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Cell Membrane-Coated Biomaterials for Bone Cancer-Targeted Diagnosis and Therapy: A Critical Update on Osteosarcoma Applications

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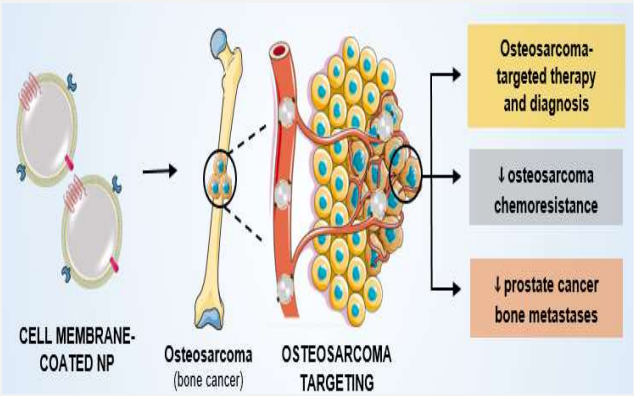
ABSTRACT

Cancer is a malignant disease of increasing concern on account of its high heterogeneity, high mortality and morbidity rates, as well as absence of targeted and effective therapeutic regimes. The recent introduction of biomimetic and nature-inspired principles in the development of nanosystems has significantly impacted cancer therapies and diagnosis. Biomembrane-surface engineered nanosystems are bioinspired nanoconstructions equipped with cell-mimicking features to improve *in vivo* interactions with surrounding biological environments and cells. These next-generation nanosized delivery systems can enhance the therapeutic efficacy and safety of conventional cancer therapies by providing highly specific, targeted, and safer nanomedicines. Herein, we have discussed the unique features of cell membrane-coated biomimetic nanodevices (including superior biocompatibility, immune evasion, and tissue-homing features) that allow for promising osteosarcoma-targeted diagnosis, therapy, and theranostics. We also summarized the recent advances in the cell membrane- and hybrid cell membrane-coated nanosystems for both primary bone cancer and metastatic scenarios, especially prostate cancer-derived bone metastases. Future perspectives and challenges toward successful clinical translation are also highlighted.



Keywords: Biomimetic coating, bone cancer, osteosarcoma, cell membrane-coated, nanosystem, hybrid cell membrane-coated, osteosarcoma-targeted medicine

1. Introduction

Cancer, a malignant disease of increasing prevalence, ranks amongst the leading causes of mortality and morbidity globally [1-4]. Osteosarcoma (OS), also called osteogenic sarcoma, is the most common malignant bone disease in children and adolescents [5-7]. This serious and life-threatening bone malignancy is associated with the proliferation

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of malignant mesenchymal cells [5, 8]. Typically, OS is marked by: (i) significant bone destruction (osteolysis); (ii) accelerated disease progression; (iii) high tumor aggressiveness; (iv) early dissemination and systemic metastasis (mostly in the lungs); and (v) elevated mortality rates [5-9]. Metastatic lesions occurrence is a strong indicator of poor prognosis [6, 9]. The five-year survival rates are usually < 30% in metastatic OS patients, whereas non-metastatic OS patients have survival rates > 70% [8, 10]. Early clinical diagnosis of OS is very challenging due to poor symptom specificity. Current therapeutic regimes include tumor surgical resection alongside adjuvant chemotherapy; however unwanted side effects of chemotherapeutics largely hinder their clinical implementation [5, 8].

The advent of nanoparticles (NPs) has undoubtedly marked an important turning point in the diagnosis and therapy of various diseases [11-13]. Despite decisive advances in both therapeutic efficacy and safety goals, the rapid clearance, poor biocompatibility, and the lack of specific tissue-homing features of nanomaterials *per si*, have been emphasized as concerning issues towards their successful clinical translation [14-16]. Recently, the design of bioinspired nanosystems with cell-mimicking functions has been receiving particular attention to enhance their performance *in vivo* [17-19]. So far, various cell-derived membranes have been coating NPs, including those derived from red blood cells [20], white blood cells [17], platelets [21], stem cells [22, 23], and cancer cells [18]. Each cell membrane type provides specific donor cell-related features. The development of hybrid cell membranes is a current tendency to combine the biofunctionalities of different cell membranes on a single nanosystem. The present review covers the recent advances in the cell membrane- and hybrid cell membrane-coated nanodevices for precise and safe OS-targeted clinical diagnosis, therapy, and theranostics. Their applicability for both primary OS cancer and metastatic scenarios, namely prostate cancer-derived bone metastases, will be discussed.

2. Biomimetic nanosystems as next-generation drug delivery systems

In the last years, different strategies have been applied in the rational design of nanosized materials to enhance their biocompatibility, immune evasion ability, specific targetability to diseased tissues, and ultimately therapeutic efficacy [24, 25]. A schematic illustration regarding the three generations of nanosystems is presented in **Figure 1**, which comprises:

The first generation of NPs: Development of PEGylated NPs to reduce *in vivo* interactions with the immune system, making them undetectable by the mononuclear phagocytic system.

The second generation of NPs: Design of cell-targeted NPs by surface functionalization with cell-targeting ligands that endow them with active specific-tissue homing features.

The third generation of NPs: Fabrication of cell membrane-coated NPs to combine the biopharmaceutical benefits of NPs with the biointerfacing features of natural cell membranes.

