL14+RS09@cRGD-M could repolarize TAMs, remodel the tumor microenvironment, and amplify targeting therapeutic efficacy.

Exosome-based nanoparticles have also been applied for OS treatment. Targeted nanoparticles can be fabricated by modifying exosomes with targeting moieties [77,78]. In addition, exosome-derived non-coding RNAs have a crucial part in the progression of tumor development. Studies have reported that long non-coding RNA maternal expression gene 3 (lncRNA MEG3) exhibited potent tumor remission [79]. Huang et al. [80] developed engineered exosomes by combining exosomes with lncRNA, and they modified the exosomes with cRGD and entrapped MEG3 (cRGD-Exo-MEG3) for targeted treatment of OS, as shown in Fig. 5A cRGD-Exo-MEG3 might improve drug delivery to OS cells in vitro and in vivo, elevating the tumor-targeting efficiency of MEG3 and remarkably enhancing its anti-tumor effect against OS (Fig. 5B).

CRISPR/Cas9 is a potent gene editing tool, which presents promising

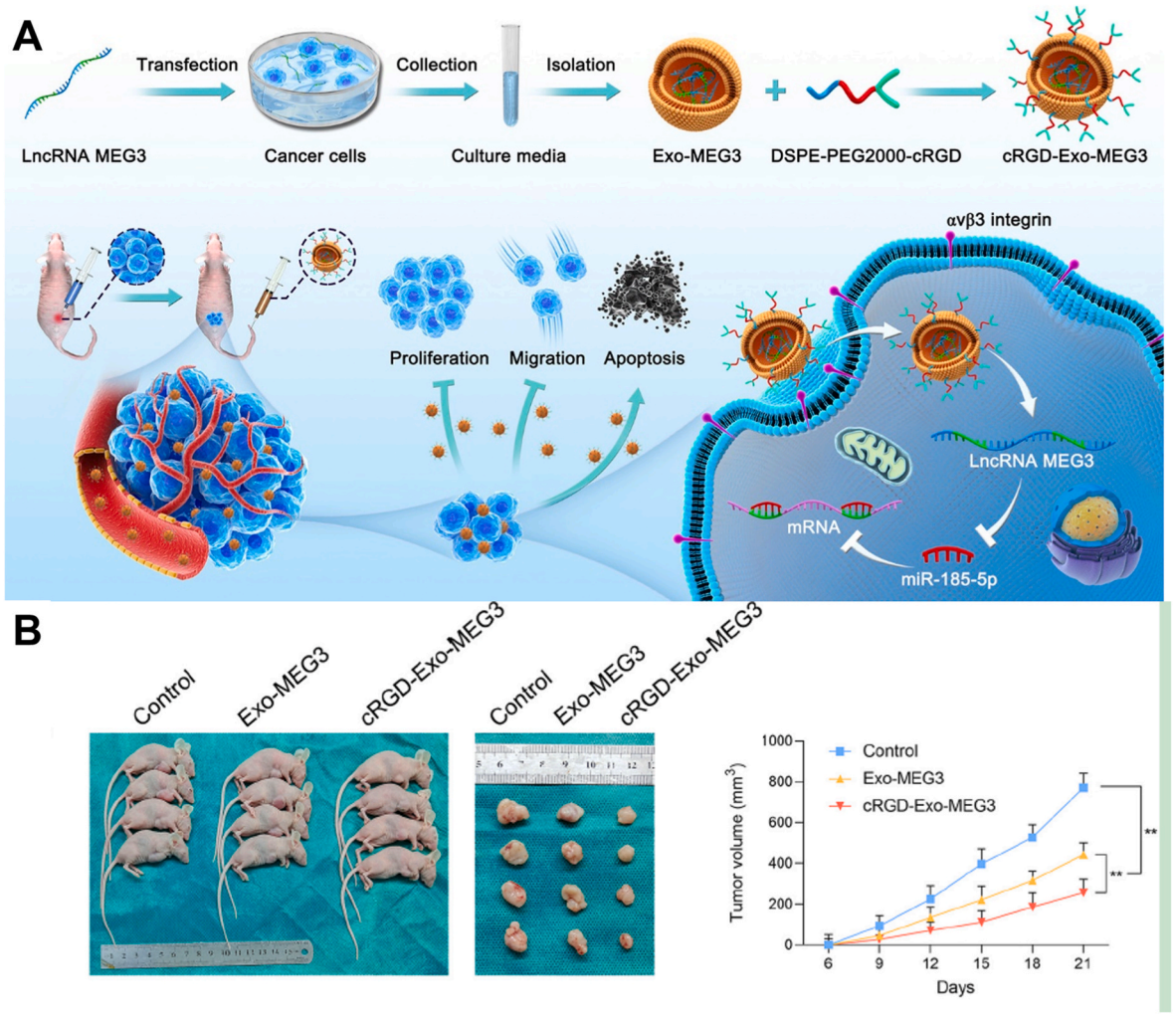

Fig. 5. Preparation of cRGD-Exo-MEG3 and its use in targeted treatment of OS. (A) Schematic diagram of the preparation process and the therapeutic mechanism of cRGD-Exo-MEG3 against OS cells. (B) In vivo anti-tumor therapy of cRGD-Exo-MEG3. The volumes of subcutaneously transplanted tumors in MNNG/HOS tumor xenograft BALB/c-nu mice were recorded [80]. Copyright 2022, Elsevier.

potential in biomedical applications [81]. On this basis, Du et al. [82] leveraged a genome-wide CRISPR/Cas9 screening approach to identify the Rad18 gene, a key driver of doxorubicin (DOX) resistance in OS cells. Mechanistically, Rad18 promoted homologous recombination (HR)-mediated DNA repair by stabilizing the MRE11-RAD50-NBS1 (MRN) complex, thereby enabling tumor cells to evade the DNA damage induced by DOX. The results revealed that elevated Rad18 expression in OS tissues was related to poor response to chemotherapy and prognosis. Subsequently, siRad18 was loaded into RGD peptide-engineered targeted exosomes (RGD-EXO) to overcome OS DOX resistance. RGD-EXO enhanced tumor-specific accumulation, effectively silenced Rad18, and amplified DNA damage and apoptosis in OS cells. In 143B tumor xenograft BALB/c nude mice, siRad18-loaded RGD-EXO, combined with DOX remarkably suppressed the OS progression. This study provides a proof-of-concept for the synergy between precision gene editing and engineered targeted exosomes for optimizing OS therapy.

