

Biomimetic Nano-Drug Delivery System: An Emerging Platform for Promoting Tumor Treatment

Xiujuan Han^{1,2,*}, Chunai Gong^{3,*}, Qingru Yang^{1,2}, Kaile Zheng¹, Zhuo Wang^{1,2}, Wei Zhang⁴

¹Department of Pharmacy, First Affiliated Hospital of Naval Medical University (Shanghai Changhai Hospital), Shanghai, 200433, People's Republic of China; ²School of Life Sciences and Biopharmaceuticals, Shenyang Pharmaceutical University, Shenyang, 110016, People's Republic of China; ³Department of Pharmacy, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, 201999, People's Republic of China; ⁴Department of Pharmacy, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, 200433, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhuo Wang, Department of Pharmacy, First Affiliated Hospital of Naval Medical University (Shanghai Changhai Hospital), Shanghai, 200433, People's Republic of China, Email wztgyx223@163.com; Wei Zhang, Department of Pharmacy, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, 200433, People's Republic of China, Email jydzw1981@163.com

Abstract: With the development of nanotechnology, nanoparticles (NPs) have shown broad prospects as drug delivery vehicles. However, they exhibit certain limitations, including low biocompatibility, poor physiological stability, rapid clearance from the body, and nonspecific targeting, which have hampered their clinical application. Therefore, the development of novel drug delivery systems with improved biocompatibility and high target specificity remains a major challenge. In recent years, biofilm mediated biomimetic nano-drug delivery system (BNDDS) has become a research hotspot focus in the field of life sciences. This new biomimetic platform uses bio-nanotechnology to encapsulate synthetic NPs within biomimetic membrane, organically integrating the low immunogenicity, low toxicity, high tumor targeting, good biocompatibility of the biofilm with the adjustability and versatility of the nanocarrier, and shows promising applications in the field of precision tumor therapy. In this review, we systematically summarize the new progress in BNDDS used for optimizing drug delivery, providing a theoretical reference for optimizing drug delivery and designing safe and efficient treatment strategies to improve tumor treatment outcomes.

Keywords: nanoparticles, cell membrane, targeted therapy

Introduction

Malignant tumors, a significant threat to human health and life, exhibit high morbidity, metastasis, and a poor prognosis.^{1,2} With continuous advances in medical technology, progress has been made in tumor treatment. Despite these challenges, the treatment of malignant tumors remains a persistent challenge due to the unique characteristics of tumor cells, high recurrence rates, drug targeting issues, poor penetration of the biological barrier, short in vivo circulation, and the toxicity of traditional chemotherapy.³

Drug-targeted delivery systems based on nanomaterials and nanotechnology offer a promising solution. Nano-drug delivery system (NDDS) with nanoparticles (NPs) as drug carriers can enhance drug stability, solubility, enable targeted delivery and drug-controlled release, concentrating drugs at tumor sites while minimizing systemic side effects compared to free drugs.⁴⁻⁶ Although a substantial number of nanocarriers are currently under preclinical research, they still have limitations in clinical application.⁷ For example, it may be difficult to avoid cellular and autoimmune reactions in the blood of normal tissues when NPs enter the body.⁸ NPs exposed to biological fluids, such as blood, quickly interact with host proteins to form a protein corona that endows NPs with new characteristics in the biological environment and may cause unpredictable therapeutic outcomes.⁹ Moreover, the dense extracellular matrix in solid tumors limits the penetration of nanocarriers.¹⁰ Recent advances in nanotechnology focus on optimizing NP properties through surface modifications. For example, polyethylene glycol (PEG) is used to functionalize the surface of NPs to achieve immune escape and

extend their biological half-life.¹¹ Protein-modified nanocarriers also improve targeting.^{12–15} Although these materials exhibit promising prospects, there is still room for improvement in areas such as immune compatibility or targeting.^{16,17}

In recent decades, a biomimetic camouflage strategy with natural cell membranes (CMs) has attracted increasing attention for promoting tumor-targeted therapy.¹⁸ A new intelligent biomimetic nano-drug delivery system (BNDDS) was constructed by encapsulating NPs with biologically derived CMs to preserve the biological activity of the source cells without damaging the physicochemical properties and drug-carrying capacity of the NPs.¹⁹ Therefore, this multifunctional biomimetic platform shows good prospects for tumor treatment because of its excellent biocompatibility, low immunogenicity, long cycle time, tissue homing characteristics, and ability to cross biological barriers.^{20,21} Over the past 20 years, researchers have explored biomimetic membrane-camouflaged nanocarriers, offering features such as immune escape, biological barrier crossing, pharmacokinetics, and pharmacodynamic regulation, for precise and personalized tumor treatment. Visualization analyses of keyword co-occurrence from 2018 to 2023 were performed using Pajek and VOS viewer bibliometric software (Figure 1). Research studies have extensively reported on the investigation and application of BNDDS within the academic field of tumor treatment. This paper summarizes BNDDS composition, preparation, characterization, and recent developments across various BNDDS. In addition, the challenges and outlook of BNDDS for translation into clinical practice are presented.

Brief Description of BNDDS

Composition of BNDDS

BNDDS mainly consists of core particles with drug-loaded nanostructures and biomimetic outer membranes with biological activity (Figure 2). Nanomaterials for core particles are divided into three main categories: inorganic, organic, and inorganic-organic hybrids. Common organic NPs include lipid-based NPs, proteins, and polymers. These NPs exhibit good long-term safety and high biocompatibility. Since the 1990s, different liposomal and polymeric NPs have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).^{22,23} Common inorganic materials include metals and related oxides, carbon-based NPs, mesoporous silica NPs (MSNs), hollow manganese dioxide (HMnO₂), and other non-metallic nanomaterials.^{4,24} Inorganic NPs exhibit good biocompatibility and high drug

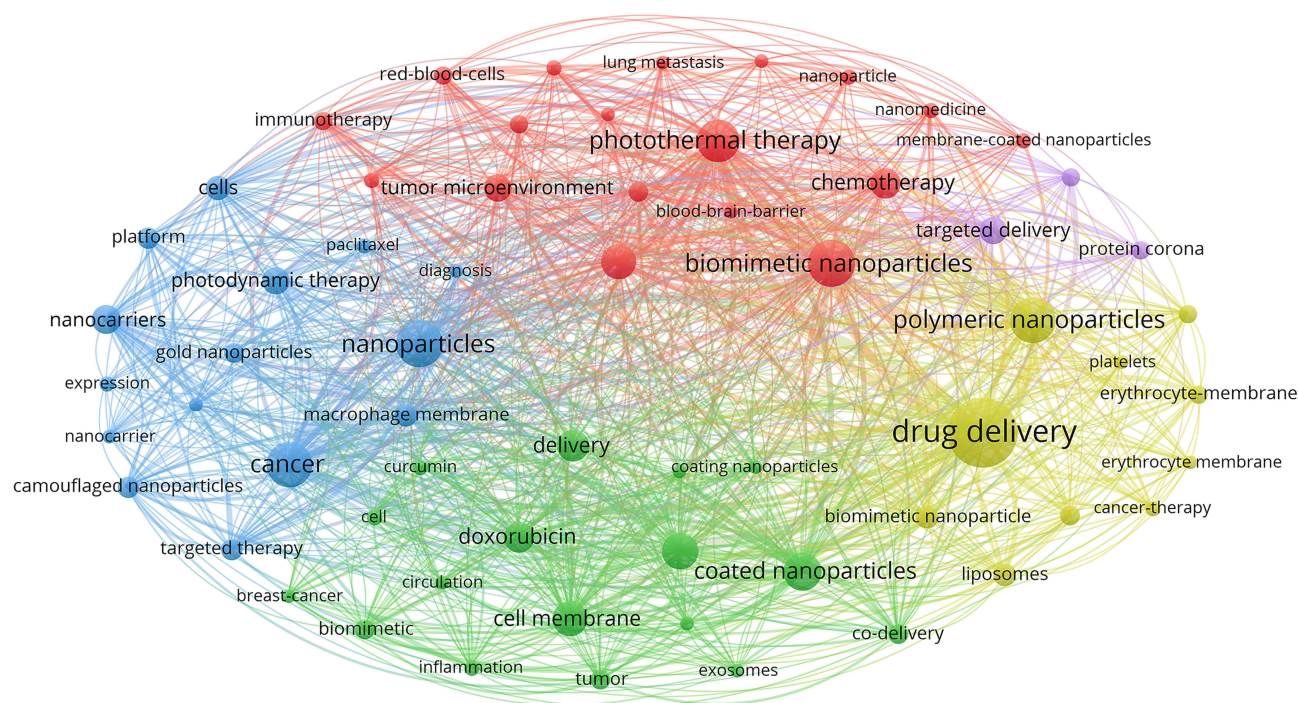


Figure 1 Network diagram illustrating keyword co-occurrences on biomimetic NPs, CM, nano-drug delivery, targeted therapy, tumor treatment.

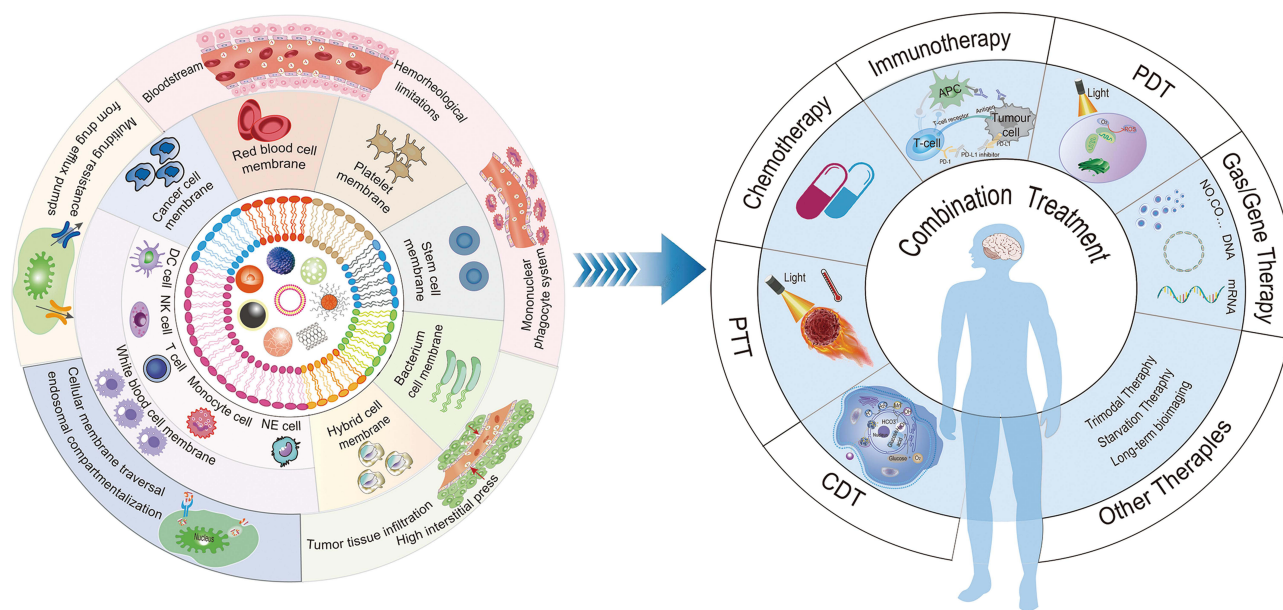


Figure 2 Biomimetic membrane coated nanoparticles for cancer therapy.

loading rates due to their unique electrical, magnetic, and optical properties, as well as variability in size, structure, and geometric shape.²⁵ Metal organic frameworks are the most common organic–inorganic hybrid nanomaterials that combine the synergistic effects of organic and inorganic materials.²⁶ NPs play a decisive role in the drug release profile, pharmacokinetic behavior, and size and shape of drug delivery systems, and different core nanomaterials have different functions. Therefore, personalized designs are required for different clinical research purposes.^{24,27} Table 1 summarizes the advantages and disadvantages of common NPs. Biomimetic materials play an important role in the packaging, protection, targeting, and improvement of NP biocompatibility. Common biomimetic materials are divided into natural

Table 1 The Advantages and Disadvantages of Common NPs

NPs		Advantages	Disadvantages	Ref.
Organic NPs	Lipid-based NPs	Payload flexibility, good biocompatibility, high bioavailability, and formulation simplicity.	Low encapsulation efficiency, low storage stability.	[30,31]
	PLGA	Biodegradability, water solubility, biocompatibility, storage stability, and high drug loading.	Low targeting rate, and increased particle aggregation.	[32,33]
	Protein	Good biocompatibility, easy surface modification, precise control of particle characteristics, and good immunogenicity.	Low overall yield.	[34,35]
Inorganic NPs	Carbon-based NPs	Light weight, high surface area, durability, and diverse applications.	Cytotoxic effects, low drug loading capacity.	[36]
	Metal NPs and other iron oxide NPs	Enhancing agents, MRI contrast, photothermal effect.	Potential organ toxicity, low solubility.	[37,38]
	MSNs	High drug loading, large surface area, and adjustable pore size.	Potential organ toxicity, limited circulation time in the blood.	[39]
Inorganic-organic hybrid NPs	MOF	High adsorption performance, variability in pore size, easy surface functionalization, high load capacity, and improved biocompatibility.	Potential toxicity.	[40–42]

Abbreviations: NPs, nanoparticles; PLGA, poly (lactic-co-glycolic acid); MSNs, mesoporous silica nanoparticles; MOF, Metal organic framework.

CMs, CM derivatives (extracellular vesicles), functionalized CMs, and CM mimics. The fate of a BNDDS is affected by two factors: the body's environment and its own characteristics. Tumor microenvironment (TME) abnormalities hinder BNDDS dispersion and penetration in solid tumors, whereas BNDDS characteristics, preparation, and drug loading affect their transport.^{28,29}

Self-Assembly of BNDDS

An intelligent BNDDS camouflaged by a biomimetic membrane typically involves three primary steps for self-assembly. (1) Biomimetic membrane preparation. The preparation of biomimetic membrane involves the extraction of CMs from different cell types. Anucleated cells, such as mature red blood cells (RBCs) and platelets, can be easily removed through hypotonic treatment or freeze-thaw cycles. However, the extraction of CMs from nucleated cells, such as cancer and T cells, is more complex. This requires the separation of plasma membranes from organs and proteins. The preparation of functionalized and hybrid CMs is complicated. In addition, extracellular vesicles derived from some cells described above have also been used as membrane coatings for NPs. However, large-scale production of BNDDS remains a major challenge for clinical translation. (2) The synthesis of drug-loaded nanoplateform cores. A variety of materials are used for NP preparation (as previously described), which can confer a high cargo capacity or excellent electrical, magnetic, and optical properties to the nanocarriers. Therefore, researchers can load drugs onto selected NPs through noncovalent encapsulation or covalent binding according to different needs and research purposes to form drug-loaded nanocores that determine the morphology, *in vivo* drug release performance, and pharmacokinetics of the BNDDS. (3) Wrapping the biomimetic membrane-based shell onto drug-loaded NPs is the most important and final step that determines the perfect preparation of biomimetic carriers. Commonly used packaging methods include co-incubation, stirring, mixing, mechanical extrusion, ultrasonication, microfluidic electroporation, and CM-templated polymerization.⁴³

Characterization of BNDDS

The chemical structure and surface proteins of these carriers play crucial roles in immune escape and internal circulation. Consequently, characterization becomes imperative post-preparation, encompassing three key objectives: (1) Verifying the complete encapsulation of NPs and biomimetic membrane. (2) Determining fundamental characteristics such as morphology, particle size, and alterations in surface charge of the modified NPs. This analysis typically employs instruments, including transmission electron microscopy and dynamic light scattering. (3) Ensuring the functionality and safety of BNDDS, including assessments of release, efficacy, and toxicity of functional proteins and nanocore drugs. However, the characterization of biomimetic CM-modified NPs remains challenging owing to the heterogeneity of the TME and the dynamic and complex nature of BNDDS entering the body.