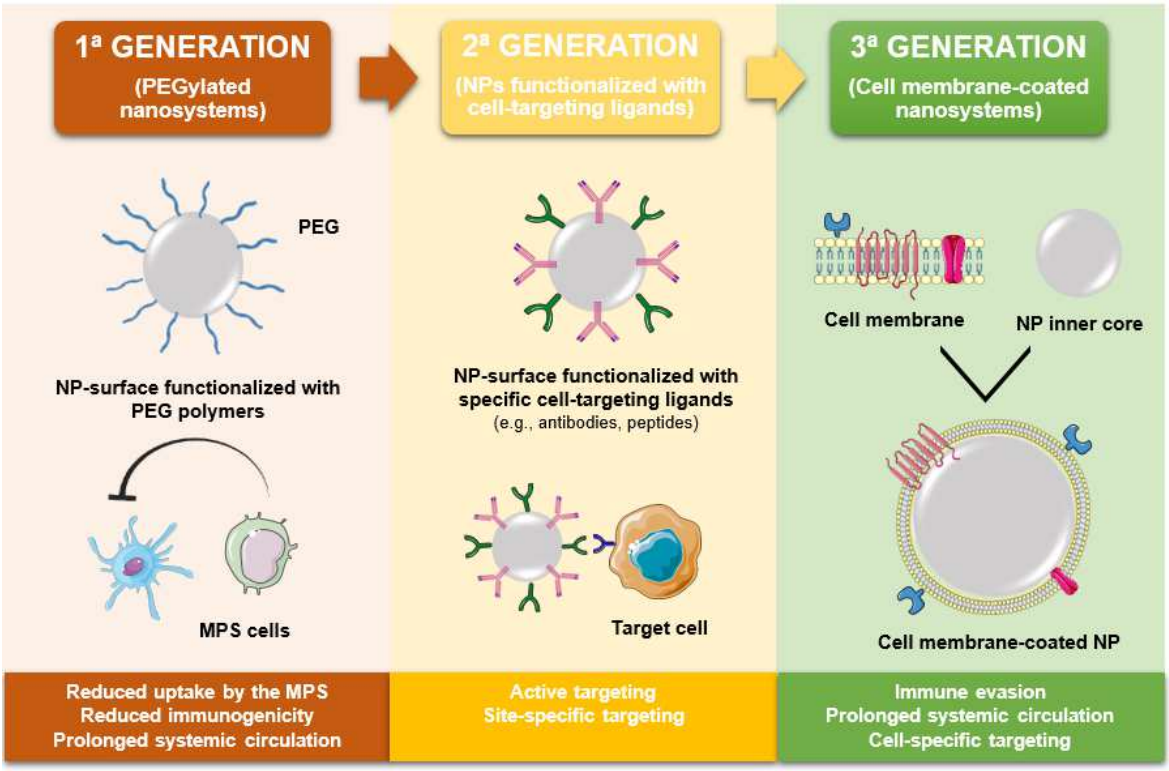

Figure 1. A schematic illustration regarding the evolution of the conceptual design of nanosystems. The first generation of NPs was based on PEG-surface functionalization to minimize unwanted uptake by the MPS, reduce immunogenicity, and prolong systemic circulation. The second generation of NPs was obtained by surface functionalization with specific cell-targeting ligands (e.g., antibodies and peptides) to enable cell-specific uptake via active targeting strategies. The third generation of NPs (referred to as biomimetic cell membrane-coated NPs) is obtained by coating NPs with cell-derived membranes. This approach endows NPs with enhanced biocompatibility, immune evasion, and cell-targeting features. Abbreviations: MPS, mononuclear phagocyte system; NP, nanoparticle; PEG, polyethylene glycol.

To reduce immune clearance, confer stealth features, and extend the blood circulation time of NPs, primary research was focused on NP surface functionalization with polyethylene glycol (PEG), a hydrophilic polymer, as PEGylated NPs are less likely to be recognized and cleared by the mononuclear phagocytic system [26, 27]. The strategy based on functionalizing the NP surface with cell-targeting ligands (such as peptides, antibodies, and small molecules) that specifically recognize and bind to receptors overexpressed at targeted tissues was then exploited to confer superior active cell-targeting features [15, 16, 24]. However, the concerns related to the immunogenicity of synthetic polymers, the high complexity of the bottom-up ligand-incorporating approaches (which can modify both the orientation and bioactivity of these ligands), as well as their inability to accurately replicate the great diversity of the cell surface repertoire, have prompted the development of nature-inspired strategies [18, 24, 28]. Although the traditional modification of synthetic NPs with cell-targeting ligands has resulted in enhanced accumulation at targeted tissues, this strategy has proven incapable of reproducing the complex array of intercellular interactions within the biological environments [29].

Biomimetic cell membrane-surface engineered nanosystems, composed of a NP core coated by an intact biomembrane layer, have been thoroughly exploited as versatile and multifunctional drug delivery nanosystems in the contemporary biomedical field [27, 30]. The manufacturing process of cell membrane-coated nanosystems typically involves three steps: (i) cell membrane extraction and cell membrane nanovesicles derivation; (ii) preparation of the NP inner core, and (iii) fusion of the NP core with the cell membrane-derived nanovesicles [17, 18]. So far, different cell membrane extraction methods have been proposed, which are largely conditioned by the selected cell membrane source. The most common one relies on hypotonic lysis of source cells, followed by homogenization, centrifugation, and purification steps. The size of the harvested membrane vesicles must be further tailored to the nanometer size by

extrusion or sonication. Finally, the coating of NP cores with intact cell membrane-derived nanovesicles can be achieved by co-extrusion, sonication, electroporation, or microfluidic devices [29, 31].

This new class of biomimetic nanosystems can significantly augment the biofunctionality of artificial nanomaterials. The emerging strategy of cell membrane coatings not only enables the accurate transfer of the cell surface repertoire to the NP surface but also confers the ability to mimic the desired behaviors and biological functions of cells, which are very difficult to replicate using the conventional modification approaches [19, 32, 33]. Such biomimetic coatings can equip NPs with superior immunological tolerance, biocompatibility, prolonged systemic circulation, privileged intercellular interactions, and highly specific tissue-homing features [29]. On account of these advantages, the use of biomimetic cell membrane-coated nanosystems has currently been preferred over the other generations of nanosystems (**Table 1**).

Table 1. Comparison of the properties of different NP-based drug delivery systems, i.e. PEGylated NPs, NPs surface functionalized with cell-targeting ligands, and cell membrane-coated NPs.

Main features	PEGylated NPs	NPs functionalized with cell-targeting ligands	Cell membrane-coated NPs
Biomimicry (Cell-mimicking features)	-	++	+++
Biocompatibility and safety	-	+	+++
Blood circulation half-life (Immune evasion)	+	-	++
Specific cell-homing features Tissue penetration	-	++	+++
Production yield Industrial scale up	++	-	+
Reproducibility	++	-	+

Abbreviations: NP, nanoparticle; PEG, polyethylene glycol.
Symbol definition: - Low property, + Slightly elevated property, ++ Elevated property; +++ Very Elevated property.

2.1. Cell membranes as biocompatible coating nanomaterials

Cells, as the essential foundation blocks of life, perform vital functions in the human body. Given the great diversity and heterogeneity of cells, each cell type is in charge of performing specific biological tasks This is due to their specific surface repertoire of biomolecules and receptors that dictate their biological activity and biofunctionality [16, 29, 34]. White blood cells, for instance, are a diverse group of immune cells primed to readily migrate into infected/tumorous tissues to activate both immune and inflammatory responses and remove foreign agents/pathogens [35-37]. Macrophages, natural killer cells, neutrophils, dendritic cells, T cells, and B cells, stand out as the main types of immune cells. These cells of the immune system are enriched with a diverse set of biomolecules (e.g. integrins, selectins, chemokine receptors, scavenger receptors), responsible for their multi-step defensive role. These include sensing biological signals, cell adhesion to the endothelial vascular wall with posterior transendothelial migration to pathological sites, and finally recognition and clearance of pathogens/tumorous cells [17, 36, 38]. Cancer cells, on the other hand, have a natural tendency to migrate into tumorous tissues similar to those from which they were derived (often referred to as homotypic tumor-homing feature). This interesting property stems from their surface repertoire of homotypic tumor ligands (e.g. CD44) that enables specific interaction with homotypic tumor cells [16, 18]. Stem cells, widely recognized for their self-renewal and differentiation features, display an intrinsic tropism to tumorous tissues and can modulate numerous tumor-related biological processes, including tumor dissemination, metastasis, and angiogenesis [23, 39]. Red blood cells, along with the other cell types, innately express biomolecules to remain undetected by the immune system, namely CD47. This "self-recognition" molecule binds with signal-regulatory protein α (SIRPα) expressed on the membrane of phagocytic cells, most notably macrophages [17, 40]. The CD47/SIRPα binding pathway provides an effective escape from immune surveillance by generating a "don't eat me" signal that impairs phagocytic recognition and clearance.