Bone marrow mesenchymal stem cells (BMSCs) are ideal candidates for large-scale production of exosomes, due to their multipotency, stability, and ease of expansion. On these grounds, Doxorubicin-loaded BMSCs-derived exosomes (Exo-Dox) were developed and their chemotaxis towards OS cells through the SDF1-CXCR4 axis was confirmed [83]. In vivo pharmacodynamic results indicated that Exo-Dox notably alleviated tumor burden and minimized cardiotoxicity, compared with free doxorubicin, ascribed to the homing ability of BMSCs-derived exosomes toward OS cells. In addition, Wang et al. [84] designed doxorubicin-loaded BMSCs-derived exosome mimetics (EM-Dox) through a sequential extrusion process. EM-Dox exhibited pH-responsive drug release and a potent inhibitory effect on OS. Moreover, EM-Dox was found to reduce systemic toxicity in cardiac and hepatic tissues, compared with free doxorubicin.

Protein template-based nanoparticles have been well-developed as the powerful nanoparticles for the treatment of OS. Transferrin-based nanoparticles have a promising potential for the management of OS, because the transferrin receptor is overexpressed in OS cells. Nakase and co-workers [85] constructed transferrin-modified liposomes to load the p53 gene (transferrin-liposome-p53) and evaluated the therapeutic effect of transferrin-liposome-p53 on OS. The transferrin-liposome-p53 group was able to inhibit the growth of osteosarcoma cells HOSM-1 by 60.7 %. In HOSM-1 xenograft nude mice, after 25 days of treatment, the average tumor size in the transferrin-liposome-p53 group was 10 % of its counterpart in the control group. The results indicated the transferrin-liposome-p53 system had the potential for OS management. Transferrin was conjugated with the human 53BP1 protein, which had an OS-treating effect, to form a binary complex [86]. Because transferrin could bind to the transferrin receptor overexpressed on the surface of OS cells, the complex was able to be efficiently internalized by the U2OS 2-6-3 human OS cell line.

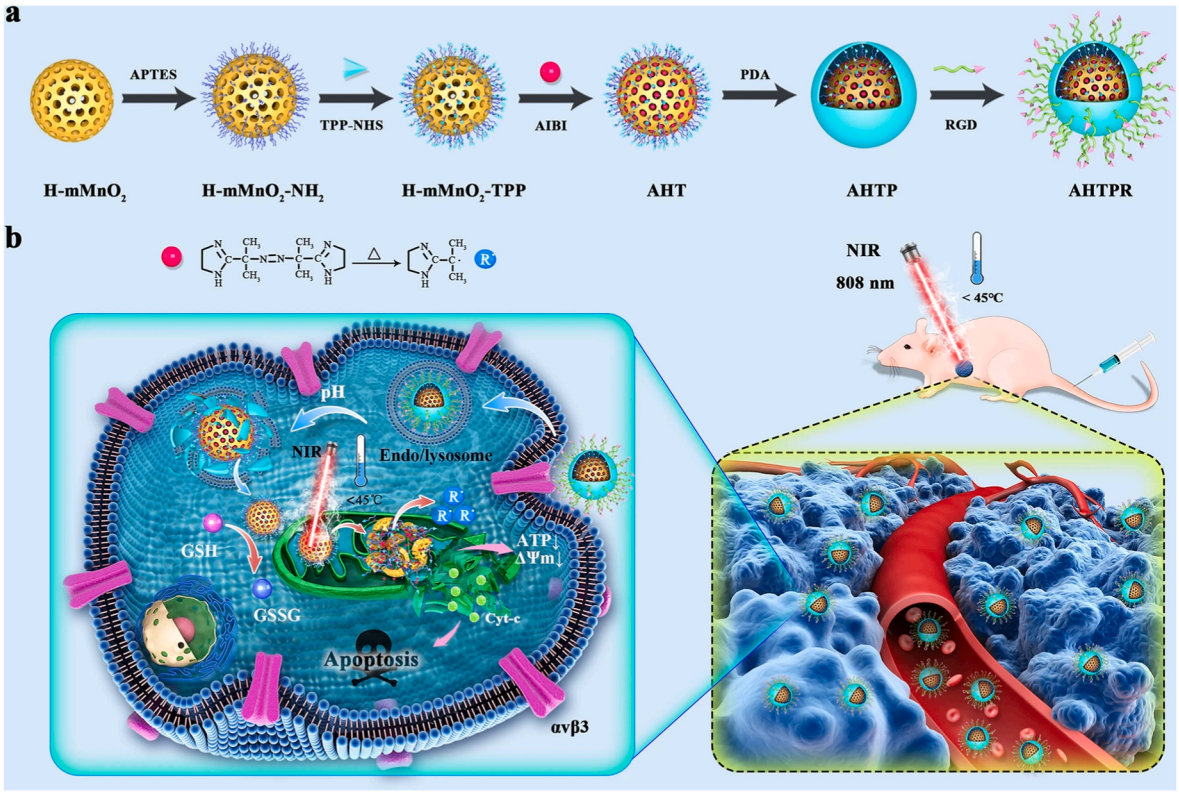

Fig. 6. Schematic diagram of the preparation process of AHTPR NPs and their therapeutic mechanism for OS treatment. AHTPR NPs were prepared by sequential synthesis of H-mMnO$_2$, mitochondria-targeting TPP modification, AIBI entrapment, PDA coating, and RGD peptide conjugation. RGD enabled tumor-specific accumulation, and the pH-responsive PDA shell ensured controlled AIBI release in the acidic tumor microenvironment. Under NIR irradiation, local hyperthermia triggered the released AIBI to generate oxygen-independent free radicals, synergized by MnO$_2$-mediated GSH depletion, leading to mitochondrial dysfunction and apoptosis in osteosarcoma cells [91]. Reproduced under terms of the CC BY license. Copyright 2021, The Authors, published by BMC Press.