Biological Barriers to Be Crossed by NDDS in the Body

Nano-drugs require a multistep cascade process after intravenous injection to exert their effects, including passing through the blood barrier, accumulating at the tumor site, infiltrating the tumor tissue, endocytosis, intracellular transport, and drug release. Any low-efficiency steps can affect the anti-tumor effect of the drug. Biomimetic nano-drug delivery platforms driven by nanotechnology have the potential to overcome biological barriers and achieve precise drug delivery. This section outlines key biological obstacles faced by NDDS when delivering drugs to tumor sites and the innovative strategies employed by NDDS to address them.

Bloodstream

Blood is the first biological barrier encountered by nanomedicines after intravenous injection into systemic circulation. To concentrate drugs at tumor sites and reduce toxicity to non-target organs, nano-drugs entering the bloodstream must evade protein adsorption, premature degradation by enzymes, and clearance by the reticuloendothelial system.⁴⁴ NP properties such as size, morphology, and surface charge affect blood clearance to a certain extent. NP biomimetic coatings can significantly circumvent blood clearance by increasing the biocompatibility of the nano-drugs. Different characteristics of biomimetic membrane have different effects on blood clearance. Among these, the source of the biomimetic membrane is one factor that affects blood clearance. Immune rejection is predominant among allogeneic

cells; however, this barrier is affected in unmodified autologous cells. Excessive modifications alter the structure of the CM and cause toxic reactions.⁴⁵ Moreover, overexpression of the IgG receptor CD64 on the cell surface may prevent immune rejection by allogeneic cells.⁴⁶

Tumor Tissue Infiltration

After being in blood circulation, NPs infiltrate tumor tissue from blood vessels with certain endothelial cell gaps, which are influenced by tumor vascular aberrations, TME, and NP properties.⁴⁷ Biomimetic NPs can cross endothelial barriers using neutrophils (NE) or genetically modified CMs with endothelial crossing capabilities.^{48,49} In addition, dysfunctional blood vessels and high interstitial pressure in tumor tissue hinder further diffusion of NPs from blood vessels to tumor tissue.⁵⁰ Anti-angiogenic drugs (AADs) can normalize tumor blood vessels within a certain time window while reducing tumor interstitial pressure to enhance drug penetration into the tumor.^{51,52}

The dense three-dimensional network structure of the extracellular matrix (ECM) also poses a significant obstacle to the diffusion-dominated transportation of nanomedicines. Furthermore, the variability of the TME, the uneven distribution of substances in tumor tissue gaps, and the interaction between drugs and the matrix are factors that hinder further drug diffusion. Therefore, enhancing the efficiency of nanomedicine penetration across this complex transportation environment into the entire tumor tissue is crucial for improving the effectiveness of chemotherapy. Engineered biomimetic nanocarriers expressing ECM-degrading enzymes can improve the therapeutic effects by breaking the ECM barrier and improving cell infiltration.⁵³

Cellular Membrane Traversal and Subsequent Endosomal Compartmentalization

Chemotherapeutic drugs usually must enter the interior of tumor cells to exert their efficacy. The steric hindrance of NPs, the dense cell matrix, and electrostatic interactions between the surface charge of NPs and tumor matrix proteins can reduce the diffusion rate.⁵⁴ After contact with the CM, nanomedicines enter the cell through various pathways, such as endocytosis and lipid fusion. Additionally, to effectively exert anti-tumor effects, it is necessary to avoid degradation of endosomes/lysosomes.⁵⁵ Effective intracellular delivery can be achieved by modifying BNDDS with tumor-penetrating peptides and tumor cell-specific recognition antibodies or ligands.^{56,57}

Multidrug Resistance from Drug Efflux Pumps

Multidrug resistance (MDR) in tumor cells is the main obstacle to the failure of chemotherapy for cancer treatment. Both intrinsic and contact-acquired drug resistance involve the expulsion of drugs from cells, resulting in low intracellular concentrations that weaken the effectiveness of the treatment. MDR results from a multi-gene and multistep combination mechanism, which may include increased drug efflux or decreased uptake, enhanced drug metabolism, augmented DNA damage repair, changed drug-target caused by mutations, deregulation of microRNAs and mechanisms of drug resistance mediated by the TME.⁵⁸ Among them, the overexpression of efflux transporters is the main cause of drug resistance to many chemotherapy drugs. In recent years, researchers have committed to developing nanotechnology-based delivery systems to overcome MDR in tumors.⁵⁹

BNDDS Based on Natural CMs

The features of NPs control the behavior of loaded drugs in vivo. Therefore, modular design strategies aimed at improving the transport efficiency of NDDS, such as including antigens corresponding to the target ligands and including molecular triggers that respond to the target microenvironment, are constantly evolving. One of the most intriguing recent methods is the direct utilization of CM components to functionalize NPs. CM-coated NPs (CM-NPs) employ biomimetic and nanotechnology techniques to envelope NP surfaces through methods such as co-extrusion, extrusion/ultrasound, frozen-thaw/ultrasound, extrusion/ultrasound, and stirring. This imparts unique surface properties, mirroring primitive cells onto NPs. This novel intelligent nano-drug targeting platform can efficiently avoid recognition and clearance by the immune system, prolonging the circulation time of drugs in the body and achieving targeted delivery of nano-drugs under the action of specific CMs.^{11,60–62} Compared with traditional functionalization methods, this top-down membrane coating approach provides a simplified method for preparing multifunctional and multiantigen NPs. Based on these advantages, NPs with CMs as a camouflage material are widely designed to promote development in biomedical fields, including

detoxification,^{63–65} tumor diagnosis and tumor therapy (tumor-targeted chemotherapy,^{66–69} photothermal therapy,⁷⁰ immunotherapy,⁷¹ starvation-activated cancer therapy⁷²).

A variety of natural CMs are used to camouflage NPs, including blood CM (platelet membrane, red CM), white CM (macrophages,⁷³ lymphocytes, dendritic cells, spongy NE membrane),^{74,75} cancer CM (CCM), stem CM, and adipocyte membrane. Depending on the cellular membranes wrapped around the NP surfaces, the corresponding CM-NPs have different advantages. In this section, we discuss the crucial advances in CM-mediated NDDS according to cell type and their corresponding uses.

Red Blood CM-Camouflaged Nano-Drug Delivery System (RBCM-NDDS)

RBCs, the most abundant cell types in blood, have the longest blood circulation time (~120 d). Mature RBCs with hemoglobin as the main component lack nuclei and most organelles, making the extraction and purification of the red blood CM (RBCM) relatively simple. High-density self-biomarkers on the RBC surface, such as CD47, ensure cell stability and immune escape characteristics, promoting their application as coating materials in drug delivery systems.⁷⁶ The introduction of RBCM-encapsulated poly (lactic-co-glycolic acid) (PLGA) biomimetic NPs marked the beginning of BNDDS based on the CM in 2011.⁷⁷ Subsequently, RBCM has been widely used to encapsulate perfluorocarbons, polymers, MSNs, magnetic materials, and metal organic frameworks (MOF) for image-guided cancer radiotherapy and chemotherapy.⁷⁸

RBCM-NDDS has been extensively developed for anticancer applications in preclinical models (Table 2), especially in drug delivery.^{79,80} Zhai et al⁸¹ used RBCM-derived vesicles to camouflage gelatin nanogel cores loaded with methylene blue and cisplatin for targeting combat metastatic breast cancer. The obtained nanocarrier possessed high tumor-targeting penetrability, effective lysosome escape, and a high lung metastasis inhibition rate without significant toxicity. To overcome the treatment limitations caused by hypoxia, Gao et al⁸² used the long-circulation properties of RBCM to prepare a BNDDS to improve hypoxia and enhance the effectiveness of tumor chemotherapy, which was superior to bare NPs in terms of circulation time, permeability, and safety. Bovine serum albumin-Chlorine e6 and glucose oxidase, loaded with MnO₂ NPs encapsulated in RBCM, have been used to treat breast cancer. The results indicate this biomimetic hybrid nanoenzyme can enhance the starvation therapy and photodynamic therapy of hypoxic tumors by self-supplying H⁺ and accelerating O₂ generation.⁸³ Liang et al⁸⁴ used RBCM to encapsulate NPs in which matrix metalloproteinase 2-cleavable peptides and miR-126-3p self-assemble. The obtained stealth BNDDS was used for

Table 2 Examples of RBCM Coating NPs in Cancer Treatment

Core	Loaded Drug	Surface Functionalization	Tumor Type	Application
MOF	GOX; TPZ		Colon cancer	Cancer starvation-assisted therapy. ⁷²
PLGA	PFC		Breast cancer	Relieve tumor hypoxia and enhance cancer radiotherapy. ⁸²
–	CACDs; siRNA		Cervical cancer	Gene and chemical combination therapy for cancer. ⁸⁷
MOs2 NPs	DOX		Breast Cancer	pH dependent targeted release chemotherapy and photothermal therapy. ⁸⁸
aBSA nanoclusters	DACHPt, ICG	cRGD- peptide	Malignant Melanoma	Light-triggered drug release and tumor-targeted delivery. ⁶⁷
NR	PTX	IL-2	Breast cancer	TME-responsive drug release and immunotherapy. ⁸⁹
PBs	J5	Folic acid	Cervical cancer	The chemo/phototherapy of cancer. ⁹⁰
PLGA	DTX	rVAR2	Melanoma	Tumor-targeted delivery. ⁹¹
PLGA	GA	Anti-EGFR-IRGD	Colorectal cancer	Tumor-targeted delivery. ⁹²

Abbreviations: MOs2, molybdenum disulfide; GOX, glucose oxidase; TPZ, tirapazamine; PFC, perfluorocarbon; CACDs, Cationic ampc chemodrugs; DOX, doxorubicin; NR, nogels; PTX, paclitaxel; ICG, indocyanine green; DACHPt, 1,2-diaminocyclohexane-platinum (II); PBs, Prussian blue nanoparticles; J5, the natural compound from *Pronephrium penangianum*; GA, gambogic acid; DTX, docetaxel; IL-2, Interleukin-2; rVAR2, recombinant VAR2CSA.

efficient lung adenocarcinoma therapy by reversing DNA methylation-induced miRNA silencing (Figure 3A). Interestingly, Miao et al⁸⁵ constructed a BNDDS using RBCM-camouflaging NPs that simulated different life stages of RBCs. Research demonstrates that particles closely emulating healthy RBCM exhibit superior anti-tumor effects, offering insights for tailored carriers and personalized treatment (Figure 3B). To overcome traditional immunotherapy limitations, Xu et al⁸⁶ developed a BNDDS by encapsulating Mn-based MOFs loaded with polyphyllin I within RBCM. BNDDS demonstrated superior anti-tumor effects compared to traditional immunotherapy by activating the cGAS/STING pathway (Figure 3C).

However, the lack of RBCM targeting is a major barrier limiting the clinical translation of RBCM-NDDS.⁷⁸ This defect can fine-tune the function of the BNDDS by further engineering the natural CM coating, which artificially endows

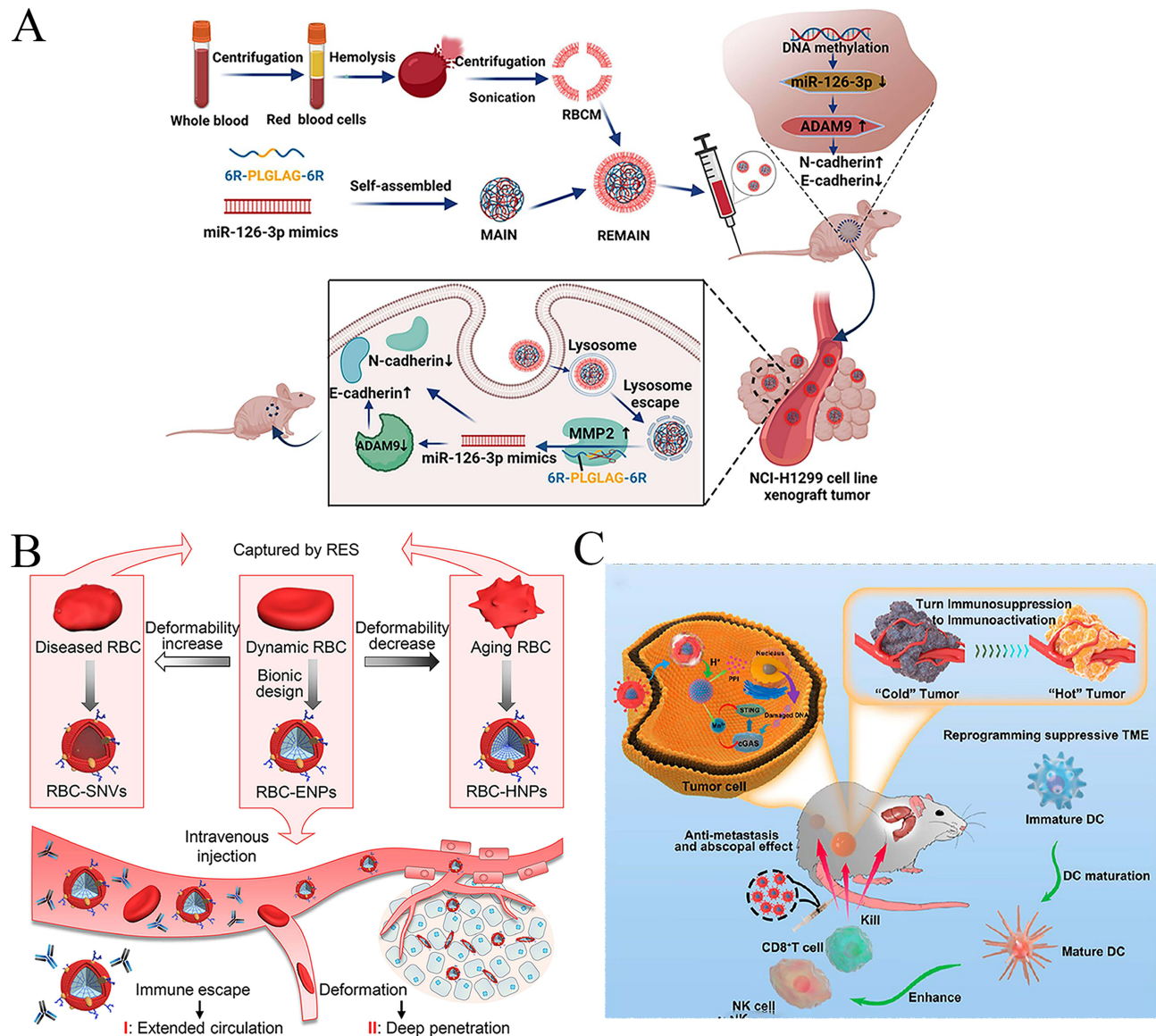


Figure 3 Preparation and application of RBCM-NPs in tumor treatment. **(A)** Schematic diagram of RBCM-NPs in gene therapy. **(B)** Design of RBC-NPs that mimic different stages of natural erythrocytes. **(C)** Schematic diagram of RBCM-NPs in immunotherapy.