The intrinsic biocompatibility and immune scaping features of cells, as well as their tropism to pathological tissues, can effectively enhance the biocompatibility, blood circulation half-life, and biodistribution of these bioinspired cell

membrane-coated nanodevices at targeted diseased tissues. As a result, the potential use of these biomimetic nanodevices in the medical field is rapidly expanding to a wide range of biomedical areas and pathological conditions [33, 41, 42].

3. Cell membrane-coated nanosystems for osteosarcoma-targeted applications

Cancer is a high-profile area of research in the domain of cell membrane-coating nanotechnology. OS clinical diagnosis, therapeutics, and theranostics comprise a more recent application of biomimetic cell membrane- and hybrid cell membrane-coated nanosystems. The potential use of these cell-mimicking nanocarriers for targeted delivery of therapeutic compounds (e.g., chemotherapeutics, nucleic acids), photothermal agents, photosensitizers, and imaging agents to OS malignant tissues has recently begun to be explored. The notorious antitumor efficacy and exciting results accomplished by these nanosystems can be attributed to their multifunctional and combinatorial features of immune evasion, prolonged systemic circulation, enhanced OS-specific targeting, and deep OS tumor-targeted accumulation.

3.1. Osteosarcoma-targeted diagnosis and therapy (theranostics)

Cancer imaging is crucial for early cancer diagnosis, monitoring of tumor progression and metastasis, and providing a more effective and accurate cancer therapy [43]. Precise and accurate localization of tumorous tissues before cancer treatment (accomplished by diagnostic imaging techniques) can substantially enhance the efficacy of anticancer therapies by providing a highly localized and specific therapeutic intervention [44, 45]. Several imaging techniques have been used for cancer diagnosis. These include, among others, fluorescence imaging, magnetic resonance imaging, and photoacoustic imaging [45].

A great deal of research has been devoted to the study of theranostics platforms, which can perform both diagnosis and therapy. The co-loading of diagnostic and therapeutic agents on the same nanocarrier or even the use of compounds containing both functions have been harnessed to achieve the goal of cancer theranostics [46].

Hollow manganese dioxide (MnO_2) NPs hold exciting potential for both magnetic resonance cancer imaging and chemodynamic therapy. This therapeutic regime employs the Fenton reaction to convert hydrogen peroxide (H_2O_2) into cytotoxic hydroxyl radicals (·OH) to kill cancer cells [47]. In a recent attempt to yield biomimetic NPs for OS-targeted magnetic resonance imaging-guided immuno-chemodynamic therapy, alendronate-modified MnO_2 NPs carrying ginsenoside Rh2 were coated by K7M2 cancer cell membranes (an OS cell line). This coating strategy endowed NPs with enhanced tropism to homotypic OS cells *in vivo* [48]. After being internalized by K7M2 cells, hollow MnO_2 NPs effectively converted the antioxidant GSH into glutathione disulfide (GSSG) and Mn^{2+}. The released Mn^{2+} ions not only enabled magnetic resonance cancer imaging *in vivo* but also decomposed H_2O_2 into ·OH for efficient tumor apoptosis *via* the Fenton reaction. Ginsenoside Rh2, an immune activator in Chinese herbal medicine, triggered immunogenic cell death (ICD) of cancer cells, leading to T cell activation and infiltration. Hence, the nanoassembly showed great promise for simultaneous OS-targeted imaging and combined immune-chemodynamic therapy, significantly increasing T-cell infiltration into tumors and inhibiting tumor growth [48].

Phototherapy, a promising and non-invasive light-triggered therapeutic modality, comprises photothermal therapy (PTT) and photodynamic therapy (PDT), each of which requires light irradiation with a near-infrared (NIR) laser to generate heat or reactive oxygen species (ROS), respectively [49, 50]. Both of these cytotoxic compounds are capable of destroying and killing tumor cells. More recently, cell membrane-coated nanosystems with notable tumor tropism have been exploited to enhance the targeted effects of phototherapy and reduce the viability of cancer cells, without harming healthy adjacent tissues [51].

PDT exploits the NIR-absorption and ROS-generation features of photosensitizers to induce photo-oxidative stress and damage to cancer cells [38[52]. Once the photosensitizers are delivered to the target tumorous tissues, they must be activated by laser irradiation to convert the surrounding oxygen molecules (O_2) present in the tumor microenvironment into ROS, most commonly singlet oxygen ($^1O_2$). Thus, the efficacy of cancer PDT is largely affected by the oxygen levels in tumor tissue [52]. In an attempt to design another theranostic biomimetic nanoplatforms for simultaneous OS imaging and targeted PDT, poly (lactic-*co*-glycolic acid) (PLGA) NPs carrying IR780 dye (a molecule with strong NIR-absorption capacity) were camouflaged by human OS cell membranes (MH-

PLGA-IR780) (**Figure 2A**) [53]. The photoacoustic and fluorescence dual imaging features of IR780 enabled the *vivo* tracking of the nanosystem. The experimental results revealed enhanced homotypic tumor-targeting and tumor bioaccumulation compared to non-coated NPs, which were ascribed to the OS membrane coating (**Figure 2B-C**). Besides, IR780 mediated OS-targeted PDT upon NIR irradiation (808 nm), which increased ROS intra-tumoral accumulation for synergistic cancer cell death via apoptosis and ferroptosis (**Figure 2D**). In summary, the biomimetic nanosystem showed great potential for accurate OS diagnostic imaging and targeted PDT [53].