Table 3
Summary of representative bioinspired nanoparticles in metastatic osteosarcoma treatment.

Type	Bioinspired nanoparticles	Cargo	Animal models	Refs
Cell membranes	143B and RAW264.7 hybrid cell membrane-coated PLGA nanoparticles	Paclitaxel	143B tumor xenograft BALB/c-nu mice	[31]
Exosomes	MG63-derived exosomes	miR-665	MG63 tumor xenograft BALB/c-nu mice	[96]
	BMSCs-derived exosomes	Rifampicin	143B tumor xenograft BALB/c-nu mice	[97]
	HUC-MSCs-derived exosomes	Rhodamine dye; Gd(III)	K7M2 tumor xenograft NU/NU nude mice	[98]
Proteins	pH-responsive BSA nanoparticles	Zoledronic acid; Methotrexate; CpG	K7M2 tumor xenograft BALB/c-nu mice	[99]
	PCP-PEG self-assembled nanoparticles	Aldoxorubicin	143B tumor xenograft BALB/c-nu mice	[100]
Peptides	STP targeting peptide-modified nanogel	Shikonin	143B tumor xenograft BALB/c-nu mice	[101]
	RGD-modified mesoporous nanoparticles	Indocyanine green	143B tumor xenograft BALB/c-nu mice	[103]
	CXCR1 targeting peptide-modified magnetic silica nanoparticles	Cisplatin	CTC-derived cells tumor xenograft BALB/c-nu mice; patient-derived tumor xenograft model	[104]
	Redox-responsive polypeptide micelles	Doxorubicin	143B tumor xenograft BALB/c-nu mice	[105]

BMSCs: Bone marrow mesenchymal stem cells; BSA: Bovine serum albumin; CTC: Circulating tumor cell; CpG: Cytosine-phosphonate-guanine; HUC-MSCs: Human umbilical cord mesenchymal stromal cells; PCP: Positively charged protein; PEG: Polyethylene glycol; PLGA: Poly(lactic acid-glycolic acid).

Kang et al. [87] developed a nanoparticle based on human serum albumin (HSA), to co-deliver alendronate sodium (AD) and doxorubicin (DOX) (HSA-AD/DOX). The results showed HSA-AD/DOX had a 5-fold higher affinity for the hydroxyapatite-collagen matrix, compared with HSA/DOX, demonstrating the potential of HSA-AD/DOX for OS management. María and co-workers [88] fabricated nanoparticles for targeted therapy of OS. They fabricated polyacrylic acid (PAA)-coated mesoporous silica nanoparticles (MSNs), and PAA was chemically conjugated with the plant lectin concanavalin A (ConA). ConA could recognize the overexpressed glycans on the surface of OS cells. Therefore, compared with the nanoparticles without ConA modification, the DOX-loaded targeted nanoparticles showed a stronger inhibitory effect on human osteosarcoma cells.

Peptide template-based nanoparticles are also widely investigated to realize OS-targeted drug delivery. Stewart et al. prepared doxorubicin-loaded micelles with diverse numbers of Asp modifications [65]. The results showed that micelles with 8 Asp modifications (Asp8) had a binding rate of up to 91 % with hydroxyapatite (HAp), while micelles with 4 Asp modifications had a 55 % binding rate with HAp. Accordingly, Asp8 could improve the targeting of DOX to OS, reduce DOX