Notes: **(A)** Reprinted with permission from Liang L, Cen H, Huang J, et al. The reversion of DNA methylation-induced miRNA silence via biomimetic nanoparticles-mediated gene delivery for efficient lung adenocarcinoma therapy. *Mol Cancer*. 2022;21(1):186. Copyright (2022) BioMed Central, Open Access.⁸⁴ **(B)** Reprinted with permission from Miao Y, Yang Y, Guo L, et al. Cell Membrane-Camouflaged Nanocarriers with Biomimetic Deformability of Erythrocytes for Ultralong Circulation and Enhanced Cancer Therapy. *ACS Nano*. 2022;16(4):6527–6540. Copyright © 2022, American Chemical Society.⁸⁵ **(C)** Reprinted with permission from Xu M, Chang Y, Zhu G, Zhu X, Song X, Li J. Transforming Cold Tumors into Hot Ones with a Metal Organic Framework-Based Biomimetic Nanosystem for Enhanced Immunotherapy. *ACS Appl Mater Interfaces*. 2023;15(14):17,470–17,484. Copyright (2023) American Chemical Society.⁸⁶

the CM-NPs with a satisfactory tumor-targeting ability. Gao et al⁹³ developed a nucleic acid nanogel, Vir Gel, which simulates the structure of a virus. It comprises a functional polypeptide-modified RBC membrane coating embedded with a nanocore of miR155. RBCM further protected and extended the circulation of miR155 in the blood based on the nanogel. Simultaneously, modification of the two targeted peptides increased drug targeting. More interestingly, peptide-modified CBM-encapsulated GC-rich DNA biomimetic pseudonuclear NPs have been developed to selectively target healthy tissues and serve as bait to prevent doxorubicin (DOX) from embedding into healthy tissues, improving the body's tolerance to DOX and reducing toxic side effects.⁶⁴ NPs with malarial RBCs for tumor-targeted drug delivery have been prepared recently and were inspired by the specific tropism of RBCs infected with malaria,⁹¹ providing conceptual proof for the use of this malaria biomimetic for tumor-targeted drug delivery (Figure 4). Modified nanovesicles (NVs) are a special type of membrane carrier. Wang et al⁹⁴ modified erythrocyte-derived mimic vesicles (MVs) with AS1411 aptamer for tumor-targeting. The BNDDS prepared with these engineered MVs showed high loading rates and low drug resistance. Collectively, taking advantage of RBCM can improve the biocompatibility of NDDS, prolong the circulating half-life, and improve the pharmacokinetic behavior of drugs, and has been widely used to enhance drug delivery and the effectiveness of immunotherapy, photochemical therapy, and gene therapy in recent years.^{95,96}

Platelet Membrane-Camouflaged Nano-Drug Delivery System (PLTM-NDDS)

Platelets are another type of anucleated blood cell that have also been widely used as a source of CMs for the surface coating of NPs. Besides their central role in hemostasis,⁹⁷ platelets have a variety of other functions, such as the ability to respond to inflammatory signals and target injured tissues, tumor sites, and areas of vascular inflammation. These disease-related functions are largely because of the expression of surface markers, such as CD47, CD55, CD59, and P-selectin glycoprotein ligand-1, which can be transferred to NPs through membrane coating. There is an intrinsic affinity between platelets and circulating tumor cells (CTCs). Considering the important physiological and pathological roles of platelets in the tumor environment, an increasing number of scientists have attempted to coat platelet membranes on the surface of NPs to endow nanocarriers with the functions of natural platelets.⁹⁸ Compared to RBC, platelets have a better targeting ability, but a small proportion of blood and poor stability are the main obstacles limiting their clinical conversion.⁸

The PLTM-NDDS has also been widely studied for tumor treatment (Table 3). The first use of PLTM as a membrane source for encapsulating NPs was reported in 2015. Compared to bare NPs, PLTM-NDDS has better immune escape and

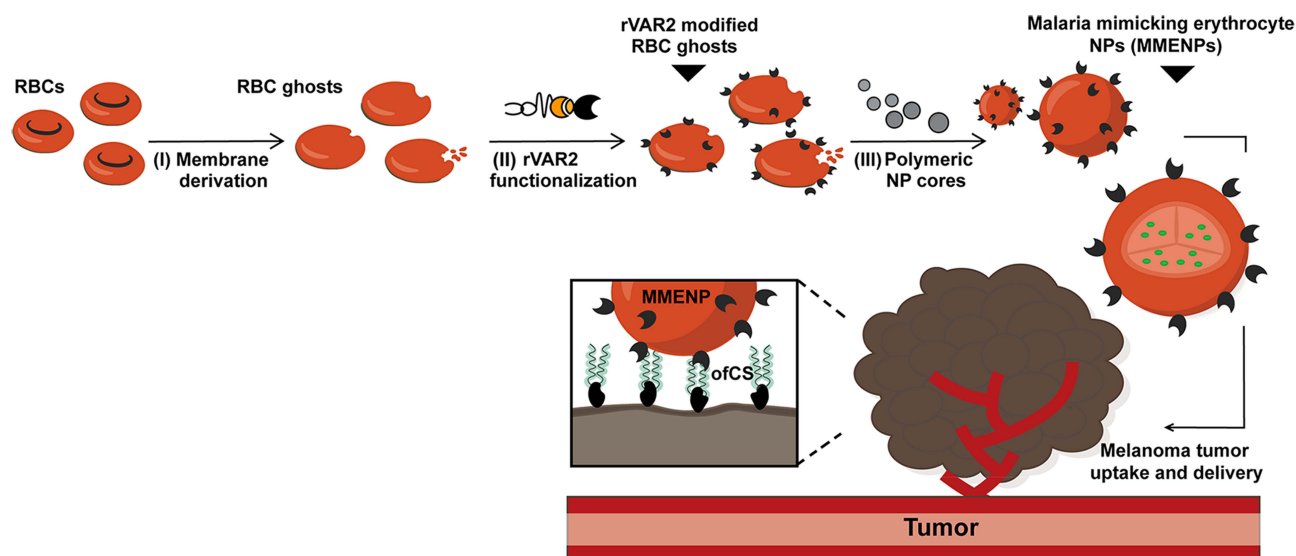


Figure 4 Schematic diagram of modified RBCM-NPs for targeted drug delivery.

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Table 3 Examples of PLTM Coating NPs in Cancer Treatment

Core	Loaded Drug	Surface Functionalization	Tumor Type	Application
Fe₃O₄	SAS		Breast cancer	Enhancing the efficacy of tumor immunotherapy. ¹⁰⁰
MSNs	Combretastatin A4; apatinib		Liver cancer	Tumor-targeted delivery and vasculature disruption. ¹⁰¹
ZIF-8 MOF	siRNA		Breast cancer	Targeted gene silencing. ¹⁰²
MOF	Loc; Oxa		Breast cancer	Targeting the TIME and enhancing immunotherapy. ¹⁰³
MON	TBP-2		Breast cancer	Precise depletion of cancer stem cells and prevention of cancer recurrence after radiotherapy. ¹⁰⁴
HGNs	–		Breast cancer	Biosafe distribution and photothermal oncotherapy. ¹⁰⁶
PLA	R848		Colorectal neoplasms; breast cancer	Local delivery of immune activators. ¹⁰⁷
PLGA	DOX, IR780		Breast cancer	Combination of photothermal diagnosis and targeted chemotherapy. ¹⁰⁸
PEOz-liposome	DOX		Colorectal cancer; breast cancer	pH-responsive drug delivery and enhancing anti-tumor activity. ¹⁰⁹
PBs	–	HRP; PD-L1 aptamer and 4T1 cell aptamer AS1411	Breast cancer	Immunotherapy and enhance targeting. ¹¹⁰
PLGA	DTX	rVAR2	BI6F10 melanoma	Targeted therapy for primary and metastatic cancer. ¹¹¹
PLGA	ICG	Anti-PD-L1 antibody	Breast cancer	Inhibition of tumor recurrence after thermal ablation therapy. ¹¹²

Abbreviations: SAS, Sulfasalazine; TIME, tumor immune microenvironment; Loc, lactate oxidase; Oxa, oxaliplatin; MON, mesoporous organosilicon nanoparticles; TBP-2, an AIE photosensitizer; HGNs, hollow gold NPs; PLA, polylactic acid; R848, resiquimod; HRP, horseradish peroxidase; PD-L1, programmed cell death-Ligand 1.

fewer toxic side effects.⁹⁹ Simultaneously, NP accurately targeted the target position due to the adhesion factor on the PLTM surface. Jiang et al¹⁰⁰ used PLTM to encapsulate mesoporous magnetic NPs (Fe₃O₄) loaded with sulfasalazine for immunotherapy. The PLTM coating enabled effective evasion of the immune system by PLTM-NDDS, leading to sufficient tumor enrichment. To achieve the combination of vascular disrupting agent (VDA) and AAD in the same nanocarrier and to improve the targeting of this carrier, Li et al¹⁰¹ self-assembled BNDDS by encapsulating PLTM on the surface of MSNs loaded with VDA and AAD, using PLTM's inflammatory tendency and interaction with CTCs to achieve precise tumor-targeting. Similarly, PLTM-NDDS has also been used for the efficient targeted delivery of small interfering RNAs (siRNAs) in vivo to achieve the silencing of target genes for anti-tumor gene therapy.¹⁰² Furthermore, immunotherapy, which modulates the TME, has become a popular topic in tumor therapy in recent years. Wang et al¹⁰³ used PLTM coated MOF NPs loaded with lactate oxidase and oxaliplatin to enhance immunotherapy. This intelligent nanoplatform autonomously modulates the immunosuppressive TME and inhibits tumor growth by depleting lactate and amplifying immunogenic cell death (ICD)-induced immunotherapy. Ning et al¹⁰⁴ designed PLTM camouflaged-cuproptosis sensitization system (PTC), a system core constructed by co-extrusion using cuprous oxide NPs and an AIE photosensitizer (TBP-2) for targeted induction of tumor cuproptosis to prevent lung metastasis of breast cancer (Figure 5). A platelet-covered platform has also been used for the targeted delivery of hirudin to eliminate thrombotic complications during tumor treatment.¹⁰⁵ More interestingly, Zou et al¹⁰⁶ developed a micro-sized cellular platelet “ghosts” (PGs) encapsulated biomimetic cascade delivery system. Compared to nanoscale PLTM encapsulated carriers, it exhibits enhanced internalization and cytotoxicity on 4T1 cells, as well as higher anti-tumor photothermal efficacy.

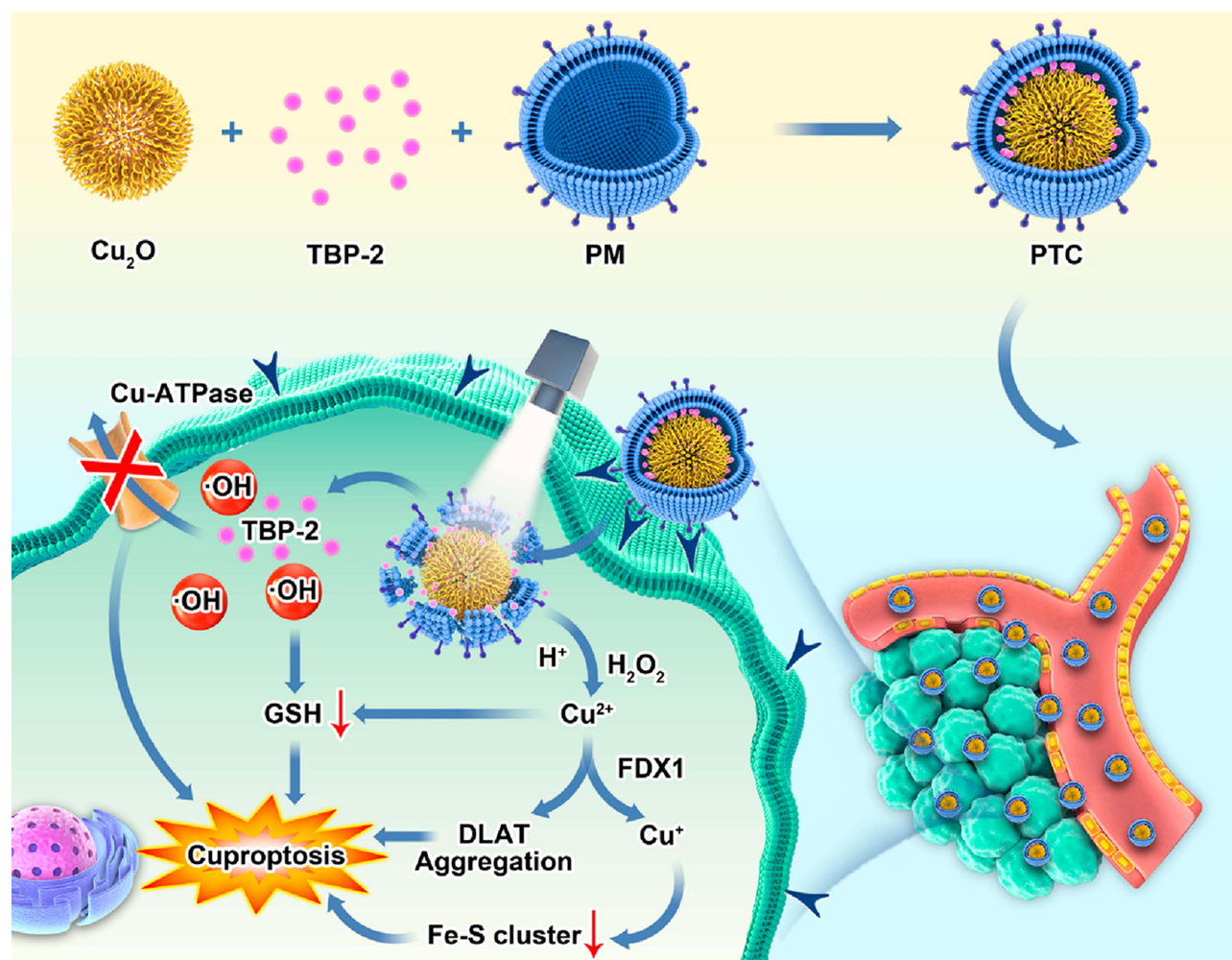


Figure 5 Schematic diagram of PLTM-NPs for boosting cuproptosis to inhibit breast cancer metastasis and rechallenge.

Notes: Reprinted with permission from Ning S, Lyu M, Zhu D, et al. Type-I AIE Photosensitizer Loaded Biomimetic System Boosting Cuproptosis to Inhibit Breast Cancer Metastasis and Rechallenge. *ACS Nano*. 2023;17(11):10,206–10,217. Copyright (2023) American Chemical Society.¹⁰⁴

Similarly, the functionalization modification of PLTM can further enhance the transport performance of BNDDS. Li et al¹¹⁰ used horseradish peroxidase and programmed death-ligand 1 (PD-L1)-modified PLTM to coat Prussian blue NPs, exhibiting excellent photothermal conversion efficiency for combined immunotherapy and photothermal therapy. The obtained BNDDS showed good tumor homing and enhanced anti-tumor effects. Exploiting the tumor homing and targeting capabilities of activated platelets in metastasis, Zhou et al¹¹¹ functionalized activated PLTM with tumor-targeting VAR2CSA malaria protein, camouflaging docetaxel-loaded NPs. The personalized BNDDS can target carcinomas, especially metastatic cancer, and provide a reference drug delivery platform to treat metastatic cancers (Figure 6). Thus, PLTM-NDDS not only provides immune escape but also facilitates active or passive tumor cell targeting, showcasing its potential as a drug carrier.