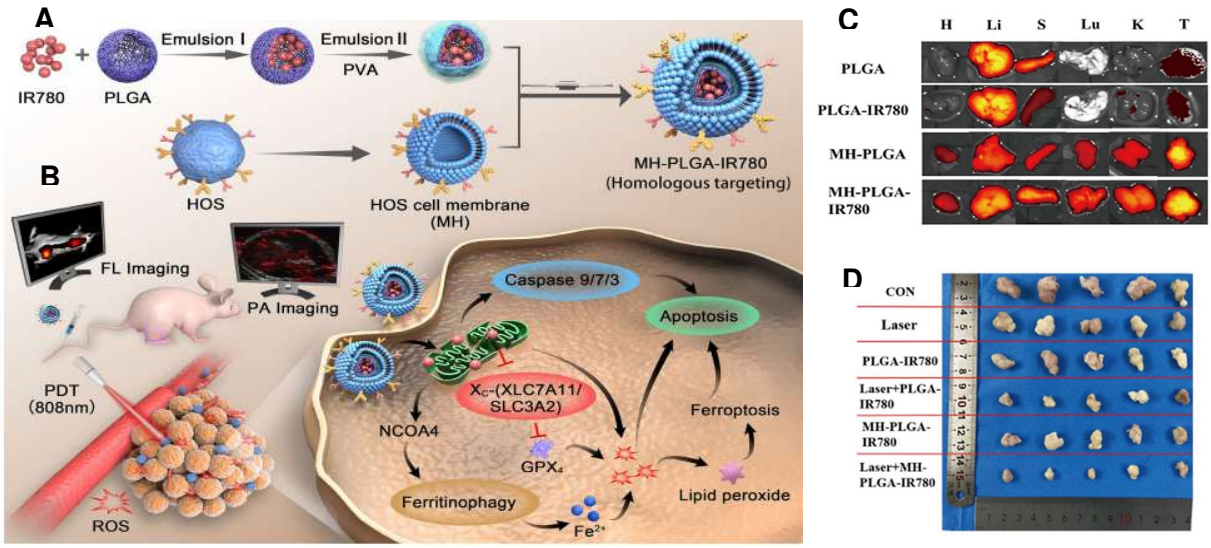

Figure 2. OS cell membrane-coated nanosystem for simultaneous OS diagnostic imaging and targeted PDT. **(A)** Schematic illustration of MH-PLGA-IR780 preparation by coating PLGA-IR780 with HOS cell membranes. **(B)** The IR780 mediated OS-targeted PDT upon NIR irradiation (808 nm) and their photoacoustic and fluorescence dual imaging features for OS diagnostic imaging. **(C)** Biodistribution of MH-PLGA-IR780 at major organs (heart, liver, spleen, lungs, kidney, and tumors) after *in vivo* administration. **(D)** Photographs of tumor tissues in tumor-bearing mice receiving different treatments. Reproduced with permission from reference [53]. Copyright BioMed Central Ltd, 2022. Abbreviations: FL, fluorescence; HOS, human osteosarcoma cell; MH, human osteosarcoma cell membrane; MH-PLGA-IR780, OS cell membrane-coated PLGA-IR780; OS, osteosarcoma; PA, photoacoustic; PDT, photodynamic therapy; PLGA, poly (lactic-co-glycolic acid); PLGA-IR780, IR780-loaded poly (lactic-co-glycolic acid) nanoparticle; ROS, reactive oxygen species.

3.2. Osteosarcoma-targeted therapy

Contemporary OS cancer therapy relies heavily on modalities marked by their high safety risks, such as chemotherapy and radiotherapy. Moreover, the high drug resistance associated with these approaches greatly affects therapeutic outcomes and patients' quality of life [33, 54]. To maximize the therapeutic efficacy and safety of cancer interventions, it is essential to adopt strategies that can increase tumor specificity. The application of cell membrane-coated nanodevices in the cancer field has sought to enhance the anticancer potential of conventional cancer therapies by enabling a more targeted and specific tumor therapy and addressing their safety concerns related to the possible toxicity at non-target tissues.

Osteolysis, the process of osteoclast-mediated bone resorption, is usually present in OS. OS cells surface-express the receptor activator of NF-κB ligand (RANKL), which is responsible for osteoclasts activation and osteolysis [55]. Hence, the double combination of zoledronic acid (ZA) and Ca^{2+} has captured considerable attention due to the recognized anti-osteolysis effects of ZA, which in combination with Ca^{2+} supply assists in bone remodeling and osteoclasts inhibition. ZA can inhibit OS-mediated osteolysis by reducing the RANKL expression in OS cells, thus suppressing osteoclasts' activation. In one study, ZA and Ca^{2+} were used to form a metal-organic framework core that was further loaded with doxorubicin (ZCD) (**Figure 3A**) [55]. To enhance biocompatibility, blood circulation time, and active targeting features to vascular endothelial growth factor receptor (VEGFR)-expressing OS tumor cells, the NP core was coated with a VEGF-functionalized red blood cell membrane (V-R) (**Figure 3B**). The core-shell NPs

(V-RZCD) showed enhanced systemic half-life and improved tumor biodistribution compared to uncoated NPs, significantly suppressing OS tumor growth *in vivo* (**Figure 3, C-E**). This study paved the way for the development of multifunctional biomimetic nanosystems with inhibitory effects on both OS-induced osteolysis and tumor development [55].