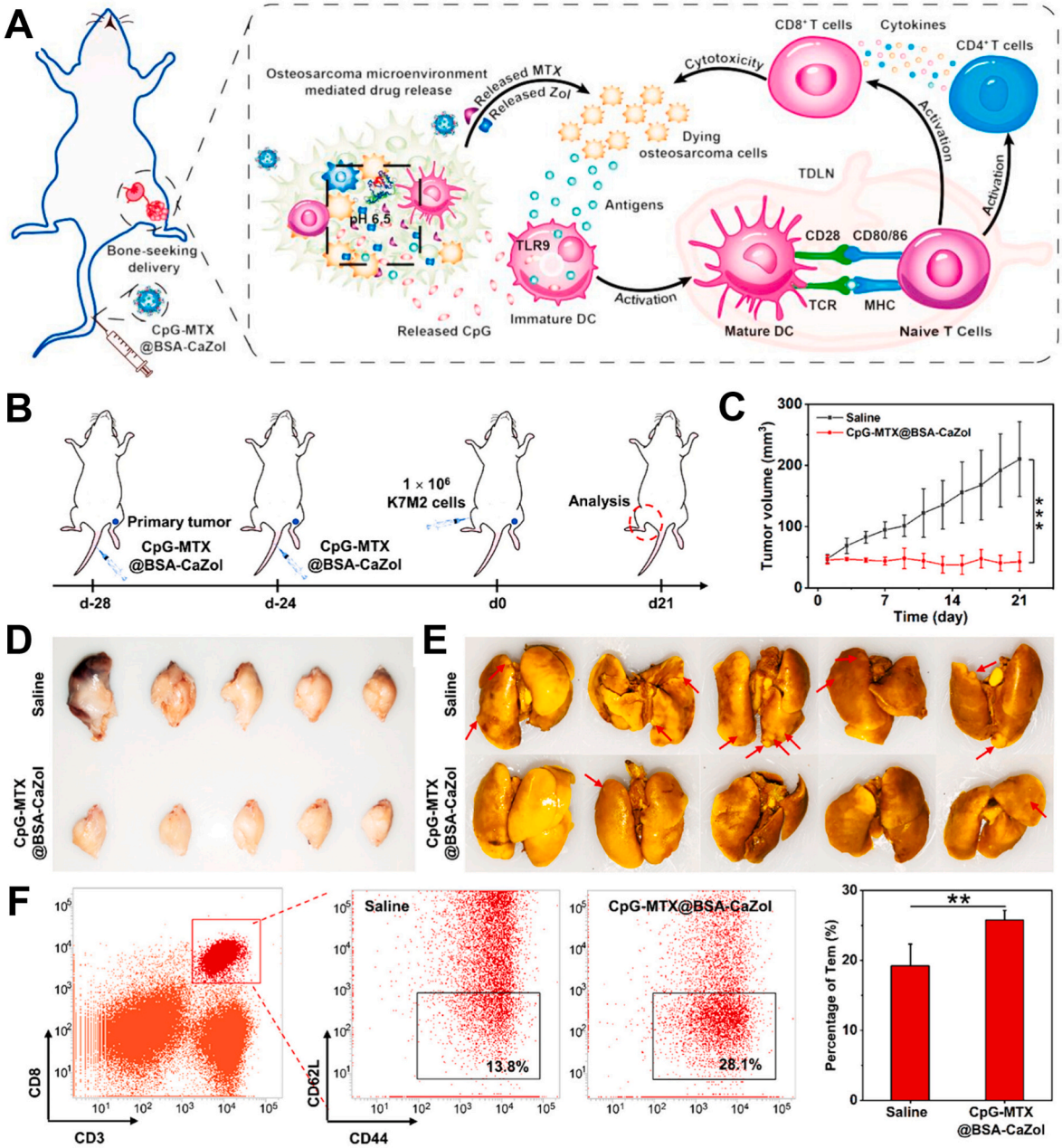

Fig. 7. Preparation of CpG-MTX@BSA-CaZol and their in-situ vaccination strategy for the treatment of OS. (A) Schematic diagram of the therapeutic mechanism of CpG-MTX@BSA-CaZol for OS through pH-triggered release of Zol, CpG, and MTX, which could facilitate the maturation of dendritic cells and activate CD8 T cells. (B) Experimental scheme for the rechallenge tests. (C) Rechallenge osteosarcoma growth curves. (D) Primary and (E) lung metastatic osteosarcoma photos acquired on day 21 (arrows indicate the pulmonary metastatic nodules). (F) Proportions of effector memory T cells in the spleen analyzed by flow cytometry on day 21 right before rechallenging mice with secondary osteosarcomas [99]. Copyright 2023, American Chemical Society.

distribution in normal tissues, and alleviate the adverse effects of DOX.

Fang et al. [89] prepared RGD-modified micelles loaded with DOX (RGD-DOX-PM). Because of the specific binding between RGD and the integrins on the surface of osteosarcoma MG-63 cells, RGD-DOX-PM exhibited targeted killing of OS cells. Compared with free RGD-pretreated cells, untreated MG-63 cells presented higher uptake of RGD-DOX-PM and about 6-fold inhibition of osteosarcoma cell proliferation. Lu et al. [90] prepared RGD-modified DOX-loaded nanocomposites with photothermal agent, Bi_2S_3@MSNs (RGD-Bi_2S_3@MSN/DOX), which presented remarkably OS-killing capabilities. Hu and co-workers [91] co-modified RGD and mitochondrial targeting ligand (4-carboxybutyl) triphenylphosphonium on nanoparticles, denoted as AHTPR NPs (Fig. 6). The RGD targeting modification enabled AHTPR NPs to target osteosarcoma cells and induce mitochondrial dysfunction and apoptosis in osteosarcoma cells.

PT peptide (PPSHTPT) resembles natural osteocalcin and can specifically bind to OS cells, and presents OS-targeted both in vitro and in vivo. Yuan and co-workers [92] conjugated PT peptide modified to semiconductor polymer nanoparticles (SPNs), endowing SPNs with OS-targeting properties. Following the PT-peptide targeting modification, SPNs could be actively taken up by OS cells within 4 h, thus enhancing the phototherapeutic efficacy for OS. The in vivo NIR-II fluorescence and photoacoustic signals were elevated by the PT-peptide modification, hence offering high-sensitivity and high-resolution imaging of OS targets. Moreover, PT-modified SPNs could realize dual-modal imaging-guided phototherapy against OS