Cancer CM-Camouflaged Nano-Drug Delivery System (CCM-NDDS)

Compared with most other donor cells, cancer cells can be easily cultured in vitro to obtain ample membranes. CCMs inherit homologous targeting and antigenic library functions, allowing them to be targeted naturally, without complex chemical modifications. CCM-NDDS can evade the immune system and specifically enrich in tumors, reducing damage to normal cells.⁶²

CCMs are widely used as a source of tumor-related antigens to construct CCM-NDDS for tumor therapy (Table 4). For example, Fang et al¹¹³ used the homologous adhesion of human breast cancer cells (MDA-MB-435) to prepare

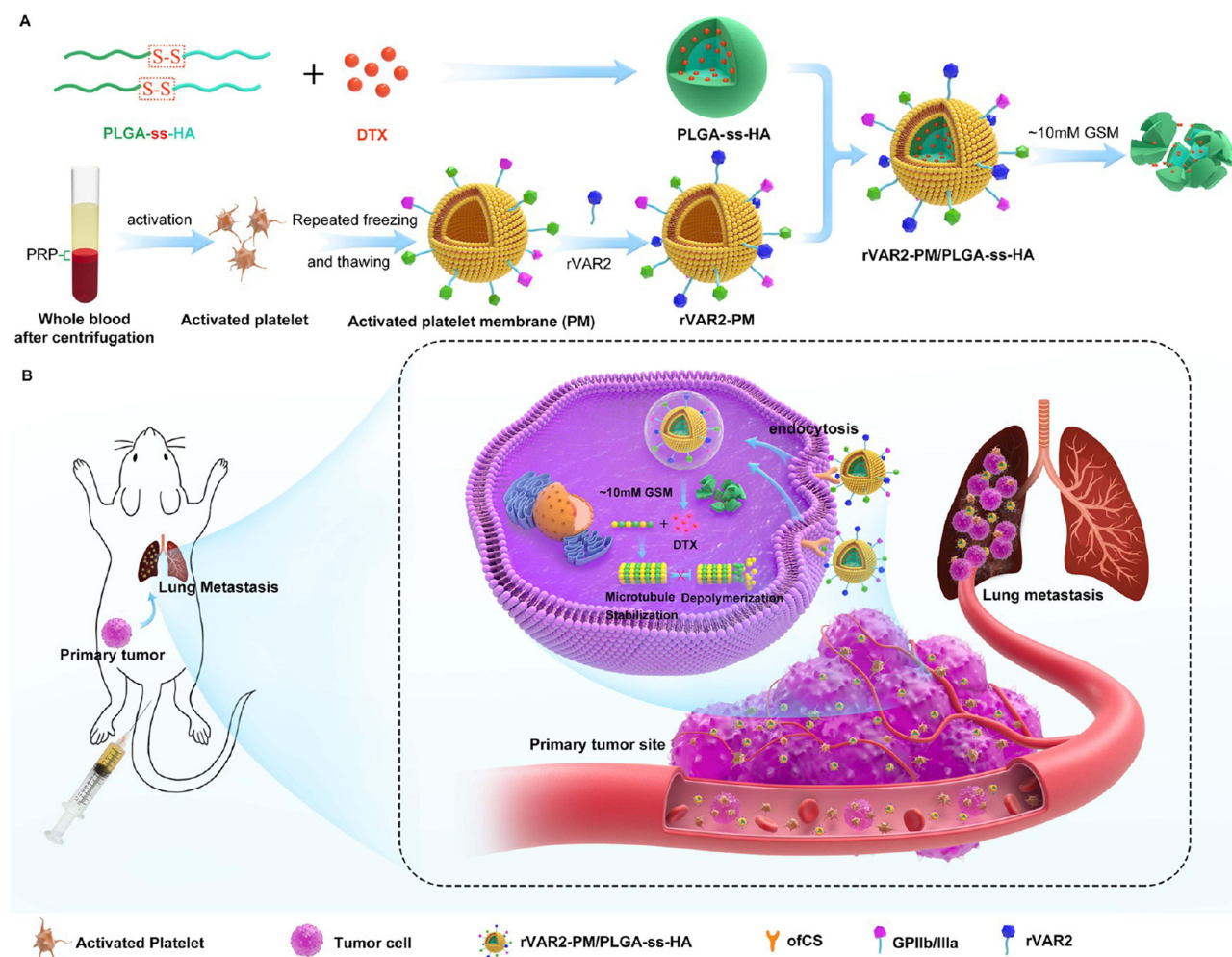


Figure 6 Schematic diagram the (A) preparation and (B) in vivo primary tumor and lung metastatic site targeted therapy of modified PLTM-NPs.

Notes: (A) and (B) reprinted with permission from Zhou M, Lai W, Li G, et al. Platelet Membrane-Coated and VAR2CSA Malaria Protein-Functionalized Nanoparticles for Targeted Treatment of Primary and Metastatic Cancer. *ACS Appl Mater Interfaces*.2021;13(22):25,635–25,648. Copyright (2021) American Chemical Society.¹¹¹

a core-shell nanostructured carrier with a complete CCM antigen array. They found that cancer CM-camouflaged NPs (CCM-NPs) were more effective for homologous targeting than traditional NPs and RBCM-NPs. Similarly, Chen et al¹¹⁴ prepared an NDDS using a PLGA nanocore loaded with indocyanine green, further coating the NPs with CCM to enhance drug targeting and immune compatibility. Xu et al¹¹⁵ reported the functionalization of osimertinib-loaded polymer NPs with tumor CMs to acquire BNDDS with dual-targeted anti-tumor therapy in vivo. Animal experiments have shown that CM-NDDS has an extended circulating half-life in vivo, and homologous targeting is mediated by cancer cell surface adhesion molecules and tumor-specific binding proteins, including Galectin-3, E-cadherin, and CD44. Similar studies incorporated CCM-NPs loaded with dacarbazine and anti-programmed cell death protein 1 antibody (aPD1) for melanoma treatment via combined chemotherapy and immune checkpoint blockade.¹¹⁶ Recently, Zheng et al¹¹⁷ developed a nanocarrier coated with triple-negative breast cancer membranes to overcome the short half-life of artesunate. These biomimetic particles can reduce shear-wave elasticity (SWE) stiffness by inhibiting the functional state of tumor-associated fibroblasts, providing a theoretical basis for predicting the efficacy of clinical neoadjuvant therapy through SWE imaging (Figure 7).

CMM-NPs are not only used for the targeted delivery of drugs to tumors, but also for multifunctional combination therapy. Li et al¹¹⁸ designed a personalized cancer vaccine by camouflaging surgically derived CCMs efficiently loaded with imiquimod (R837) for prostate cancer immunotherapy. Another NDDS with satisfactory performance was fabricated using MSNs incorporated with propranolol and CpG. The nanoscale platform was further encapsulated by CM for

Table 4 Examples of CCM Coating NPs in Cancer Treatment

Core	Loaded Drug	Tumor Type	Application	Ref.
PLGA	ICG	Breast cancer	Homologous targeting dual-modal imaging and photothermal therapy.	[114]
PHEP	Osi	Non-small cell lung cancer	Homologous targeted chemotherapy.	[115]
MSNs	DTIC	Melanoma	Combination of chemotherapy and immunotherapy for response release of TME.	[116]
PLGA	Artesunate	Breast cancer	Targeted and efficient drug delivery.	[117]
PMBEOx-COOH	R837	Prostate cancer	Homologous targeted delivery and immunotherapy.	[118]
MSNs	Pro; CpG	Melanoma	Improving tumor immunotherapy.	[119]
Ir-B-TiO₂	–	Cervical carcinoma; breast cancer	Hierarchical targeted synergistic photothermal and sonodynamic cancer imaging and therapy.	[120]
AuNCs	GEM; L-Arg	Pancreatic ductal adenocarcinoma	Enhanced chemotherapy of pancreatic tumors.	[121]
Fe₃O₄@Mn_{0.5}Zn_{0.5}Fe₂O₄@CoFe₂O₄	–	Prostate cancer	Targeted magnetic hyperthermia.	[122]
ZIF-8 NPs	EPI; GOX; hemin	4T1 cell line; RAW 264.7 cell line	Effectively inducing ICD to improve the therapeutic effect of anti-PD-L1 antibodies.	[123]
UCNP	PTD	Triple-negative breast cancer	Combining chemo-photodynamic therapy and CD73 blockade for metastatic cancer.	[124]
MOF (PCN-224)	GOX, catalase	Breast cancer	Cancer-targeted starvation and photodynamic therapy.	[125]
MSNs	GOX	Melanoma	Starvation therapy and immune checkpoint blockade.	[126]
PLGA	R837	B16-OVA melanoma	Improving the efficacy of immunotherapy.	[127]
Iron oxide NPs	The TPPI peptide; MMP2 substrate short peptide	Human lung cancer and breast cancer	Cancer immunotherapy and diagnosis.	[128]
PLGA	PTX	Lung cancer	Targeted magnetic hyperthermia.	[132]

Abbreviations: UCNPs, upconverting nanoparticles; DTIC, Dacarbazine; AuNCs, gold nanocages; GEM, Gemcitabine; nitrogen oxide donor (L-Arg); EPI, Epirubicin; PHEP, polymeric polyphosphoester; Osi, osimertinib; PTD, polymer polyethylene glycol-thioketal-doxorubicin; PMBEOx-COOH, thioglycolic-acid-grafted poly(2-methyl-2-oxazoline)-block-poly(2-butyl-2-oxazoline-co-2-butenyl-2-oxazoline); R837, Imiquimod; Pro, propranolol; CpG, cytosine-guanine dinucleotides; MMP2, metalloproteinase 2.

incorporating multifunctional biomimetic nanovaccines and the blockade of β -adrenergic signaling, which provides a potential superior candidate for enhancing cancer immunotherapy.¹¹⁹ Shen et al¹²⁰ functionalized black titanium NPs with iridium complexes and encapsulated them in the CCM for multimodal imaging and targeted synergistic NIR-II photothermal and sonodynamic therapy. Compared to non-functionalized NPs, these particles selectively accumulate in mitochondria, enhancing selectivity toward cancer cells, presenting a dual targeting concept. In another study using Au nanocores (AuNCs) with good loading capacity and photothermal performance, Zhang et al¹²¹ prepared a multifunctional biomimetic nanoplatform loaded with the chemotherapy drugs GEM and the NO donor L-Arg, achieving a combination of GEM chemotherapy, NO gas therapy, and photothermal therapy. The pancreatic ductal adenocarcinoma (PDAC) CM coating further enhanced the tumor-targeted accumulation and deep penetration of GEM, reduced the blood clearance rate of this mixed nano-drug, and reversed the resistance to traditional PDAC chemotherapy. To improve intracellular penetration efficiency, LN1 cell-penetrating peptide was added to the coating components to functionalize the NPs with optimal magnetothermal efficiency (ie, Fe₃O₄@Mn_{0.5}Zn_{0.5}Fe₂O₄@CoFe₂O₄). The obtained novel magnetic NPs with a core-shell-shell structure (TMNP) improved the magnetocaloric conversion efficiency and reduced the cancer cell migration rate (Figure 8).¹²² Anti-CD28 antibodies-conjugated CCM-NPs have also been developed as anti-cancer nanovaccines, aiming to enhance the T-cell response and efficacy. This was achieved through dual interactions with dendritic cells and T cells.¹²⁹ Li et al¹²³ constructed a self-amplifying biomimetic nanosystem, mEHGZ, which uses calreticulin-overexpressed CCM to generate NDDS. mEHGZ promotes ICD induction at the tumor site, significantly

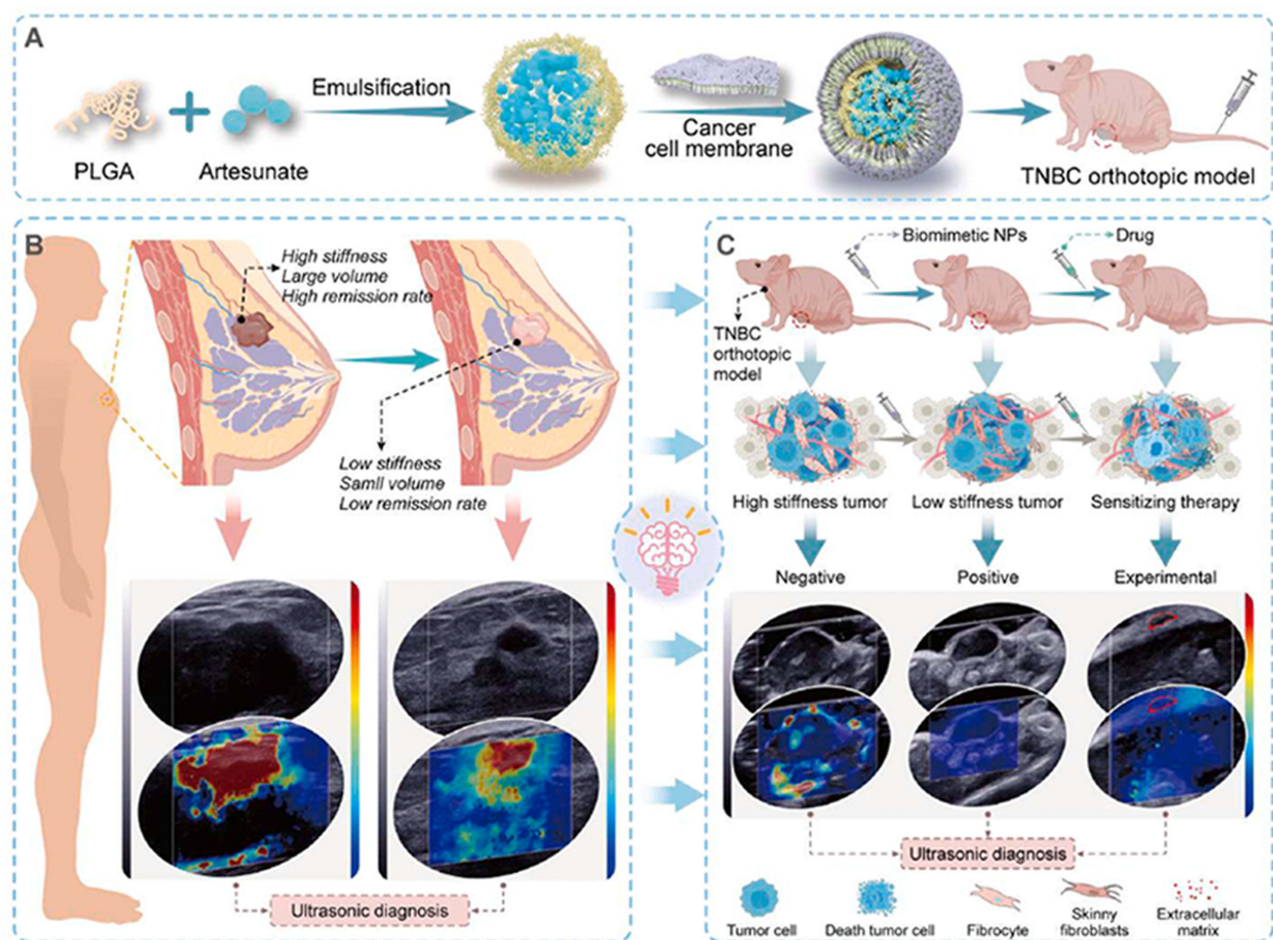


Figure 7 Schematic of the (A) preparation of CCM-NP and (B and C) discussion on the mechanism of predicting TNBC tumor treatment efficacy using shear wave elastography.

Notes: (A–C) Reprinted with permission from Zheng D, Zhou J, Qian L, et al. Biomimetic nanoparticles drive the mechanism understanding of shear-wave elasticity stiffness in triple-negative breast cancers to predict clinical treatment. *Bioact Mater.* 2023;22:567–587. Copyright © 2022 The Authors. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).¹¹⁷

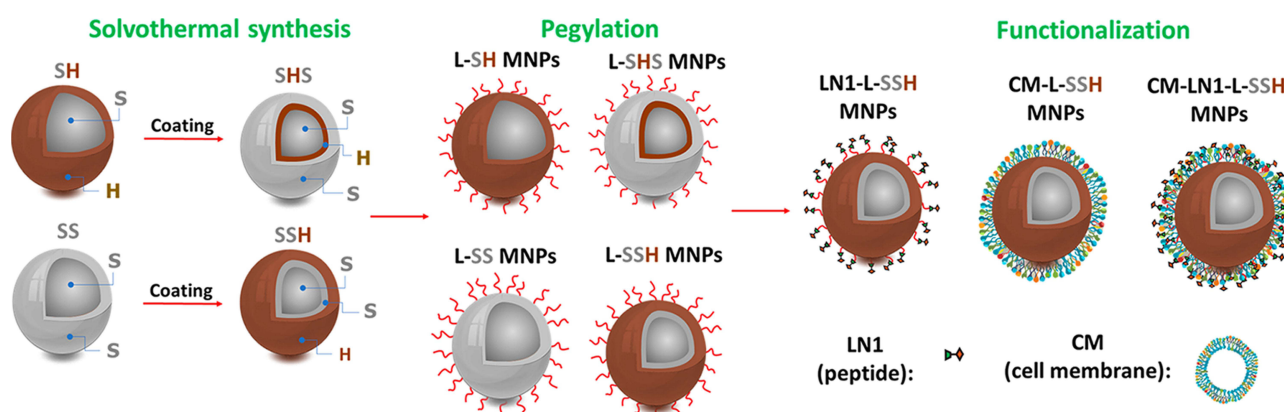


Figure 8 Application in targeted magnetic hyperthermia of the novel shape-anisotropic magnetic core-shell-shell NPs.

Notes: Reprinted with permission from Nica V, Marino A, Pucci C, et al. Cell Membrane Coated and Cell-Penetrating Peptide-Conjugated Trimagnetic Nanoparticles for Targeted Magnetic Hyperthermia of Prostate Cancer Cells. *ACS Appl Mater Interfaces.* 2023;15(25):30,008–30,028. Copyright © 2023 The Authors. Published by American Chemical Society. This publication is licensed under CC-BY 4.0.¹²²

enhancing the sensitivity of the tumor immune microenvironment (TIME) to PD-L1 antibodies. Similarly, genetically engineered NSCLC cell lines that overexpress programmed death-1 (PD-1) developed biomimetic NVs for efficient cargo transport targeting non-small cell lung cancer.¹³⁰ Qi et al¹³¹ developed a generic cell-friendly supramolecular strategy based on noncovalent interactions to engineer supramolecular CM vesicles for tumor photodynamic therapy and immunotherapy, providing a new approach for the surface modification of bionic NDDS.