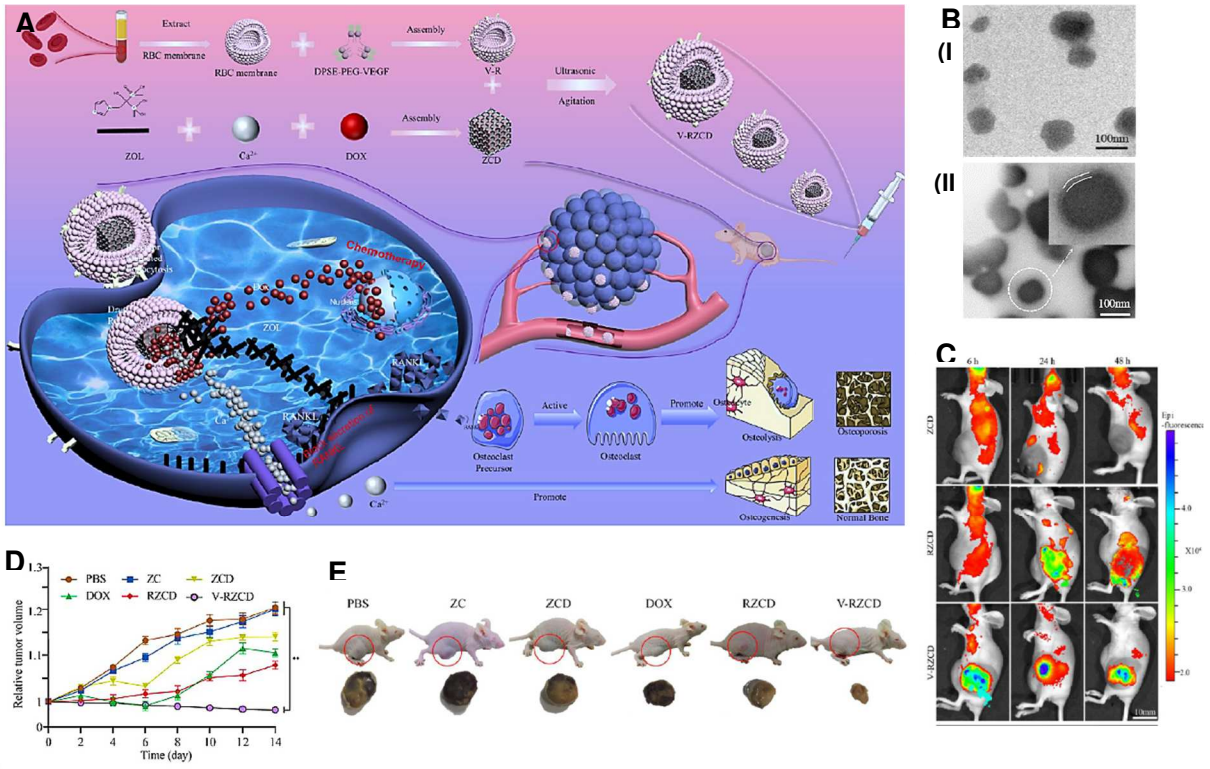

Figure 3. Red blood cell membrane-coated nanosystem for simultaneous inhibition of OS-induced osteolysis and OS tumor growth. **(A)** Schematic illustration of V-RZCD preparation by coating ZCD cores with V-R shells. **(B)** TEM images of **(I)** ZCD and **(II)** V-RZCD (a core-shell nanostructure can be observed). **(C)** Distribution of ZCD, RZCD, and V-RZCD in tumor-bearing mice after *in vivo* administration. **(D)** Relative tumor volume curves of tumor-bearing mice receiving different treatments. **(E)** Photographs of tumor tissues in tumor-bearing mice receiving different treatments. Reproduced with permission from reference [55]. Copyright American Chemical Society, 2021. Abbreviations: DOX, doxorubicin; OS, osteosarcoma; RZCD, red blood cell membrane-coated ZCD; TEM, transmission electron microscopy; VEGF, vascular endothelial growth factor; V-R, VEGF-functionalized red blood cell membrane; V-RZCD, ZCD core coated with V-R; ZA, zoledronic acid; ZCD, metal-organic framework core composed of Ca^{2+} and ZA loaded with DOX.

Cancer PTT, another type of phototherapy, is a non-invasive modality that employs light-absorbing photothermal agents capable of absorbing NIR radiation (808 nm) and generating cytotoxic heat to eradicate cancer [56]. Although effective, this strategy has been hampered by the lack of tumor-targeting of NPs and poor biodistribution of photothermal agents at targeted tumorous tissues [57]. To tackle this concern, silica NPs loaded with indocyanine green (a photothermal agent) were coated with an OS cell membrane for OS-targeted PTT. The nanoassembly displayed homotypic tumor-targeting features, enhanced tumor accumulation, and effective hyperthermia-induced tumor cell ablation upon NIR light irradiation [57].

Chemotherapy constitutes the standard therapeutic regime for eradicating cancer. Nevertheless, cytotoxic side effects, lack of tumor-targeting, and chemoresistance impair its therapeutic efficacy [56]. Thus, combining chemotherapy with other anticancer approaches such as PTT may be beneficial for producing synergistic anticancer effects to markedly increase the antitumor efficacy compared to the respective monotherapies. In one study, polydopamine NPs containing 7-ethyl-10-hydroxycamptothecin (SN38, a hydrophobic anticancer drug) were coated by mesenchymal stem cell membranes [58]. The membrane coating endowed NPs with superior biocompatibility,

reduced uptake by macrophages, enhanced systemic half-life, and augmented OS-targeting features. This resulted in higher uptake of the nanosystem by OS tumor cells for efficient suppression of tumor growth *in vivo*. The biomimetic nanosystem showed promising results for chemo-PTT synergy, by combining the chemotherapeutic potential of SN38 with the heat-generating property of polydopamine NPs [58].

Chemoresistance, often associated with oxidative stress cell defense, is a concerning issue in effective OS therapy. As the first-line chemotherapy, cisplatin is widely used for OS therapy; however, chemoresistance emergence largely limits their efficacy [59]. Ferroptosis, a cell death type featured by the accumulation of ROS, has captured attention for attenuating cisplatin resistance. Recently, gold nanocages carrying RSL3 (glutathione peroxidase 4 (GPX4) inhibitor) were coated by cisplatin-resistant 143B-R cancer cell-derived membranes (an OS cell line) for cisplatin-resistance OS-targeted therapy (**Figure 4A**) [59]. Due to the homotypic tumor-targeting abilities of the OS cell membrane, the biomimetic nanosystem (named C-R-AuNC) showed targeted accumulation at homotypic 143B-R cells (**Figure 4B**). Notorious antitumor effects were observed *in vitro* and *in vivo*. These were ascribed not only to the enhanced photothermal effects of gold nanocages upon NIR irradiation, which could trigger ICD of cancer cells (**Figure 4C**) but also to the ability of RSL3 to promote ferroptosis cell death by inhibiting GPX4 activity (**Figure 4D**). In summary, this study combines ferroptosis, OS-targeted PTT, and ICD to reduce OS chemoresistance, elicit robust antitumor immune responses, and eradicate cancer (**Figure 4E**) [59].