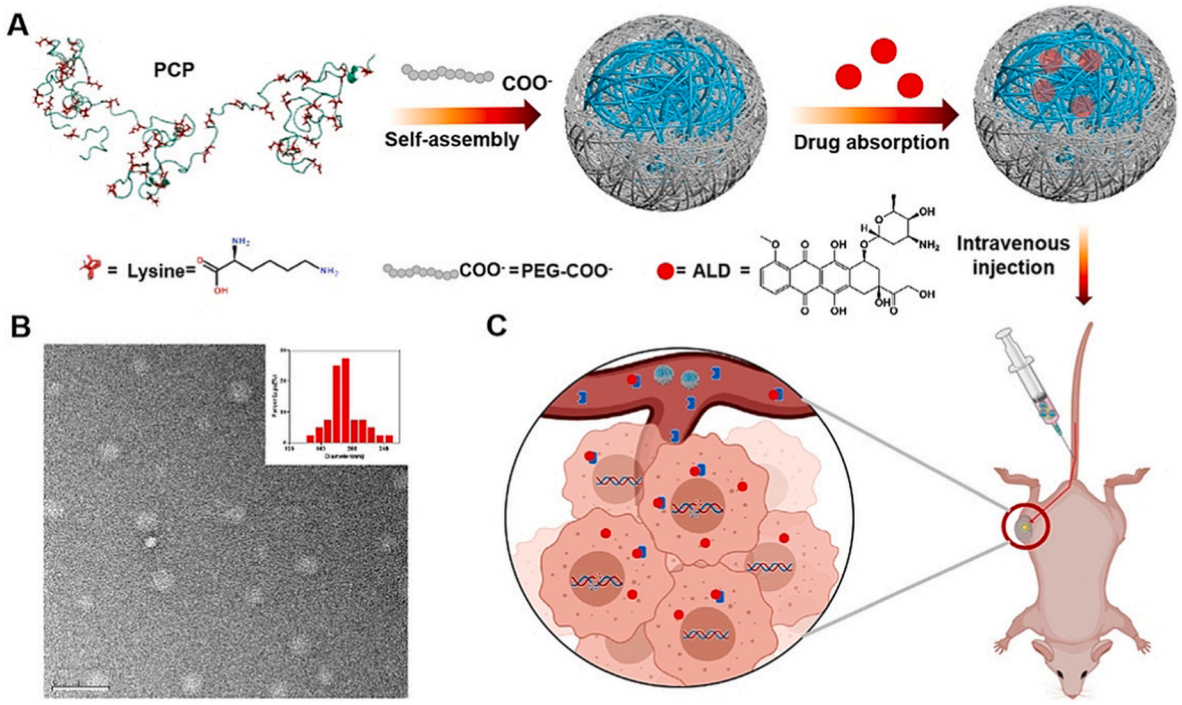

Fig. 8. Schematic diagram of the preparation process of PCP-PEG-ALD nanoassemblies and their use for OS treatment. (A) PCP-PEG-ALD nanoassemblies were prepared by cationic PCP and anionic PEG via electrostatic interactions, followed by hydrophobic entrapment of ALD. (B) TEM image and size distribution of PCP-PEG-ALD nanoassemblies. PCP-PEG-ALD nanoassemblies presented a uniform spherical structure, with an average diameter of approximately 200 nm (Scale bar: 500 nm). (C) PCP-PEG-ALD nanoassemblies were administrated into osteosarcoma xenografts in mice for in vivo study [100]. Copyright 2021, John Wiley and Sons.

without systemic toxicity. These results demonstrated that PT-modified SPNs have a promising potential as precise theranostic nanoparticles, synergistically enhancing imaging sensitivity and therapeutic outcomes in OS.

OS is highly heterogeneous, and common tumor-targeting peptides often suffer from the risk of off-target effects when they are employed to target highly mutated cancers [93]. Using phage display technology to select the specific targeting peptides for highly mutated cancers could overcome the challenge of the lack of tumor-specific targeting moieties. Lin et al. [94] used phage display technology to screen a specific tumor-targeting peptide with the sequence TPPPRVPLLTFGS, and modified this peptide onto the surface of two-dimensional nanodiscs. OS cells showed remarkably elevated uptake of the nanoplates modified with the specific tumor-targeting peptide, which could greatly extend the retention time of the nanodiscs at the tumor site (up to 24 d). Meanwhile, the specific tumor-targeting peptide remarkably reduced adverse effects caused by the off-target effect, achieving precise targeting for highly heterogeneous OS. These results indicated that specific tumor-targeting peptides have the promising potential for personalized management of OS.

3.2. Metastatic osteosarcoma (MOS)

Over the past decade, targeted therapy for MOS has attracted widespread attention. Researchers are exploring the use of targeting specific molecular abnormalities in OS cells, as well as the precise identification of different cell markers or pathways, to enhance treatment efficacy while reducing non-target organ distribution. Bioinspired nanoparticles can improve specific targeting properties by recognizing the homotypic characteristics of OS cells and tissues. Herein, we will introduce the applications of diverse bioinspired nanoparticles for the management of MOS (Table 3).

The osteosarcoma 143B cell membranes and macrophage RAW264.7 cell membranes were co-extruded in equal amounts, to obtain paclitaxel (PTX)-loaded hybrid membrane-coated PLGA nanoparticles (PTX-PLGA@[143B-RAW] NPs) for the management of MOS [31]. PTX-PLGA@[143B-RAW] NPs presented osteosarcoma targeting properties, high cellular uptake by 143B cells, and desirable anticancer effects against 143B cells. Furthermore, in 143B tumor xenograft mice, PTX-PLGA@[143B-RAW] NPs could not only inhibit osteosarcoma growth and migration, but also show negligible adverse effects.

Exosome-based nanoparticles are also gaining more and more attention in MOS therapy. Recent advances proved that miR-665 suppressed osteosarcoma proliferation [95]. Zhang and co-workers [96] loaded miR-665 into exosomes (miR-665 Exo) for the management of osteosarcoma. The results showed that miR-665 Exo presented excellent targeting and anti-cancer effects both in vitro and in vivo. Additionally, miR-665 Exo displayed desirable safety.

Chen et al. [97] prepared rifampicin-loaded BMSC-derived exosomes (EXO-RIF), which facilitated the uptake of rifampicin by OS cells, and elevated its inhibitory effects on OS proliferating, migrating, and invading. In vivo experiments showed that EXO-RIF could target OS, induce OS apoptosis, and enhance survival rates in 143B-tumor-bearing nude mice, indicating a potential for the treatment of MOS. Abello and co-workers [98] employed a near-infrared dye and an MRI contrast agent gadolinium to label exosomes from human umbilical cord mesenchymal stromal cell (HUC-MSC) and detected their distribution in ectopic osteosarcoma-bearing mice using in vivo MRI and near-infrared imaging. The results showed that 24–48 h after intravenous injection, HUC-MSC exosomes accumulated continuously in the osteosarcoma, while labeled lipid nanoparticles accumulated only in the tumor for the first 3 h after injection. These results indicated that HUC-MSC exosomes had better osteosarcoma targeting properties than lipid nanoparticles.