Stem CM-Camouflaged Nano-Drug Delivery System (SCMs-NDDS)

Stem cells (SCs) are a class of cells with an unlimited or immortal capacity for self-renewal that produces at least one type of highly differentiated daughter cells. Mesenchymal SCs (MSCs) are important members of the stem cell family, are easy to acquire, and have strong value-added abilities.¹³³ MSCs can interact with tumor cells, different components of the TME, and the immune system through complex signaling networks, showing an inflammatory tendency and tumor tropism. Simultaneously, MSCs lacking co-stimulatory factors (such as B7-1, B7-2, and CD40-L) and low expression of human leukocyte antigen and major histocompatibility complex class I can bypass the host immune response and protect themselves from immune attacks by producing special immunosuppressive factors.¹³⁴ Therefore, wrapping NPs with MSC membranes not only enhances biocompatibility but also maximizes the therapeutic effect of NPs by mimicking the targeting capabilities of MSCs.¹³⁵ Thus far, SCM-NDDS has been widely used in research on breast cancer, glioblastoma, cervical cancer, bone tumors, acute myeloid leukemia, oral squamous cell carcinoma, and other tumor models (Table 5). Different sources of MSCs have varying therapeutic potentials for different diseases because of disparities in accessibility, content, proliferation, immunoregulation, and cytokine profiles.¹³⁶

Because of their inherent homing ability and immune compatibility, MSCs show great potential in the field of tumor-targeting drug therapy.¹³³ Animal experiments have shown that SCM-encapsulated nanocomposites loaded with mitoxantrone are enriched at tumor sites and effectively inhibit tumor growth. Compared to single nanocomposites, MSCs/NP systems exhibited a swifter migration rate toward malignant glioma cells (U87).¹³⁷ Another study showed that tumor cell

Table 5 Examples of SCM Coating NPs in Cancer Treatment

Core	Loaded Drug	Surface Functionalization	Tumor Type	Application
DNA-templated NPs	MTX		Glioblastoma	Tumor-targeted chemotherapy. ¹³⁷
PLGA	DOX		Xenograft liver cancer	Tumor-targeted chemotherapy. ¹³⁸
PDA	SN38		Bone tumors	Synergistic chemo-photothermal therapy. ¹³⁹
UCNP	ZnPC; MC540		Cervical carcinoma	Targeted photodynamic therapy. ¹⁴⁰
Fe₃O₄@PDA NPs	siRNA		Prostatic cancer	Imaging guided photothermal therapy and gene therapy. ¹⁴¹
LNP	sgRNA, CXCL12 α		Acute myeloid leukemia	Construction and local delivery of scaffolds simulating bone marrow microenvironment. ¹⁴²
PLGA	PTX		Breast cancer	Tumor-targeted chemotherapy. ¹⁴³
Nanogel	DOX		Cervical carcinoma	Tumor-targeted chemotherapy. ¹⁴⁴
MOF	DOX		Oral squamous cell carcinoma	Tumor-targeted chemotherapy. ¹⁴⁵
Hollow MnO₂	PTX	TAT peptide	Lung cancer	Nuclear targeted chemotherapy. ¹⁴⁶
Cu-MOF	siRNA	TP0751-peptide	Small cell lung cancer	Reprogramming copper metabolism and cuproptosis-based synergistic therapy. ¹⁴⁷
HGNs	DOX	MUC-I aptamer	Breast cancer	Targeted drug delivery and pH-responsive drug release. ¹⁴⁸

Abbreviations: MTX, methotrexate; PDA, polydopamine nanoparticles; SN38, 7-ethyl-10-hydroxycamptothecin; ZnPC, zinc phthalocyanine; MC540, merocyanine 540; LNP, lipidoid nanoparticle; CXCL12 α , a chemokine.

uptake of PLGA NPs coated with a human umbilical MSC membrane was three times more efficient than that of uncoated identical NPs, and biomimetic NPs exhibited greater tumor toxicity.¹³⁸ Similarly, Li et al¹⁴⁹ prepared MSC membrane-encapsulated mesoporous silica NPs (MSN @ M) for treating malignant liver cancer. Compared with MSN, MSN @ M have a lower phagocyte clearance rate and stronger tumor-targeting and penetration ability in vivo. Moreover, the MSC membranes significantly enhance the drug loading capacity of MSN @ M and contribute to the sustained release of DOX.

SCM-encapsulated NPs are widely used in gene therapy, tumor imaging, photothermal therapy, and photodynamic therapy (Table 5). For example, Zhang et al¹³⁹ designed polydopamine NPs disguised by stem CMs for synergistic chemotherapy and photothermal therapy of malignant bone tumors. Gao et al¹⁴⁰ developed MSNs coated with mesenchymal stem cell (BMSC) membranes for photodynamic therapy (PDT) of tumors. Mu et al¹⁴¹ prepared a membrane nanocomposite for delivering siRNA using magnetic NPs coated with SCM. Besides targeting solid tumors, Ho et al¹⁴² developed a local CRISPR-Cas9 delivery system that targeted leukemia SCs (LSCs) to enhance gene editing efficiency and acute myeloid leukemia therapeutic efficacy. To enhance the targeting and bone marrow luminal residence time, MSC membrane-coated nanofiber (MSCM-NF) scaffolds were loaded with LNP-Cas9 RNP and the chemokine CXCL12. Furthermore, the release of CXCL12 induced in vitro migration of LSCs onto the MSCM-NF scaffolds, resulting in knockout of the interleukin-1 receptor accessory protein (IL1RAP) gene. In turn, IL1RAP knockout reduced the colony-forming ability and leukemic load of LSC. Satisfactory targeting can also be achieved by further engineering modifications of the SCM-NDDS to fine-tune its functionality. Xie et al¹⁴⁶ developed hollow manganese dioxide (HMnO₂) NPs disguised by TAT peptide-modified human umbilical cord MSCs for targeted drug delivery. The newly obtained BNDDS showed excellent nuclear targeting ability. Genetic engineering modification of CM protein expression is another powerful method that has been used to produce CM-camouflaged NPs (CM-NPs) with higher functions. In a study by Chang et al,¹⁵⁰ human pluripotent SCs were genetically engineered through CRISPR/Cas9 mediated gene knockout to express anti-glioblastoma (GBM)-chimeric antigen receptor (CAR) constructs with T-specific CD3 ζ or NE-specific γ -signaling domains. CAR NEs with optimal anti-tumor activity were produced to deliver and release TME-responsive NPs specifically and noninvasively to target GBM. This combination of chemotherapy and immunotherapy exhibited excellent and specific anti-GBM activity, enhancing drug delivery precision and prolonging the life of female tumor-bearing mice (Figure 9).

White Blood CM-Camouflaged Nano-Drug Delivery System (WBCMs-NDDS)

Leukocytes, including monocytes, macrophages, lymphocytes, natural killer (NK) cells, and dendritic cells, are blood cells widely distributed in the bloodstream and lymphatic system. They can migrate to sites of inflammation outside blood vessels, actively deforming and eliminating pathogens. White blood cells (WBCs), play a crucial role in various stages of cancer development through specific targeting and immune monitoring.¹⁵¹ In contrast, the reticuloendothelial system plays an important role in the circulation duration and clearance of NPs from the blood.¹⁵² Based on these functions, researchers have coated the surfaces of NPs with WBCMs to endow them with a wide range of activities, including prolonging blood circulation, recognizing and presenting antigens, enhancing the targeting ability and biocompatibility, slowly controlling drug release, and lowering in vivo toxicity (Table 6). However, the characteristics of some WBCs that promote tumor progression are key issues that deserve further attention.⁸ The WBCMs currently used for BNDDS construction are macrophage (M ϕ), dendritic cell (DC), neutrophils (NE), T-lymphocyte, and NK CMs. Among these, most research has focused on BNDDS using M ϕ membranes.

M ϕ Membranes

M ϕ are the most abundant xenogeneic innate immune cells in the TME.¹⁵³ M ϕ possess surface markers like CD11b or CD49d that interact with chemokines and inflammatory factors expressed in tumor tissue, allowing them to specifically target certain tumor cells.¹⁵⁴ Simultaneously, according to the polarization state, tumor type, and disease stage, tumor-associated macrophages can promote and prevent cancer growth. Therefore, M ϕ serve as both therapeutic targets and drug carriers.¹⁵⁵ In addition, M1 macrophage-derived NVs can act as immunomodulators, inducing the conversion of tumor-related macrophages to the M1 type and promoting the therapeutic effect of anti-PD-L1 antibodies.¹⁵⁶ Currently,

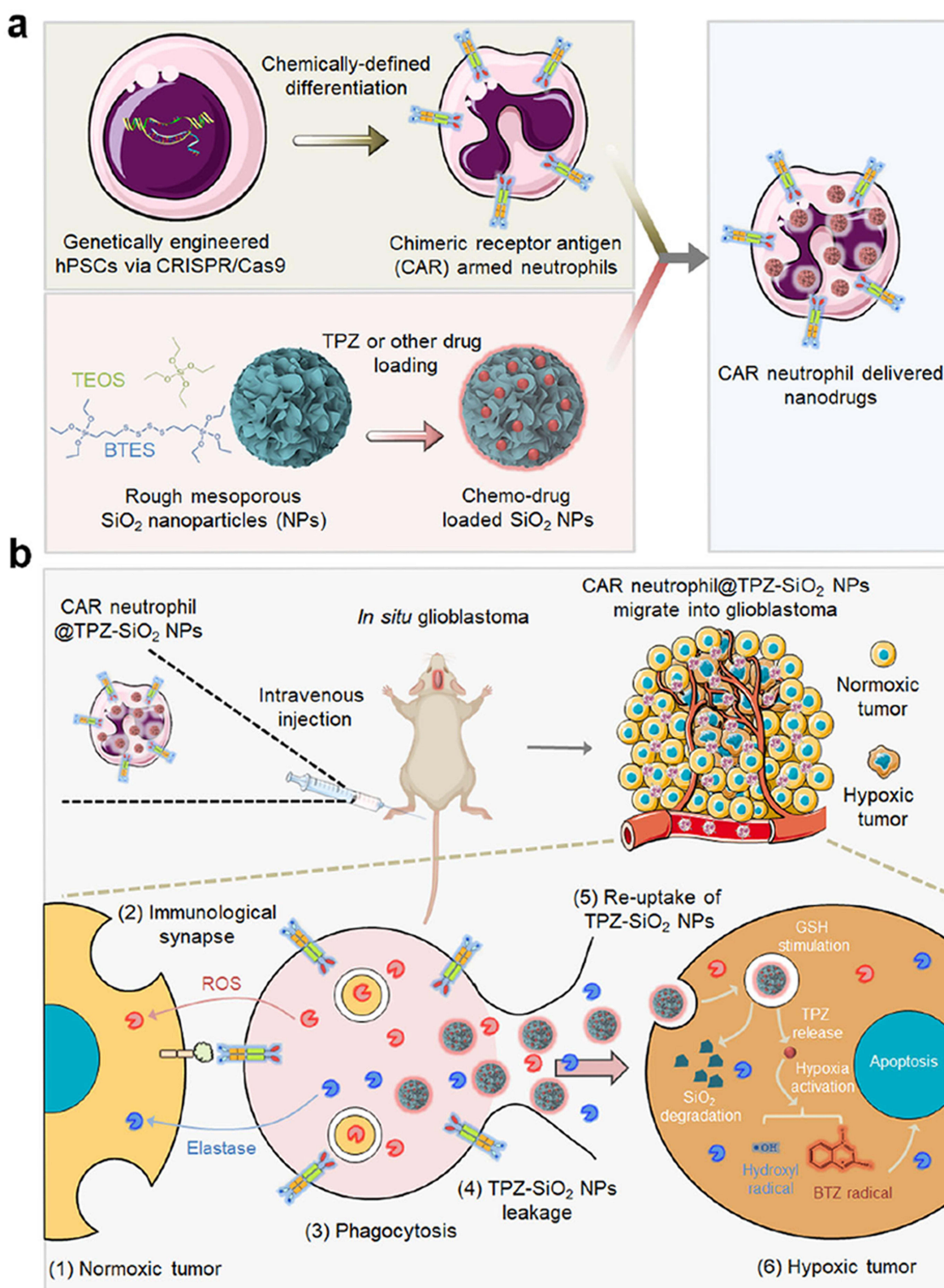


Figure 9 Schematic diagram of (a) the preparation of chimeric antigen receptor (CAR)-neutrophil-NPs using genetically engineered human pluripotent stem cells and (b) the mechanism of its roles for glioblastoma chemo-immunotherapy.

Notes: (a) and (b) Reprinted with permission from Chang Y, Cai X, Syahirah R, et al. CAR-neutrophil mediated delivery of TME-responsive nano-drugs for glioblastoma chemo-immunotherapy. *Nat Commun.* 2023;14(1):2266. Copyright © The Author(s) 2023, <http://creativecommons.org/licenses/by/4.0/> License.¹⁵⁰

Table 6 Examples of WBCMs-NDDS in Cancer Treatment

Source Cells	Core	Loaded Drug	Tumor Type	Application	Ref.
Mø	PPiP-polymer	PTX	Breast cancer	Tumor-targeted chemotherapy	[157]
	Soy lecithin	DOX, QDs	Breast cancer	Improving tumor imaging and tumor-targeted chemotherapy	[159]
	DSPE-PEG	IR-792	Glioblastoma	Passing through the blood-brain barrier to achieve photothermal therapy	[160]
	UCNP	Rose Bengal	Breast cancer	Improving photodynamic immunotherapy	[163]
	MSNs	DOX, catalase, R848	Liver cancer	Active targeting of tumors and enhancing the efficacy of immunotherapy	[164]
NEs	Lipid-DNA NC	DOX-MPK Ti; Pa	Metastatic breast cancer Melanoma	Targeting lung metastasis sites for chemotherapy Magnetic guided tumor-targeting and immune regulation	[165] [166]
	PEG-PLGA	–	Pancreatic cancer	Tumor-targeted chemotherapy	[172]
	PPDG/D micelle	DOX	TNBC	Restraining myeloid-derived suppressor cells-mediated immunosuppression and formation of pre-metastatic niche	[174]
	BSA	DAC	Triple-negative breast cancer	Photothermal-induced tumor Immunotherapy by triggering pyroptosis	[175]
	PLGA	IL-2	Ovarian cancer	Boost T-cell-Based immunotherapy for cancer	[180]
DC	PLGA	RAPA	Glioma	Targeted tumor chemotherapy combined with immunotherapy	[182]
	PLGA	DTIC	Melanoma	Tumor immunotherapy	[185]
	PLGA	PTX	Gastric cancer	Tumor-targeted chemotherapy	[186]
T-cell	BSA	ORY-1001	4TI TNBC; B16F10 melanoma; CT26 colon cancer	Tumor-targeted immunotherapy	[187]
NKs	MSNs	IR780	Huh-7 HCC	Provide high specificity for hepatocellular carcinoma	[188]
	PLGA	TCPP	4TI breast cancer	Improves blood circulation, enhances proinflammatory M1-macrophages polarization	[196]
	–	OXA; I-MT	Breast cancer	Achieving tumor-targeting and induce macrophages to polarize into M1 type	[197]
	Liposomes	DOX	Breast cancer	Tumor-targeted chemotherapy	[198]

Abbreviations: PPiP-polymer; amphiphilic bola-pattern polymer was functionalized with a cationic 2-aminoethyl-diisopropyl group (PPiP); QDs, imaging agent quaternary quantum dots; IR-792, near-infrared I_b (NIR-I_b) fluorescence dye; NC, Fe₃O₄ magnetic nanocluster; Ti, TGF- β inhibitor; Pa, PD-I antibody; BSA, bovine serum albumin; DAC, decitabine; RAPA, rapamycin; ORY-1001, a potent and selective lysine-specific histone demethylase 1 (LSD1) inhibitor; TCPP, 4,4',4',4'-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid); OXA, oxaliplatin; I-MT, I-methyl-d-tryptophan.

various delivery vectors, including gold based nanoplateforms, up-conversion NPs, liposomes with emtansine, and MSNs, have been integrated into macrophage membranes and have shown high targeting, low immunogenicity, and good systemic circulation stability to treat malignant tumors, including breast cancer, colorectal cancer, melanoma, and glioma.