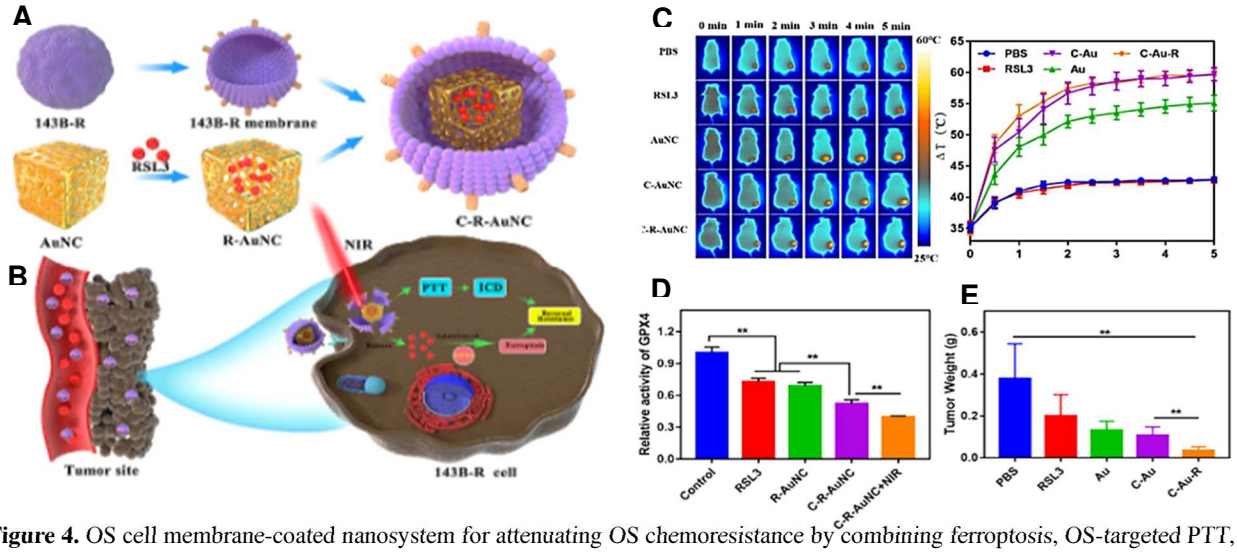

Figure 4. *OS cell membrane-coated nanosystem for attenuating OS chemoresistance by combining ferroptosis, OS-targeted PTT,* and ICD. **(A)** Schematic illustration of C-R-AuNC preparation by coating R-AuNC cores with 143B-R cancer cell membranes (an OS cell line). **(B)** The tumor-targeted accumulation of C-R-AuNC at homotypic 143B-R cancer cells *in vivo* for efficient cancer cell death via combinatorial ferroptosis, PTT, and ICD. **(C)** The temperature rise of 143B-R tumor-bearing mice receiving different treatments after being exposed to NIR irradiation (808 nm)**. (D)** Evaluation of GPX4 activity in 143B-R tumor-bearing mice receiving different treatments. **(E)** Tumor weight changes of tumor-bearing mice receiving different treatments. Reproduced with permission from reference [59]. Copyright Elsevier, 2021. Abbreviations: AuNC, gold nanocage; C-R-AuNC, 143B-R cell membrane-coated R-AuNC; GPX4, glutathione peroxidase 4; ICD, immunogenic cell death; NIR, near-infrared; OS, osteosarcoma; PTT, photothermal therapy; R-AuNC, RSL3-loaded AuNC.

Cancer starvation therapy is an effective therapeutic cancer approach. This strategy utilizes glucose oxidase (GOx) to consume O_2 and glucose, producing gluconic acid and H_2O_2. This starves tumor cells of glucose (a nutrient required for tumor growth) [60]. Recently, a triple combination of PTT, chemodynamic therapy, and cancer starvation therapy was investigated for OS-targeted therapy. In this study, mesoporous Fe_3O_4 NPs were selected as inner cores to co-deliver perfluoropentane and GOx [60]. These NPs have been investigated for simultaneous PTT and chemodynamic therapy due to their notorious photothermal effects upon NIR irradiation and Fenton reaction-induction features. The nanosystem was further coated by K7M2 cell membranes, which provided homologous tumor-targeting features. In addition to starving tumor cells of glucose, GOx could further increase the efficiency of chemodynamic therapy by releasing H_2O_2 that can be subsequently converted to cytotoxic ·OH by the Fenton reaction. Perfluoropentane, with a

strong O_2 storage capacity, was employed as an O_2 supplier to increase the efficacy of the triple combinatorial therapy. Overall, the biomimetic nanosystem showed effective OS-suppressive effects *in vivo,* reaching a tumor inhibition rate of 90.5%, via simultaneous OS-targeted PTT, chemodynamic therapy, and cancer starvation therapy [60].

Carrier-free nanodrugs, obtained by self-assembly of different drugs without using inert materials, have been explored as promising drug delivery systems. Recently, cell membrane-coated carrier-free nanodrugs were studied for OS-targeted therapy [61]. To do this, floxuridine (a water-soluble thymidylate synthase inhibitor) and methotrexate (a hydrophobic anticancer compound) were self-assembled into carrier-free nanodrugs via non-covalent forces (hydrogen bonds) (**Figure 5A-B**). The supramolecular NPs consisting of two chemotherapeutic drugs (M:F NPs) were coated by WELL5 cancer cell membranes (an OS cell line) (**Figure 5C**) [61]. OS membrane coating increased systemic half-life and endowed the nanosystem with enhanced biocompatibility and homotypic tumor-targeting features. The stability of the drugs in the poorly acidic tumor microenvironment was substantially improved; however, when faced the more acidic intracellular environments the two drugs were completely released. In summary, the OS cell membrane-coated carrier-free nanodrug assembly (CCNP) showed remarkable antitumor efficacy *in vivo*, by inhibiting the pi3K/AKT/mTOR signaling pathway (**Figure 5B**), which resulted in efficient cancer cell apoptosis and OS tumor eradication (**Figure 5D-E**) [61].