Protein template-based nanoparticles have also been developed for drug delivery in the management of MOS. Wang et al. [99] developed a pH-responsive bioinspired nanoparticle based on bovine serum albumin, co-loading zoledronic acid (Zol), methotrexate (MTX), and the immunomodulator cytosine-phosphonate-guanine (CpG, an unmethylated short-stranded oligodeoxynucleotide), for synergistic

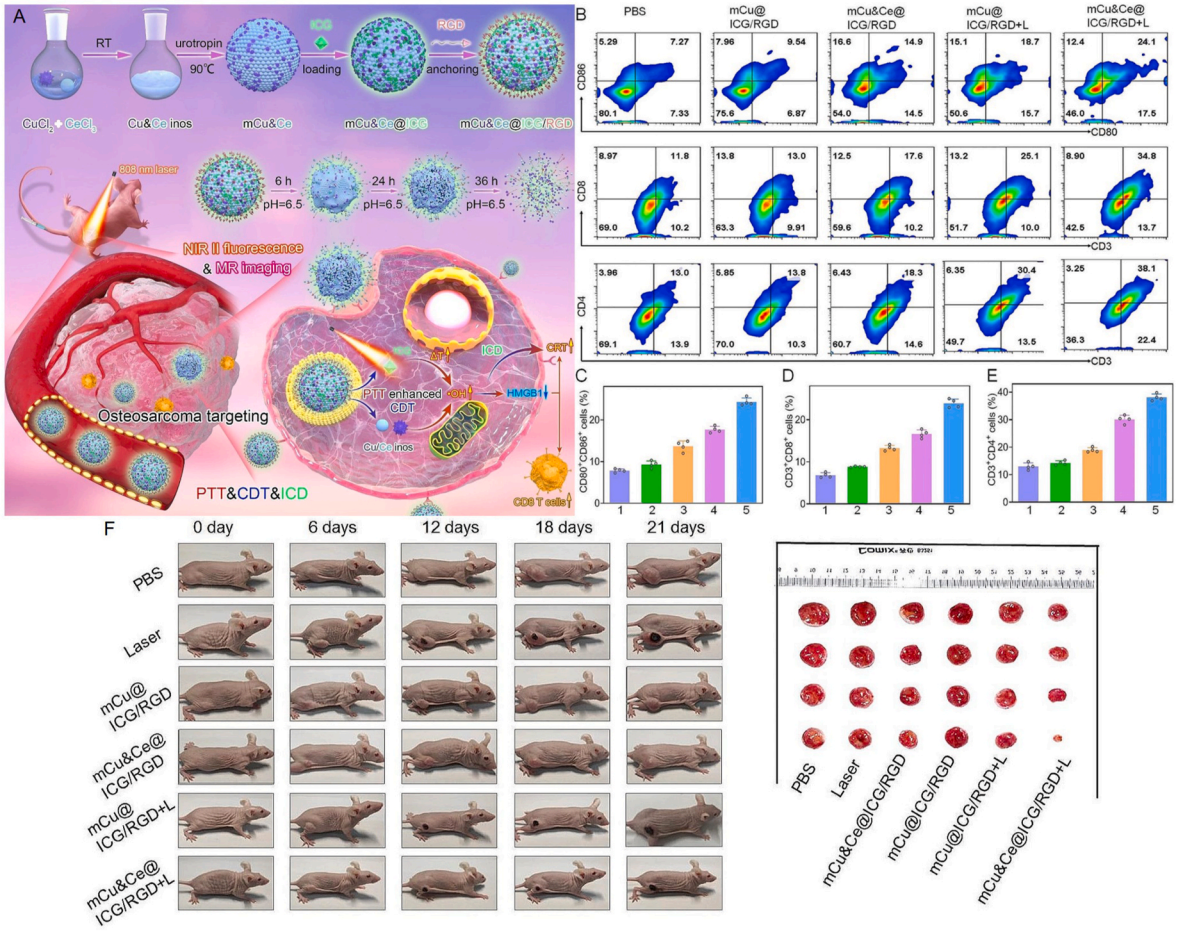

Fig. 9. Preparation of mCu&Ce@ICG/RGD and its use in the theranostics of metastatic OS. (A) Schematic diagram of the preparation process of mCu&Ce@ICG/RGD for NIR-II fluorescent/MR dual-modal bioimaging-guided synergistic tumor suppression by PTT&CDT&ICD. (B) Flow cytometer analysis of DCs maturation in tumor-drained lymphatic node, CTLs, and helper T cells in tumor tissues. Quantitative percentage of above (C) DCs, (D) CTLs, and (E) helper T cells. 1–5 refers to PBS, mCu@ICG/RGD, mCu&Ce@ICG/RGD, mCu@ICG/RGD + L, and mCu&Ce@ICG/RGD + L, respectively. (F) In vivo anti-tumor therapy of mCu&Ce@ICG/RGD. The volumes of subcutaneously transplanted tumors in 143B tumor xenograft BALB/c-nu mice were recorded [103]. Reproduced under terms of the CC BY license. Copyright 2024, The Authors, published by BMC Press.

chemo-immunotherapy of osteosarcoma (Fig. 7A). The nanoparticles could target osteosarcoma cells, release drugs in the acidic microenvironment of OS, and accumulate in the tumor for approximately a week. Moreover, the nanoparticles inhibited the development and lung metastasis of OS, promoted the maturation of dendritic cells and activated CD8 T cells (Fig. 7B–F). Accordingly, the nanoparticles could exert an in-situ vaccination effect. Therefore, this nanoparticle had a promising potential for synergistic chemoimmunotherapy of primary and metastatic OS.