Based on Mø's inherent tumor-targeting and immune affinity, Mø membrane-NDDS has been widely used in effective cancer imaging, enhanced cancer photothermal therapy, tumor-targeted chemotherapy, and other tumor treatment strategies.⁸ Zhang et al¹⁵⁷ developed a pH-sensitive NP delivery system (Mø-m-NPs) for human breast cancer cell lines. These pH-sensitive NPs respond to pH differences in the TME and are controlled to release anti-tumor drugs. As a homing navigator, surface modification of NPs with Mø membranes promotes their accumulation at tumor sites, enhances their anti-tumor effect, and decreases their cytotoxicity. Another study loaded sub-5 nm PEGylated gold (Au) NPs onto the shuttle machine Mø, achieving active or passive delivery of tumors. Although the delivery efficiency of the obtained NPs is lower than free NPs, this safe delivery platform can prevent ultrasmall NPs from translocating across biological barriers during tumor-targeting while overcoming the specificity limitations of passive and active tumor-targeting delivery NP models.¹⁵⁸ Liang et al¹⁵⁹ used Mø membrane to wrap liposome cores loaded with the anti-cancer

drug DOX and the imaging agent quaternary quantum dots (QDs) for improving tumor imaging and anti-metastasis therapy. The Mø membranes in this biomimetic platform not only promote NPs in evading immune clearance, prolonging circulation in the bloodstream, and effectively targeting tumors, but also stabilize the structure of artificial liposomes, preventing substance leakage. Another study demonstrated that Mø membrane-decorated DSPE-PEG loaded with near-infrared Ib (NIR-Ib) fluorescent dye IR-792 can penetrate the blood-brain barrier and selectively aggregate at tumor site, achieving a combination of NIR-Ib imaging and NIR-Ib imaging guided photothermal therapy, significantly inhibiting the growth of glioma.¹⁶⁰

Biomimetic nanoplateforms based on monocytes/macrophages have been used for multifunctional co-occurrences to improve the therapeutic effects on tumors. For example, an ultrasound-driven white blood CM-coated gallium nanoswimmer loaded with DOX was developed for enhanced photothermal and chemical cancer treatments. This nanoswimmer exhibits multifunctionality, including active movement, anti-biofouling properties, cancer cell recognition, imaging, drug delivery, and photothermal cancer treatment, providing a new multifunctional platform for medical applications.¹⁶¹ Ding et al¹⁶² modified the Mø membrane with folic acid ligands and luciferase NanoLuc and encapsulated the photoreceptor CRY2 and its interacting partner CIB1 plasmid. In a mouse model of retinoblastoma, the camouflaged NP-based optogenetic system demonstrated a strong ability to target tumors and effectively load plasmids (Figure 10). Tumor-associated macrophage membrane-loaded NPs prepared by Chen et al¹⁶³ selectively accumulated in the TME, which eliminated the growth of primary tumors and had a significant inhibitory effect on tumor metastasis. Recently, a novel core/shell structure nanoplateform has been developed, comprised MSNs coated with macrophage CM and simultaneously loaded with catalase, DOX and resiquimod (R848). The multifunctional platform actively targets tumor sites through ligand binding, facilitating hypoxia reversal and improving the immunosuppressive TME through various pathways. These include supplying oxygen in situ via catalase, inhibiting the adenosine A2AR pathway in regulatory T (Treg) cells, inducing ICD in tumor cells with DOX, and enhancing CD8⁺ T-cell activation with R848. The results showed that the expression of regulatory T cells in the tumor tissue decreased to 9.79%, and the tumor growth inhibition rate reached 73.58%, considerably enhancing the effectiveness of anti-tumor immunotherapy.¹⁶⁴

NE Membranes

NEs are the most abundant circulating leukocytes in the human circulatory system, accounting for 40–70% of all human leukocytes. They also participate in proinflammatory and immune responses against pathogens, but when faced with microbial challenges or tissue injury, some reactions are nonspecific, causing damage to normal tissues. NEs can inhibit or promote tumor growth and play important roles in tumorigenesis, development, and treatment.^{167,168} NEs contribute to malignant tumor metastasis by targeting CTCs through adhesion factors and ligands, mediating the formation of an ecological niche before cancer metastasis.¹⁶⁹ Based on these characteristics, nanocarriers simulating NEs have been widely studied to identify and inhibit tumors.

Animal experiments have shown that NE-encapsulated PLGA NPs loaded with carfilzomib, a proteasome inhibitor, can target and capture CTCs and effectively inhibit cancer metastasis by enhancing homing to the pre-metastasis niche.¹⁷⁰ Similarly, Zhang et al¹⁷¹ constructed BNDDS using a zeolitic imidazolate framework-8 (ZIF-8) coated with an NE membrane, which was co-loaded with glucose oxidase (GOx) and chloroperoxidase (CPO). The obtained biomimetic system demonstrated good immune compatibility and inflammatory targeting by simulating natural NEs, and produced seven times more reactive hypochlorous acid than natural NEs through enzymatic cascade reactions. NEs membranes also allow carriers to cross biological barriers (blood-pancreatic and blood-brain barriers). Cao et al¹⁷² designed a formulation of NE membrane-encapsulated NPs (NNPs) loaded with celastrol and demonstrated in animal models that the formulation could overcome the blood-pancreatic barrier for in vivo pancreas-specific drug delivery. Similar experiments demonstrated that NE-mediated delivery of anti-cancer drugs inhibits the recurrence of postoperative malignant gliomas.¹⁷³ Xia et al¹⁷⁴ introduced an innovative approach by creating a sponge-like NE CM-wrapped nanosystem (NM/PPcDG/D), merging sponge NPs and anti-inflammatory agents. This BNDDS exhibits a natural affinity for postoperative inflammatory sites, reduces the recruitment and function of myelogenous Sexual inhibition cells (MDSCs), and thus alleviates immunosuppression in 4T1 tumor resection models. Combined with the ICD effect of DOX, it effectively inhibits lung metastasis and reduces vascular permeability, mitigating the implantation of CTCs in the lungs. This provides a new treatment plan for improving the effectiveness of postoperative tumor treatment. In another

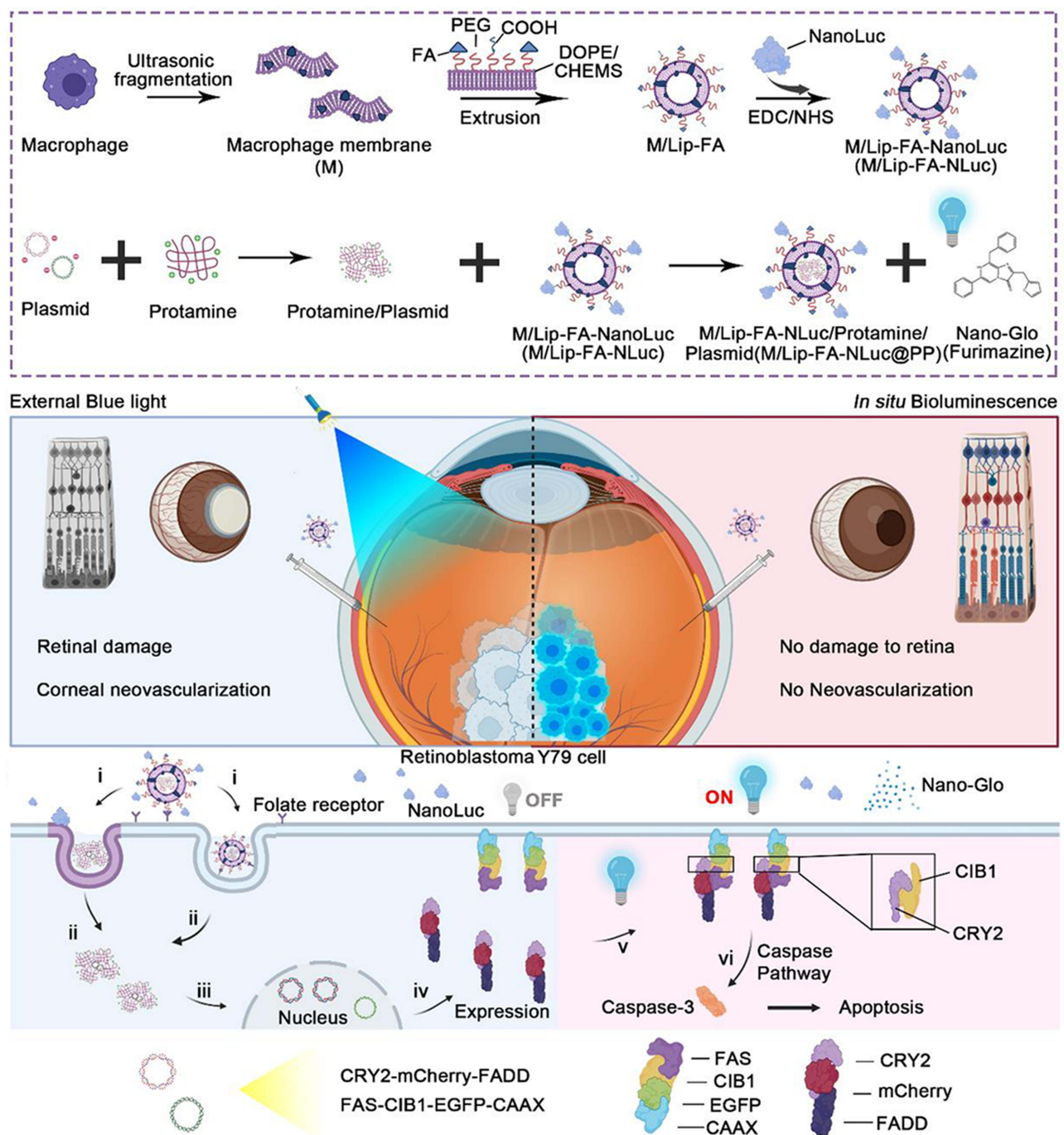


Figure 10 Schematic diagram of MM-NPs in situ bioluminescence-driven optogenetic therapy.

Notes: Reprinted with permission from Ding J, Lu J, Zhang Q, et al. Camouflage Nanoparticles Enable in Situ Bioluminescence-Driven Optogenetic Therapy of Retinoblastoma. *ACS Nano*. 2023;17(8):7750–7764. Copyright (2023) American Chemical Society.¹⁶²

study, researchers designed bovine serum albumin NPs conjugated with anti-CD11b and IR-820, loaded with decitabine (DAC), to enable precise drug delivery and photothermal-induced tumor immunotherapy. The NDDES uses anti-CD11b to target activated NEs in the bloodstream, achieving precise targeting of tumor areas in the postoperative inflammatory microenvironment. Incorporating IR820 provides a photothermal control system, allowing the NDDES to escape from the cell carrier. Simultaneously, the released DAC upregulates gasdermin E, and laser irradiation activates caspase-3, which causes cell pyroptosis and regulates the immunosuppressive microenvironment while inducing persistent and powerful immune memory, preventing lung metastasis (Figure 11).¹⁷⁵

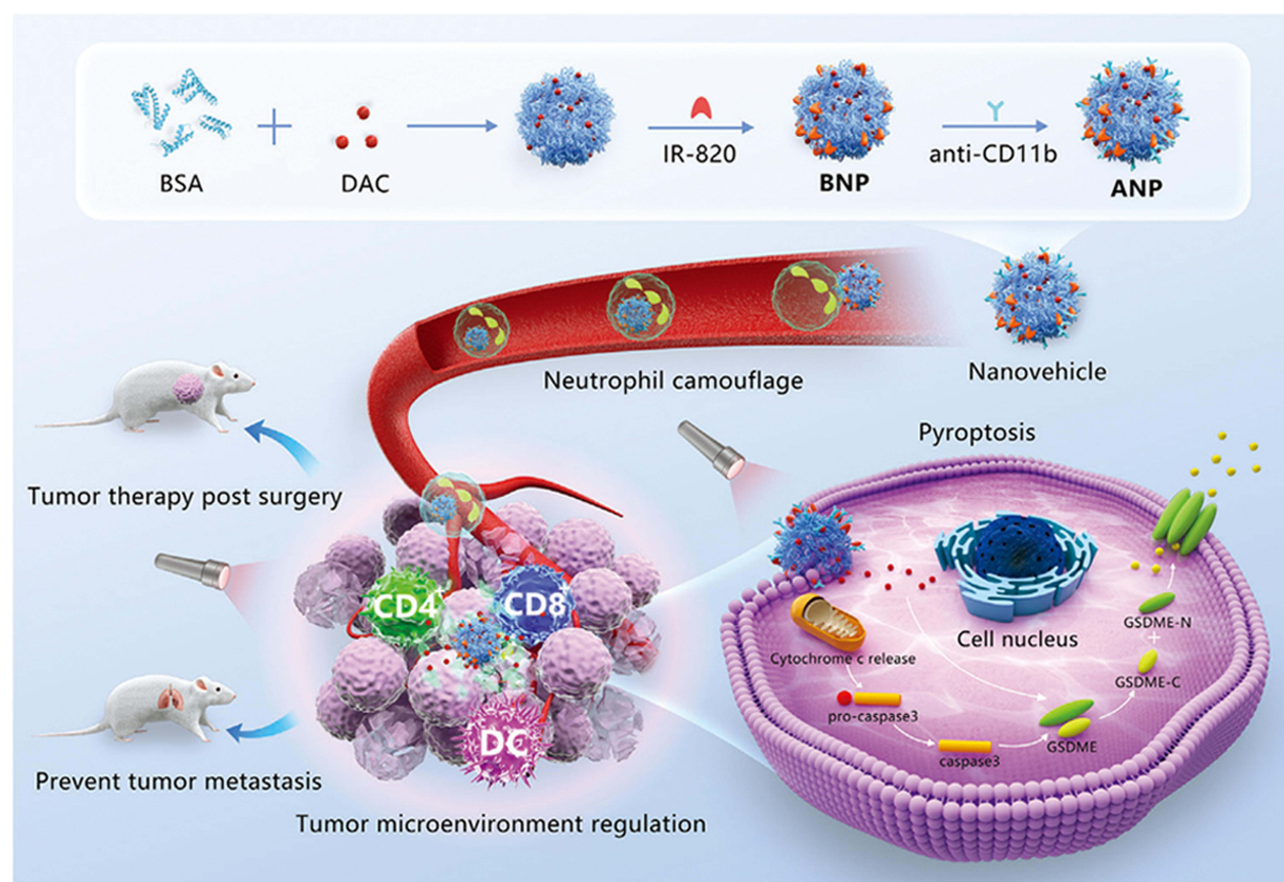


Figure 11 Schematic diagram of NEM-NPs for photothermal-induced tumor immunotherapy by triggering pyroptosis.