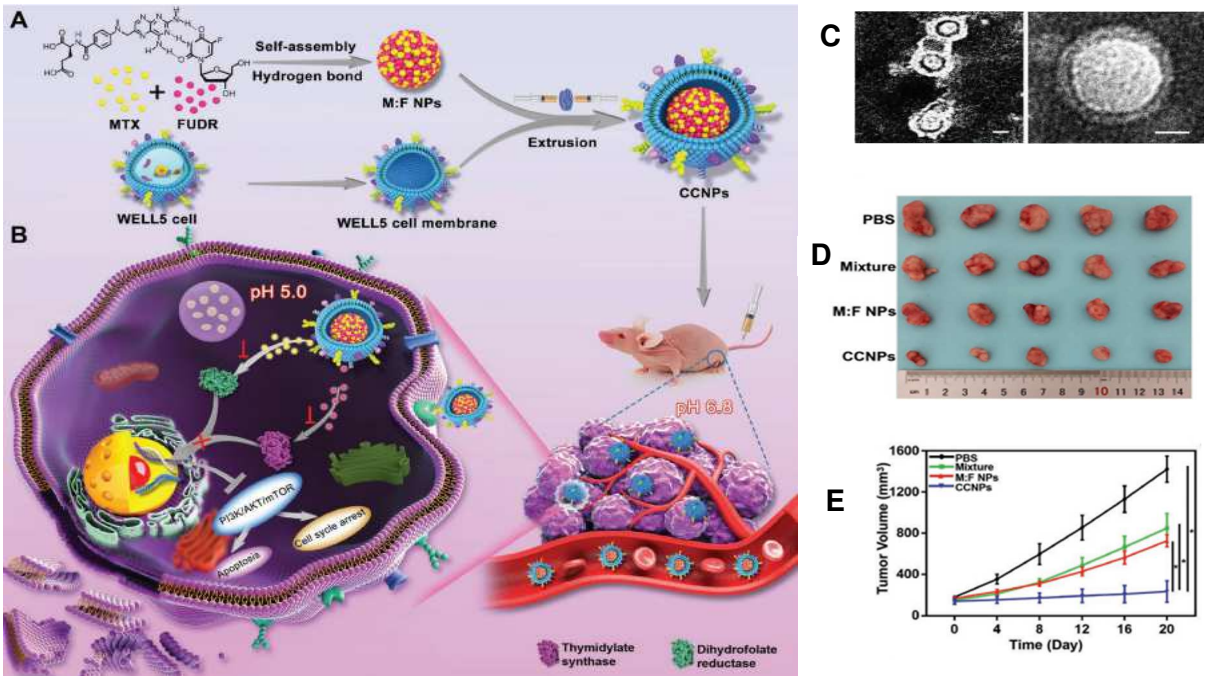

Figure 5. OS cell membrane-coated carrier-free nanodrug for OS-targeted chemotherapy. **(A)** Schematic illustration of CCNPs preparation by coating M:F NP cores with WELL5 cell membranes. **(B)** The *in vivo* effects of the biomimetic nanosystem. Anticancer drug floxuridine inhibits the activity of thymidylate synthase, while methotrexate inhibits the activity of dihydrofolate reductase, for synergistic OS cell apoptosis by inhibition of the pi3K/AKT/mTOR signaling pathway. **(C)** TEM characterization of CCNPs (a core-shell nanostructure can be observed). **(D)** Photographs of tumor tissues in tumor-bearing mice receiving different treatments. **(E)** Tumor volume curves of tumor-bearing mice receiving different treatments. Reproduced with permission from reference [61]. Copyright Wiley-VCH Gmb, 2022. Abbreviations: CCNP, OS cell membrane-coated M:F NP; OS, osteosarcoma; FUDR, floxuridine; M:F NP, carrier-free supramolecular NP obtained by self-assembling of anticancer drugs MTX and FUDR via hydrogen bonds; MTX, methotrexate; TEM, transmission electron microscopy.

Apart from single-cell membranes, hybrid-cell membranes have also been studied for OS-targeted chemotherapy. In one study, paclitaxel-loaded PLGA NPs were coated with hybrid membranes obtained by co-extruding OS cell membranes and macrophage cell membranes through porous membranes [62]. The hybrid cell membrane-coated NPs showed prolonged systemic circulation, superior tumor-targeting abilities, and enhanced uptake by OS cells, compared to non-coated NPs, due to the homotypic tumor-targeting of tumor cells and intrinsic tumor tropism of macrophages. *In vitro* studies showed the pronounced uptake of the biomimetic nanosystem and paclitaxel by OS cells, inducing

efficient tumor apoptosis, while *in vivo* studies demonstrated its superior tumor-targeting abilities and antitumor effects, as demonstrated by the superior inhibition of tumor growth. In addition, the nanosystem significantly reduced paclitaxel-induced toxicity compared with free paclitaxel. This is due to the increased drug accumulation at tumor cells and reduced accumulation in healthy tissues. Hence, this study provided a highly effective and safer hybrid cell membrane-coated, paclitaxel-loaded nanosystem for OS-targeted chemotherapy [62].

4. Cell membrane-coated nanosystems for bone metastatic disease-targeted therapy

In addition to targeting primary OS tumorous tissues, the ability of cell membrane-coated NPs to target prostate cancer-derived bone metastases has also been reported [63, 64]. Bone metastasis is a clinical outcome frequently observed in prostate cancer patients [65]. In advanced stages, prostate cancer cells can disseminate from the primary tumor site to the bloodstream generating distance metastatic tumors [66, 67]. These malignant prostate cancer cells spread most often to the bone tissue (to which they have an enhanced tropism), creating a metastatic bone focus that progressively deteriorates bone tissue structure and impairs bone function. This greatly impacts both the patient's quality of life and survival rates [66, 67].

Bone metastatic castration-resistant prostate cancer represents a clinical challenge due to its high metastatic rates, especially bone metastases accounting for 90% of all metastatic scenarios. In such cases, docetaxel constitutes the first-line treatment; however, the high docetaxel resistance rates represent an alarming issue [63]. Sterol regulatory element-binding protein 1 (SREBP1) has been related to prostate cancer progression and metastasis. Thus, small interfering RNA (siRNA) targeting SREBP1 (siSREBP1) has been recognized as a key target to suppress tumor progression and metastasis, and increase prostate cancer sensitivity to docetaxel by downregulation of the PI3K/AKT signaling pathway. Having this mind, docetaxel and siSREBP1 co-loaded lipoic acid and cross-linked peptide-lipoic acid micelle nanoplatform (LC/D/siR) was prepared (**Figure 6A**), and then coated with a bone marrow mesenchymal stem cell and prostate cancer cell hybrid membrane (**Figure 6B-C**) [63]. The hybrid cell membrane-coated nanosystem (PB@LC/D/siR) could preserve the homologous tumor-targeting ability of prostate cancer cells, and the bone-homing features of bone marrow mesenchymal stem cells, efficiently targeting both prostate cancer cells and the bone metastatic niche. The nanosystem produced notorious antitumor and antimetastatic effects *in vivo*, inhibiting both the prostate cancer progression and growth (**Figure 6D**) and the degree of bone metastasis (**Figure 6E-F**). Thus, by reducing the dissemination and spread of metastatic prostate cancer cells to the bone tissues, PB@LC/D/siR displayed notorious bone protective effects *in vivo* [63].

In another study aimed at combining chemotherapy, gene therapy and immunotherapy against prostate cancer-derived bone metastases, a biomimetic nanosystem was designed by coating polydopamine NPs, co-loaded with doxorubicin and siRNA targeting PD-L1 protein (PD-L1 siRNA), with mesenchymal stem cell membranes [64]. PD-L1 protein (overexpressed in tumors) binds specifically to PD-1 protein, expressed on T cells, preventing them from killing tumor cells. Thus, PD-L1/PD-1 blockage has achieved considerably interest for cancer immunotherapy. PD-L1 siRNA can reduce PD-L1 expression on tumor cells and restore the T cells antitumor activity. Doxorubicin, a chemotherapeutic drug and ICD-inducer, can simultaneously induce apoptosis and ICD of cancer cells, producing synergistic antitumor effects in combination with PD-L1 siRNA. The nanosystem accumulated efficiently at tumor sites *in vitro* and *in vivo*, producing remarkable antitumor and antimetastatic effects. Effective suppression of tumor growth and reduced dissemination of metastatic prostate cancer cells to the bone tissues were achieved by this cell-mimicking nanosystem [64].