A nanoparticle formed by self-assembly of positively charged protein (PCP), polyethylene glycol (PEG), and the prodrug aldoxorubicin (ALD), denoted as (PCP-PEG-ALD) (Fig. 8A) [100]. As exhibited in Fig. 8B, the PCP-PEG-ALD had a particle size of about 200 nm with uniform morphology, controlled drug release, and showed desirable biocompatibility. Furthermore, PCP-PEG-ALD exhibited extremely potent anti-tumor efficacy, remarkably inhibiting OS proliferation and reducing lung MOS.

Peptide template-based nanoparticles are also widely employed in this domain. Li and co-workers [101] fabricated a shikonin (SHK)-loaded redox-responsive nanogel (STP-NG) modified with the STP targeting peptide, denoted as STP-NG/SHK. The results showed the STP-NG/SHK group remarkably decreased osteosarcoma lung metastasis, with an obvious marked reduction in average lung weight, alleviated tumor burden, and a substantial elevation in long-term survival rate (with a 90-day survival rate of 71.4 %). Targeting OS cells with STP provides a novel approach for active targeting drug delivery for the management of MOS.

Immunogenetic cell death (ICD) is a type of cell death that stimulates an immune response by releasing antigens and sending out danger signals, which presents great advantages in immunotherapeutic strategies for cancer treatment [102]. As a paradigm, Cheng and co-workers [103] developed an RGD-modified ICG-loaded mesoporous Cu and Ce based oxide nanoparticles (mCu&Ce@ICG/RGD) for the theranostics of metastatic osteosarcoma. As represented in Fig. 9A, the RGD targeting modification enabled mCu&Ce@ICG/RGD to realize OS targeting. Upon 808 nm light activation, on one hand, mCu&Ce@ICG/RGD exhibited NIR-II fluorescence beyond 1000 nm, and MRI signal of osteosarcoma bearing lymphatic metastasis. On the other hand, mCu&Ce@ICG/RGD presented a synergistic effect on PTT, chemodynamic therapy (CDT), and immunotherapy by ICD for the treatment of MOS. As expected, mCu&Ce@ICG/RGD presented a remarkable inhibition effect on tumor cells and prolonged survival 143B-tumor-bearing mice (Fig. 9F). Furthermore, mCu&Ce@ICG/RGD elevated $CD80^+$ and $CD86^+$ dendritic cells by approximately 24.1 % in tumor-draining lymph nodes, as exhibited in Fig. 9B and C. Concurrently, cytotoxic T cells ($CD8^+$ and $CD3^+$) and helper T cells ($CD4^+$ and $CD3^+$) infiltrated tumors, as presented in Fig. 9D and E. The robust antitumor immunity could be attributed to ICD triggered by hyperthermia and ROS amplification.

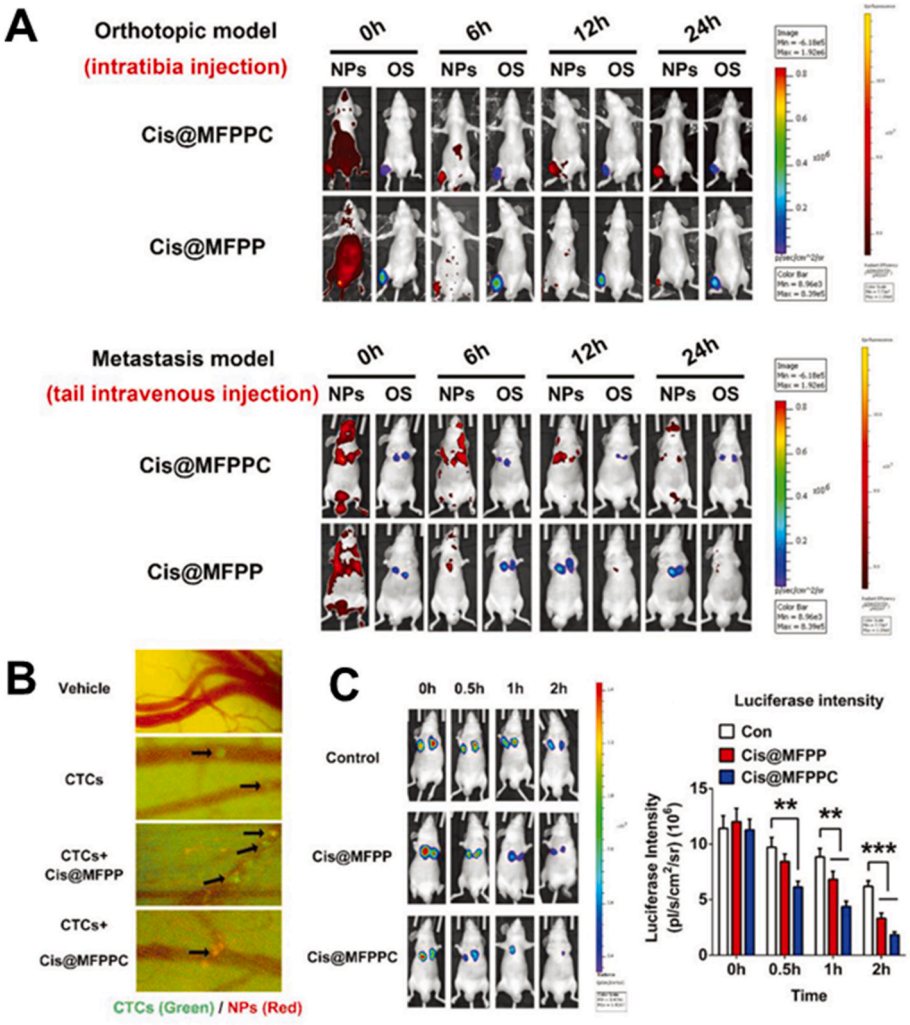

Fig. 10. The use of Cis@MFPPC in the treatment of orthotopic and lung metastatic OS. (A) Representative bioluminescence (CTC-derived cells) and fluorescence (NPs in red) imaging of the orthotopic osteosarcoma model and lung metastasis model at 0, 6, 12, and 24 h after i.v. injection of Cis@MFPP (15 mg/kg) or Cis@MFPPC (15 mg/kg). (B) Real-time monitoring of Cy7-labeled nanoparticles and GFP-labeled CTCs in the circulating blood in vivo. (C) The CTC survival in the lungs [104]. Copyright 2019, John Wiley and Sons.