Notes: Reprinted with permission from Yu X, Xing G, Sheng S, et al. Neutrophil Camouflaged Stealth Nanovehicle for Photothermal-Induced Tumor Immunotherapy by Triggering Pyroptosis. *Adv Sci*. 2023;10(15):e2207456. Copyright © 2023 The Authors. *Advanced Science* published by Wiley-VCH GmbH. This is an open access article under the terms of the <http://creativecommons.org/licenses/by/4.0/> License.¹⁷⁵

DC Membranes

DCs, originating from pluripotent hematopoietic SCs in the bone marrow, are the most effective antigen-presenting cells that can proficiently ingest, process, and present antigens.^{176,177} These cells play a crucial role not only in the intrinsic immune response but also in initiating adaptive immune responses and influencing the type of immune response, which ultimately assists in immune responses.¹⁷⁸ DC vaccine is a safe and effective therapeutic strategy that has made considerable progress in basic science research and clinical therapeutic areas.¹⁷⁹

Animal studies have demonstrated that DC-coated PLGA NPs loaded with IL-2 inherit DC antigen presentation and T-cell stimulation abilities, enhancing T-cell activation. Compared with traditional DC vaccines, mini-DC-NP nanovaccines exhibit more potent tumor treatment and prevention capabilities.¹⁸⁰ Remarkably, Liu et al¹⁸¹ proposed a novel personalized nanovaccine formulation that can directly activate both naive T cells and exhausted T cells. The formulation was developed utilizing recombinant adenovirus-engineered mature DCs, with major histocompatibility complex class I (MHC-I) molecules, anti-PD1 antibodies, and B7 co-stimulatory molecules simultaneously anchored on the membrane of mature DC through cell reprogramming. This approach effectively inhibits tumor cell growth through antigen self-presentation and immunosuppression reversal, leading to optimal therapeutic outcomes. NDSS based on DC membranes can also efficiently cross biological barriers and target the TIME. Ma et al¹⁸² used activated mature dendritic cell membrane (aDCM) to encapsulate a PLGA copolymer loaded with rapamycin (RAPA) to prepare aDCM @PLGA / RAPA. In vivo and in vitro results show these NPs effectively penetrate the blood-brain barrier and activate CD8+T cells, reshaping the glioma TIME and significantly inhibiting tumor growth, providing a simple and effective platform for personalized immunotherapy (Figure 12). In another study, DC membranes were encapsulated on nanoaggregates of

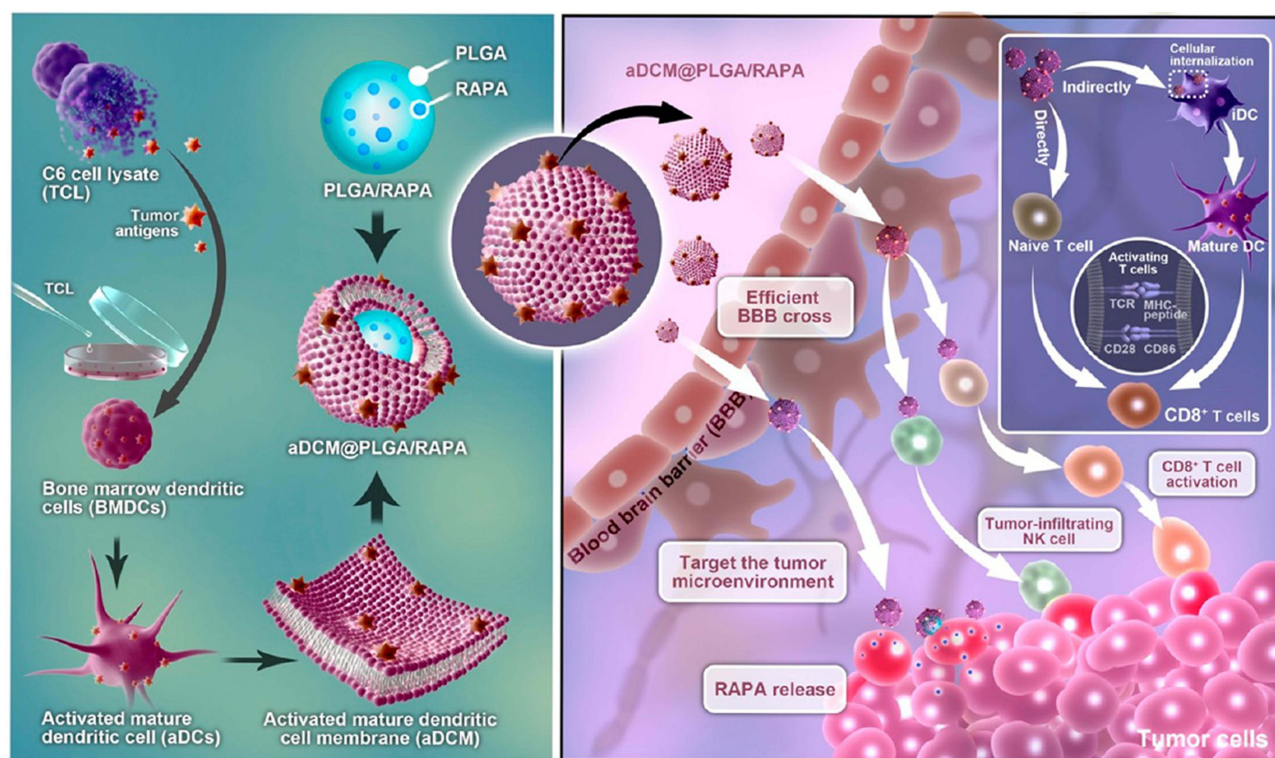


Figure 12 Schematic diagram of DCM-NPs activate immunotherapy through direct or indirect pathways.

Notes: Reprinted with permission from Ma X, Kuang L, Yin Y, et al. Tumor-Antigen Activated Dendritic Cell Membrane-Coated Biomimetic Nanoparticles with Orchestrating Immune Responses Promote Therapeutic Efficacy against glioma. *ACS Nano*. 2023;17(3):2341–2355. Copyright (2023) American Chemical Society.¹⁸²

near-infrared aggregation-induced emission emitters (NIR-AIEgens) to form biomimetic AIE photosensitizers (DC@BPBBT dots) with antigen presentation and “free-riding” capabilities. Extracellular membrane allows DC@BPBBT dots to target endogenous T cells, selectively aggregating AIE molecules onto the lipid droplets of tumor cells, ultimately increasing the tumor delivery rate approximately 1.6 times.¹⁸³

T-Lymphocyte CMs

T lymphocytes, derived from bone marrow hematopoietic SCs (BMSCs), are widely present in the human body and mainly participate in cellular immune processes. As the main immune cells in the TIME, T lymphocytes play an important role in controlling the occurrence and development of tumors. High-density cytotoxic CD8+T cells and CD4+T helper cells are associated with favorable prognosis of various cancers. In contrast, Treg cells suppress anti-tumor immunity by influencing the proliferation and activation of cytotoxic CD8+T cells.¹⁸⁴ Because of the abundance of proteins that bind to tumor cells, such as adhesins LFA-1 and PD-1, and inflammatory tendencies on T-CMs, many studies have used T-CMs to disguise NPs for cancer treatment by “active targeting” or “immune checkpoint”.

To address the challenge of cancer immunotherapy, Kang et al¹⁸⁵ coated T-CMs from the EL4 cell line on PLGA NPs to prepare a biomimetic carrier-TCMNP for melanoma immunotherapy. Dacarbazine-loaded BNDDS TCM-NPs target tumors through proteins originating from T-CMs and kill cancer cells by releasing anti-cancer molecules and inducing Fas ligand-mediated apoptosis. This strategy is more cost-effective and less time-consuming than adoptive T-cell transfer therapy. Compared to immune checkpoint blockades, TCM-NPs exhibit lower systemic toxicity owing to their higher tumor-targeting efficiency and multiple treatment mechanisms. Zhang et al¹⁸⁶ camouflaged the paclitaxel-carrying PLGA nanocore with a human cytotoxic T-lymphocyte membrane, demonstrating excellent tumor-specific recognition (Figure 13). Similarly, Zhai et al¹⁸⁷ created a cytotoxic T-lymphocyte membrane-decorated epigenetic nanoinducer (OPEN) loaded with ory-1001 for cancer immunotherapy. The outer shell of the vector was engineered using PD-1. The T-lymphocyte membrane endows OPEN with the ability to specifically recognize and block a variety of immune

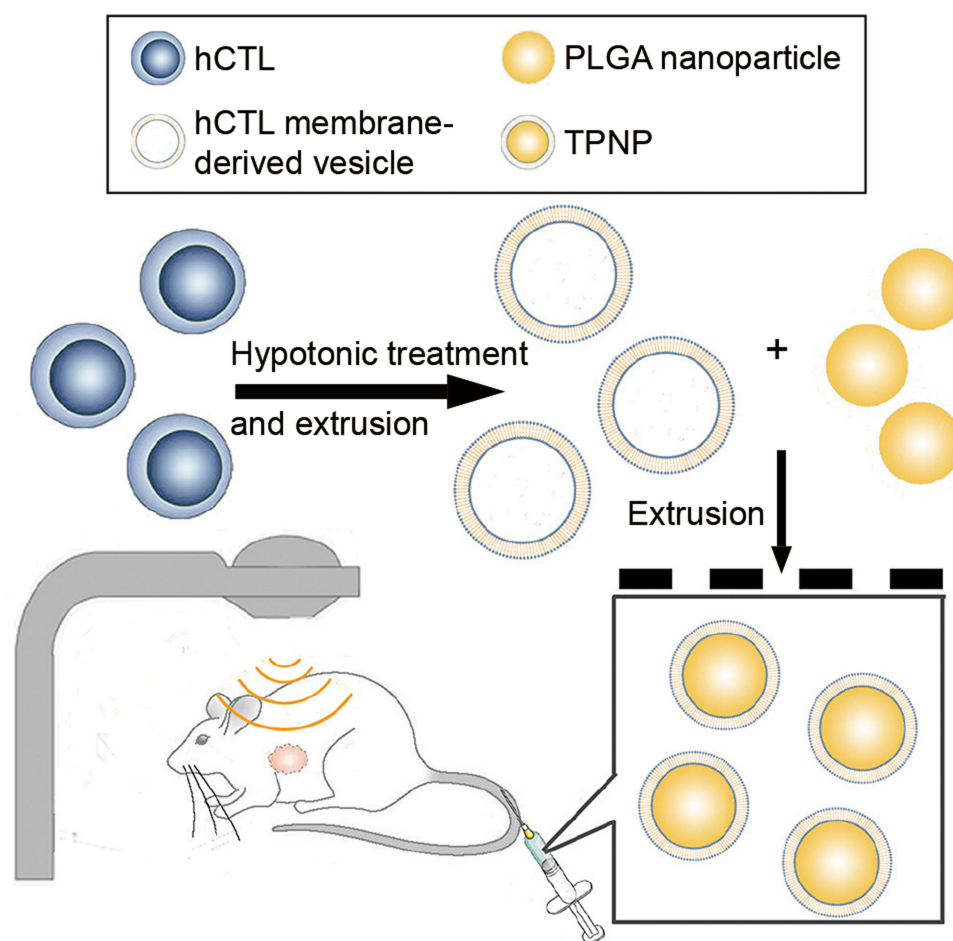


Figure 13 Preparation and application of TCM-NPs (TCM-NPs) in tumor treatment.

Notes: Reprinted with permission from Zhang L, Li R, Chen H, et al. Human cytotoxic T-lymphocyte membrane-camouflaged nanoparticles combined with low-dose irradiation: a new approach to enhance drug targeting in gastric cancer. *Int J Nanomedicine*. 2017;12:2129–2142. Copyright (2017) Dove Medical Press Ltd, Open Access.¹⁸⁶

checkpoint ligands. This strategy supplements interferon in tumors and blocks interferon-induced immune checkpoint upregulation, increasing the recruitment, proliferation, and activity of tumor-infiltrating lymphocytes. OPEN shows significant anti-tumor effects in various tumor models.

NK CMs

NK cells serve as the primary defense against tumors in the innate immune system.¹⁸⁹ Unlike T and B lymphocytes, they can identify and destroy tumor cells directly via the perforin/granzyme and Fas/FasL pathways without the need for antigen pre-sensitization.¹⁹⁰ Surface-activated and inhibitory receptors are responsible for coordinating NK cell activity. This ongoing balance of activation and inhibition enables NK cells to maintain self-tolerance and efficiently target tumors.¹⁹¹ NK cells hold great potential as effector cells for adoptive immune therapy in cancer treatment.¹⁹² However, the therapeutic effect is compromised by immunosuppression in the TME. Therefore, several studies are underway to create new nanomedicines that regulate the interactions between immune and tumor cells.^{193,194}

Based on the efficient recognition of tumors by NK CMs, NK CM-encapsulated NPs (NKCM-NPs) have shown great potential for enhancing the tumor-targeting homing ability of NDDS.¹⁹⁵ For example, Deng et al¹⁹⁶ developed NK CM-camouflaged NPs to enhance anti-tumor immune efficiency and photodynamic therapy. The obtained BNDDS inherited the antigen spectrum of natural NK cells and induced or enhanced the polarization of proinflammatory M1 macrophages. In animal experiments, this biomimetic nanostrategy demonstrated good tumor elimination and inhibition ability against ovarian cancer (Figure 14). Du et al¹⁹⁷ created self-assembled NKCM-NPs for chemioimmunotherapy of breast cancer. The NK CM-camouflaged modification of NDDS enhances the highly effective targeting ability of breast cancer cells. It can also trigger tumor-

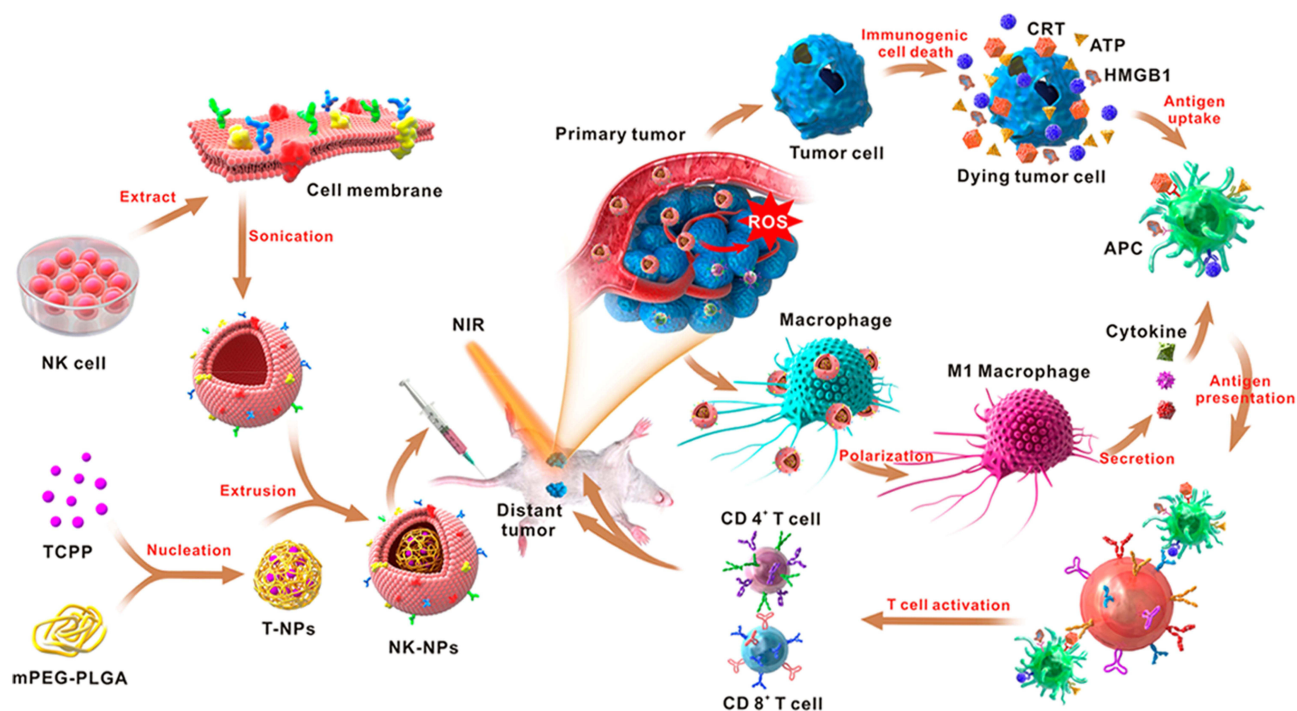


Figure 14 Schematic diagram of NKCM-NPs in photodynamic therapy combined with chemoimmunotherapy.

Notes: Reprinted with permission from Deng G, Sun Z, Li S, et al. Cell Membrane Immunotherapy Based on Natural Killer Cell Membrane Coated Nanoparticles for the Effective Inhibition of Primary and Abscopal Tumor Growth. *ACS Nano*. 2018;12(12):12,096–12,108. Copyright (2018) American Chemistry Society.¹⁹⁶

specific immune responses by inducing macrophage polarization toward the tumor-suppressive M1 phenotype. Another NEM-NDDS prepared for targeted tumor therapy showed good biocompatibility and extended drug circulation time.¹⁹⁸ Furthermore, in recent years, there has been significant focus on NK cells as potential targets for immunotherapy.