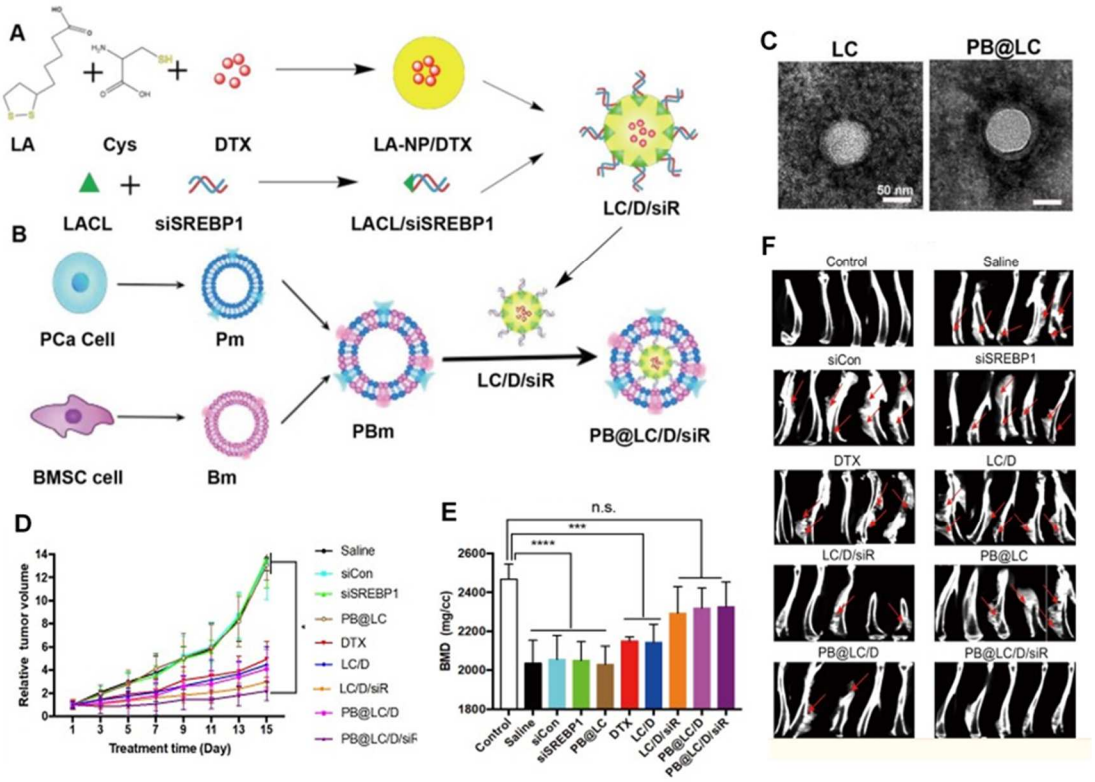

Figure 6. BMSC and PCa cell hybrid membrane-coated nanosystem for combinatorial therapy of prostate cancer-derived bone metastases. **(A)** Preparation of LC/D/siR NPs by co-loading LC NPs with DTX and siSREBP1. **(B)** Coating of LC/D/siR cores with hybrid membranes (obtained by fusing the membranes of BMSCs and PCa cells). **(C)** TEM images of **(I)** non-coated LC NPs and **(II)** PB@LC NPs (a core-shell nanostructure can be observed). **(D)** Relative tumor volume curves of bone metastatic castration-resistant prostate cancer-bearing mice receiving different treatments. **(E)** BMD measurement of the tibias of bone metastatic castration-resistant prostate cancer-bearing mice after different treatments. **(F)** Dissemination of metastatic prostate cancer cells to the bone tissues after different treatments (red arrows indicate the degree of bone injury). Reproduced with permission from reference [63]. Copyright Ivyspring International Publisher, 2020. Abbreviations: BMD, bone mineral density; BMSC, bone marrow mesenchymal stem cell; DTX, docetaxel; LA, lipoic acid; LC, LA and cross-linked peptide-LA micelle nanoplatform; LC/D/siR, LC NPs co-loaded with DTX and siSREBP1; NP, nanoparticle; PB@LC, hybrid cell membrane-coated LC; PB@LC/D/siR, hybrid cell membrane-coated LC/D/siR; PBm, BMSC and PCa cell hybrid membrane; PCa, prostate cancer; siSREBP1, siRNA targeting SREBP1; TEM, transmission electron microscopy.

5. Challenges and future perspectives

The emerging nanotechnology of biomimetic cell membrane coatings holds great potential to enhance the cell-targeting specificity, *in vivo* performance, and therapeutic efficacy of nanoscale materials. This approach has brought out the best in synthetic nanomaterials by giving them a more biological and biocompatible nature.

However, several challenges must be considered when translating these next-generation nanosystems into clinical practice. The main current concerns include: (i) preparation process complexity; (ii) reduced reproducibility; (iii) batch-to-batch heterogeneity; (iv) difficult industrial scale production and scale-up; (v) difficult clinical implementation; and (vi) lack of studies regarding short- and long-term viability in humans, in addition to all the ethical and regulatory issues that may arise from this [17, 34, 68]. The complex fabrication of these nanosystems can result in unwanted contamination or incomplete removal of the intracellular content. Another substantial obstacle to the employment of cell membrane-coated nanosystems concerns the possibility of the coating methods (most notably co-extrusion through porous membranes and sonication) damaging the structure and biological functions of the protein markers located on the cell membranes. This can compromise both the therapeutic efficacy and safety goals of these nanoplatforms [17, 23]. Thus, innocuous coating procedures with negligible impact on cell membrane surface proteins are urgently needed. Besides, since the large-scale production of cell membrane-coated NPs remains a significant

obstacle to clinical translation, new production techniques should be investigated for the clinical-scale, stable and reproducible fabrication of these nanosystems [38, 69]. Hence, considering the immense potential of these biomimetic nanosystems for diagnostic and therapeutic applications, the aftermentioned hurdles must be successfully overcome prior to implementing these bioinspired cell-mimicking nanodevices in clinical practice.

6. Conclusions

OS, an aggressive malignancy that occurs in bone tissue, constitutes the most common bone cancer affecting premature ages (children and adolescents). Biomimetic cell membrane-coated nanosystems have been successfully used for OS-targeted diagnosis, therapy, and theranostics. The scope of these nanosystems includes not only primary OS cancer but also metastatic scenarios, particularly prostate cancer-derived bone metastases.

Nanoscale materials have been exploited in this field either as a carrier for anticancer drugs and imaging agents to OS malignant sites and/or as an active compound *per si* due to their intrinsic pharmacological features. Surface functionalization of NPs with intact cell membranes can provide immune evasion, prolonged systemic half-life, and enhanced OS-specific targeting features. This enhances not only the specificity and efficacy of the therapeutic regimes but also their safety by reducing off-target toxicity in healthy tissues. In addition to single-cell membranes, the combination of distinct cell membranes to yield hybrid cell membranes, that associate the functionalities of each membrane, is also under investigation in OS settings. In summary, both cell membrane- and hybrid cell membrane-coated NPs represent a promising avenue for highly specific, effective, and safer OS-targeted applications. However, further research is needed in this field to improve OS clinical interventions, a bone malignancy of increasing concern.

Authors' contributions

All authors contributed to drafting and revising of the paper and agreed to be responsible for all the aspects of this work.

Declaration of competing interest

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