Accordingly, mCu&Ce@ICG/RGD has been proven to be a promising nanoplatform for MOS theranostics.

Circulating tumor cells (CTCs) are tumor cells that detach from the primary tumor and enter the bloodstream. In metastatic cancers, CTCs are crucial in that they are the initiators and a key step in the process of tumor metastasis. Han and co-workers [104] utilized a CXCR1-targeting peptide, which could target CTCs, to construct cisplatin-loaded nanoparticles that targeted MOS. The nanoparticles could accumulate drugs in OS CTCs, thereby effectively suppressing OS growth and lung metastasis in CTC-tumor-bearing nude mice (Fig. 10).

Yin et al. [105] prepared DOX-loaded redox-responsive polypeptide micelles for the management of OS lung metastasis. The micelles could target osteosarcoma cells, reduce the cardiac distribution of DOX, and alleviate adverse effects. In vivo pharmacodynamic results showed that in the orthotopic 143B tumor xenograft nude mice, the mice in the DOX-loaded micelles group had a remarkably reduced number of metastatic lung nodules, and the average lung weight of the 143B-tumor--bearing mice was significantly lower than that of the control group. These results demonstrated the promising potential of the DOX-loaded micelles for the management of osteosarcoma lung metastasis.

4. Conclusions

This review highlights the transformative potential of bioinspired nanoparticles for the management of OS and opens up new avenues for research and development. Nevertheless, multiple aspects must be carefully considered to facilitate further advancement of bioinspired nanoparticles for OS treatment and its clinical translation.

Firstly, as a malignant tumor, OS exhibits a high degree of intratumoral heterogeneity, which limits the efficacy of single-ligand targeting strategies. For instance, RGD peptides, which are widely employed to target αvβ3 integrins, present off-target binding to other cells, because of the presence of αvβ3 integrins on the surface of endothelial and stromal cells. The off-target RGD peptide could reduce the tumor-specific accumulation of RGD-modified nanoparticles and increase systemic toxicity [106]. Dual- or triple-ligand target functionalization could improve specific targeting by requiring concurrent distinct biomarker recognition on target cells [107]. In addition, several aberrant stimuli within the tumor microenvironment (TME), such as pH, ROS, GSH, and matrix metalloproteinase (MMP), could enable the temporally and spatially controlled release of cargos in response to these aberrant stimuli.

Secondly, research into the trajectory of nanomedicine highlights biosafety risks as the leading factor in project discontinuations [108].

Although bioinspired nanoparticles derived from nature present superb biocompatibility, attractive biodegradability, and low immunogenicity, some of them have the potential to accumulate in the liver and spleen, thereby posing risks of chronic inflammation, especially with non-degradable synthesized cores of inorganic nanoparticles [109]. Therefore, it is crucial to carefully evaluate the biosafety of all ingredients in the formulations of the bioinspired nanoparticles. In addition, utilizing patient-specific nanoparticles, such as cell membranes or exosomes derived from a patient's own MSCs or immune cells, has the potential to mitigate immunogenic risks and provide a promising potentially efficacious approach to personalized medicine for OS.

Thirdly, the scalability and reproducibility of bioinspired nanoparticles are hindered by labor-intensive production methods and batch-to-batch variability. Cell membrane-based nanoparticles struggle with high cost and low loading capacity, and exosome-based nanoparticles suffer from composition variability and cumbersome extracted steps. Fortunately, several novel techniques have opened new avenues for addressing these obstacles. For instance, high-throughput microfluidic platforms enable single-step preparation of exosomes with precise control over size (PDI$<$0.1) and membrane composition, which clearly outperforms traditional methods of preparing exosomes, such as ultracentrifugation. In addition to microfluidics, tangential flow filtration (TFF) has been applied to extract exosomes [110]. Compared with ultracentrifugation, TFF could enhance yield by 3–5 fold while preserving critical surface markers (CD63, CD9) of exosomes. Notably, scaling microfluidic and TFF technologies leads to a reduction in production costs while ensuring reproducibility.

Lastly, while preclinical studies dominate current research, validation of long-term safety and therapeutic efficacy in humans demands costly, large-scale clinical trials. Furthermore, the absence of harmonized international regulatory frameworks complicates the approval processes of bioinspired nanoparticles, exacerbated by material heterogeneity and inconsistent characterization methodologies. The rigorous evaluation of physicochemical parameters (e.g., size, dispersity, metabolic stability) of bioinspired nanoparticles is critical yet difficult, because the nanoparticles are more complicated than conventional drugs. Additionally, the lack of expertise in industrial-scale production further delays commercialization. Addressing these challenges requires interdisciplinary collaboration to align regulatory standards, optimize analytical methods, and streamline manufacturing workflows.

As we stand on the brink of this new era in cancer therapy, it is evident that bioinspired nanoparticles represent more than an incremental improvement. Instead, they mark a fundamental shift towards more intelligent, responsive, and patient-centered approaches to the treatment of OS. Continued interdisciplinary collaboration between nanotechnology, molecular biology, and clinical medicine, will be essential in realizing the full potential of bioinspired nanoparticles in OS treatment. The journey from bench to bedside is fraught with challenges, but the promise of the bioinspired nanoparticles for the management of OS illuminates a hopeful path forward in the quest to conquer OS.

CRediT authorship contribution statement

Kai Cui: Writing – original draft, Conceptualization. **Fei Ren:** Writing – review & editing. **Jian Yu:** Supervision, Software. **Hong Pan:** Supervision.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Data availability

No data was used for the research described in the article.

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