Bacterial Membrane-Camouflaged NDDS (BM-NDDS)

Bacterial membranes (BMs) have been proposed as attractive vaccine materials because of their immunogenic antigens with intrinsic surface adjuvant properties.¹⁹⁹ BMs play an important role in immune responses by stimulating the innate immune system and promoting adaptive immune responses. Scientists wrap BMs around synthetic nanocores, endowing NPs with complex biological characteristics similar to BMs and simulating the process of bacteria presenting natural antigens to the immune system.²⁰⁰ Patel et al²⁰¹ used BN-NPs comprising BMs and imine groups enveloping the core of PC7A/CpG peptides to treat syngeneic melanoma and neuroblastoma in situ. The experimental results showed that the combination of radiation and BN-NPs enhanced the local antigen capture and immune stimulation. However, toxicity is a problem that needs to be addressed in the clinical transformation of vaccine platforms based on BMs.

Bacterial outer membrane vesicles (OMV), spherical bilayer NPs released from the bacterial outer membrane, are a unique form of BM. These vesicles possess immunogenic antigens similar to those of the parental bacteria, making them valuable for enhancing the stability and targeting capabilities of NPs when used as CM coating materials.²⁰² Gao et al²⁰³ separately wrapped β -Cyclodextrin (β -CD) and Adamantane (ADA)-modified gold NPs with *Escherichia coli* OMVs. Upon intravenous injection, these NPs were selectively engulfed by phagocytic immune cells and then self-assembled into considerable intracellular aggregates through host–guest interactions, demonstrating enhanced targeting efficiency and therapeutic effects in melanoma tissues. Chen et al²⁰⁴ developed mesoporous polydopamine (MPD) nanocore mimetic NPs encapsulated in bilayer membrane vesicles (DMVs) derived from VNP20009, combining biocompatibility and immune activation. This synergy between MPD-mediated photothermal therapy and immunotherapy through DMV amplification proved effective. This study showed that the intravenous injection of MPD@DMV was superior to the intratumoral injection in terms of its long-term immune effects (Figure 15).

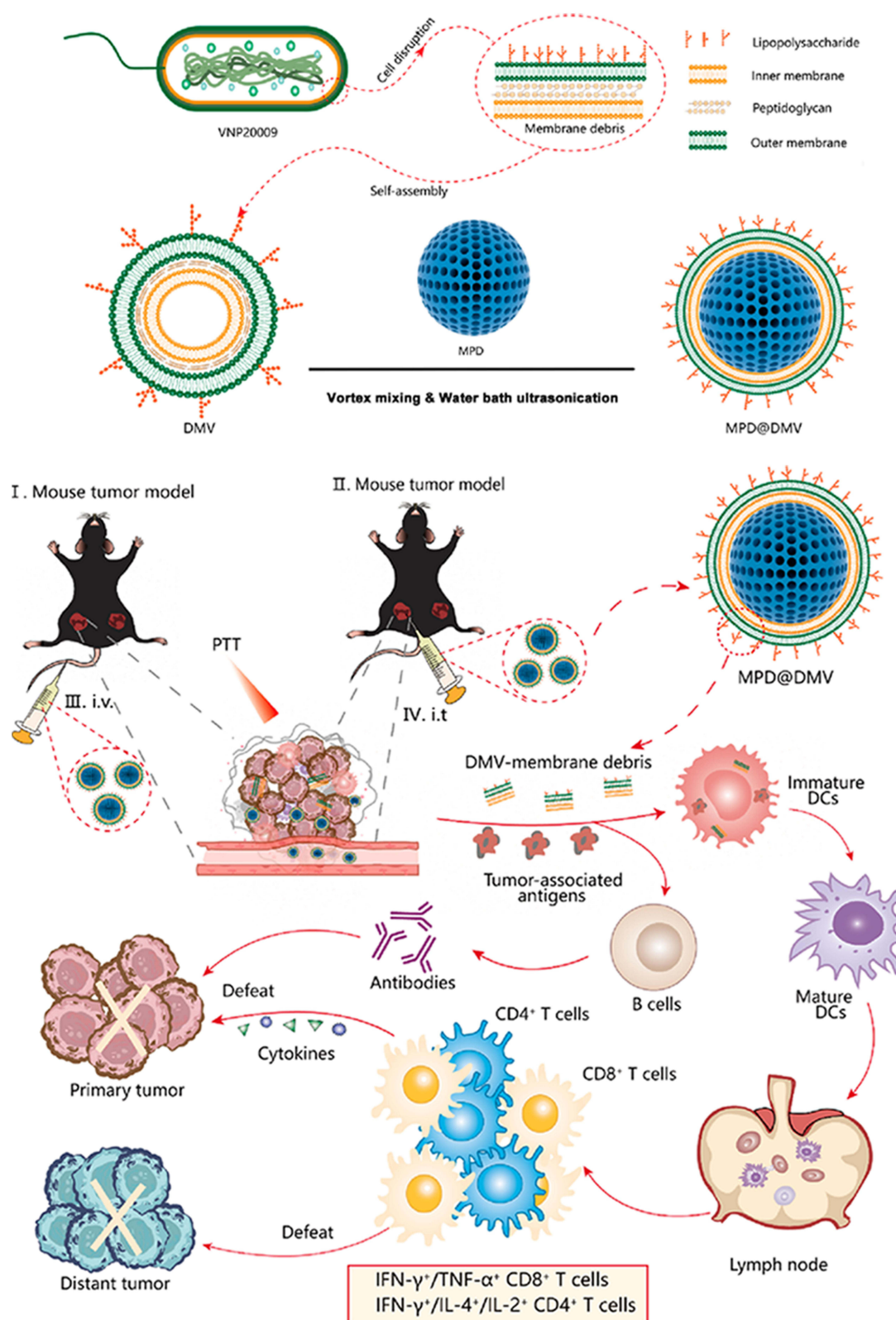


Figure 15 Schematic diagram of BM-NPs in photothermal therapy collaborative immunotherapy. Reproduced, with permission.

Notes: Reprinted with permission from Chen W, Song Y, Bai S, et al. Cloaking Mesoporous Polydopamine with Bacterial Membrane Vesicles to Amplify Local and Systemic Anti-tumor Immunity. *ACS Nano*. 2023;17(8):7733–7749. Copyright (2023) American Chemical Society.²⁰⁴

Extracellular Nanovesicle-Camouflaged NDDS (EV-NDDS)

Extracellular nanovesicles (EVs), comprising exosomes and microbubbles, act as significant mediators in cell communication, migration, signal transduction, and disease pathogenesis.^{205,206} EVs inherit antigens and properties of the source cells, and are released by natural cells.^{207,208} It is recognized as a potentially favorable lipid bilayer nanocarrier for treating cancer due to its high capacity for intracellular uptake, excellent ability to be compatible with living organisms, low toxicity, ability to hold high amounts of drugs, easy modifiability, and potential for large-scale manufacturing.^{209,210} Nonetheless, drug delivery systems using EVs remain restricted in industrial production due to their insufficient quantities.²¹¹

Recently, EVs have been widely used to design actively targeted biomimetic nanomedicines. Zhao et al²¹² constructed biomimetic NPs by wrapping an exosome membrane derived from autologous breast cancer cells onto cationic bovine serum albumin coupled with siS100A4. This biomimetic carrier possesses selective targeting of the pre-lung metastasis niche and good biocompatibility while protecting siS100A4 from degradation. Similarly, extracellular vesicle membranes derived from M2 macrophages have been used for preparing biomimetic NPs to achieve effective drug accumulation in the lungs.²¹³ Irradiated tumor cell-derived microparticles have also been shown to enhance drug particle targeting.²¹⁴ Surface modification methods, similar to natural CMs, also apply to EVs to enhance their precise targeting and tumor penetration ability. A specific anti-glioma-targeted delivery system, using angiopep-2 and TAT peptide-functionalized small extracellular vesicles, efficiently crosses the blood-brain barrier, targets gliomas, penetrates tumors, and achieves precise glioma chemotherapy, minimizing drug-related toxicities.²¹⁵

Bacterial extracellular vesicles (BEVs), which are promising natural nanocarriers,²¹⁶ have shown great potential in various treatments, including drug delivery,²¹⁷ tumor immunotherapy,²¹⁸ and the treatment of infectious diseases.²¹⁹ Particularly, preparing BEV-based nanovaccines has become a research hotspot in recent years.^{220,221} For example, Li et al²²² proposed an in situ vaccine based on OMVs from *E. coli* BL21-CodonPlus (DE3) to promote immune-mediated tumor clearance after photothermal therapy by orchestrating antigen capture and immune regulation. Similar to functionalized mammalian CMs, bacterial OMVs can also enhance the anti-tumor effect of biomimetic NPs through OMV genetic engineering or surface modification.²²³ In another interesting study, a universal modular platform involving avidin-based vaccine antigen cross-linking (AvidVax) was developed for the rapid assembly of antigens of interest on OMV surfaces. Unlike previous covalent binding strategies, which were mainly limited to protein and peptide antigens, the AvidVax method can accurately and uniformly load multiple subunit antigen molecular arrays. The development of this platform has significantly affected the vaccine industry (Figure 16).²²⁴

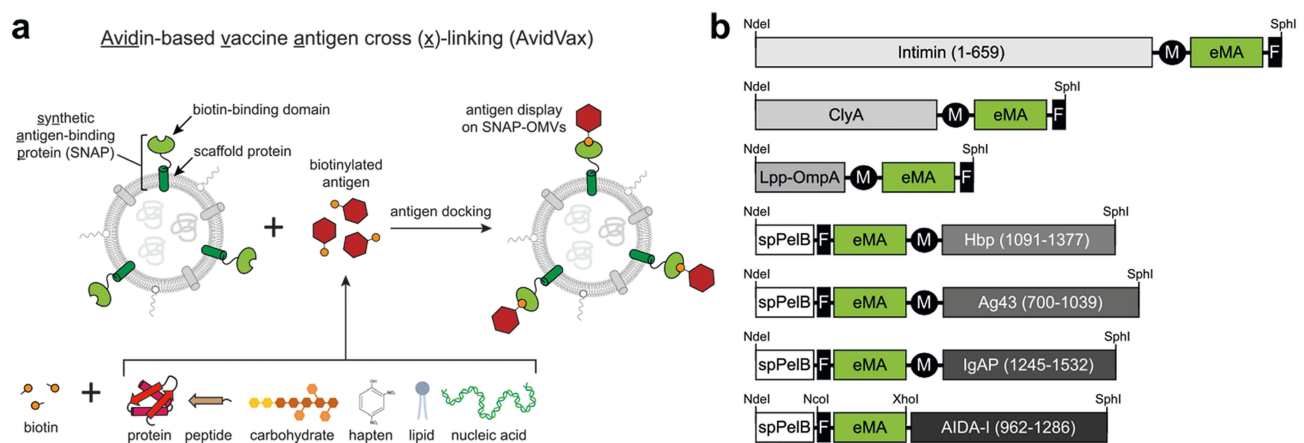


Figure 16 Schematic diagram of the modular nanovaccine based on rapidly self-assembling OMVs. (a) Schematic of Avidin-based vaccine antigen crosslinking (AvidVax) technology. (b) Genetic architecture of synthetic antigen-binding protein (SNAP) constructs tested.

Notes: (a) and (b) reprinted with permission from Weyant KB, Oloyede A, Pal S, et al. A modular vaccine platform enabled by decoration of bacterial outer membrane vesicles with biotinylated antigens. *Nat Commun.* 2023;14(1):464. Copyright © 2023, The Author(s), Creative Commons CC BY license.²²⁴

Other CM-Camouflaged NDDS

In addition, some special cell types have been designed for drug delivery. For example, tumor-associated fibroblasts (TAFs), an important component of the TME, have multiple functions, such as secreting various inflammatory and growth factors, reshaping the extracellular matrix, and developing resistance to various treatments. TAFs play a dual role in promoting and inhibiting tumor occurrence, development, and metastasis.²²⁵ In addition, TAFs can crosstalk with both cancer cells and infiltrating immune cells in the TME.²²⁶ Li et al²²⁷ camouflaged near-infrared (NIR)-absorbing semiconducting polymer NPs with activated fibroblasts (AF) for combined photodynamic and photothermal therapy. The CM coating provides homologous targeting of cancer-related fibroblasts, facilitating the accumulation of NPs in tumors and enhancing the effectiveness of photo-diagnosis and phototherapy. In another example, Zhang et al²²⁸ used a PD-1-expressing hek293T CM to encapsulate a sinophorin sodium-binding human serum albumin-perfluorotributylamine nanoemulsion, which was used for synergistic photodynamic immunotherapy of hypoxic 4T1 breast tumors and distant metastases. Interestingly, unlike traditional membrane encapsulation strategies, Niu et al²²⁹ patched heparin-based NPs (DNs) loaded with DOX onto the surface of natural grapefruit extracellular vesicles (EVs) to achieve efficient drug delivery with 4-fold drug loading.

Hybrid Membrane-Camouflaged NDDS (HM-NDDS)

NPs disguised by single-CMs exhibit various characteristics. However, owing to differences in cellular functions, different natural CM-encapsulated NDDS have deficiencies in certain functions, such as poor targeting of the RBCM. Therefore, to further enhance the advantages of CMs while improving tumor homing and tissue penetration, reducing toxic side effects, and obtaining acceptable biodistribution and therapeutic indices for drugs and NPs, researchers have used specific synthesis techniques to fuse several CMs to form hybrid membranes.²³⁰ The resulting formulations inherit the specific functions of the respective membranes, and the newly synthesized hybrid membranes are endowed with the corresponding functions by adjusting the ratio of the source membranes to achieve the organic integration of multiple functions into the same NPs. Successfully developed hybrid CM-NPs include RBC-PLT hybrid CM-coated NPs, RBC-cancer hybrid CM-coated NPs, PLT-WBC hybrid CM-coated NPs, DC-cancer hybrid CM-coated NPs, PLT-cancer stem cell hybrid CM-coated NPs, PLT-cancer hybrid CM-coated NPs, Mø-cancer hybrid CM-coated NPs, and bacterial vesicle-cancer hybrid CM-coated NPs (Table 7).

In 2017, RCM and PLT hybrid CMs were developed as the first hybrid membrane sources for encapsulating NDDS.²³¹ Subsequently, an increasing number of studies have used mixed CMs as envelopes to disguise NPs. Targeting cancer cells in the TME is an important area of oncology research. Wang et al²³² coated hollow copper sulfide NPs (CuS NPs) loaded with DOX with a hybrid CM of RBCs and melanoma cells (B16-F10 cells) for combined photothermal/chemotherapy in melanoma. Compared with bare CuS NPs, this multifunctional platform showed highly specific self-recognition of the source cell line in vitro and a significantly prolonged circulation lifetime in vivo. This enhances the homogeneous targeting ability inherited from source cytogenetics. Likewise, Rezaei et al²³³ established a different NDDS using 4T1 CCMs, RBCMs, and hybrid erythrocyte cancer membranes to disguise reduction-sensitive chitosan NPs loaded with DOX to enhance the efficacy of chemotherapy in breast cancer. The results showed that compared with free nanocarriers, membrane camouflage carriers exhibited prolonged circulating life and enhanced tumor homotype-targeting chemotherapy drug delivery both in vitro and in vivo. Interestingly, the homotypic targeting characteristics of breast cancer cells were increased by optimizing the RBCM:4T1CM ratio. Ma et al²³⁹ evaluated the ability of PLGA NPs wrapped with glioma-associated stromal cell (GASC)-glioma cell fusion CMs to target gliomas in the TME. The hybrid CM-encapsulated NPs, inheriting the membrane proteins of the glioma and GASC membranes, exhibited slower blood clearance and higher tumor-targeting efficiency and binding affinity compared to the nanoformulations coated with CCMs alone. Another novel NDDS with a hybrid membrane was developed, which was constructed using NE and macrophage membrane-camouflaged PLGA NPs loaded with RAPA. This nanoplatform efficiently coordinated and promoted the transport through the blood-brain barrier and the targeting efficiency of gliomas.²⁴⁶ Interestingly, a hybrid membrane of exosomes and Golgi membranes was modified on the surface of PLGA NPs embedded with retinoic acid (RA) to prepare GENPs. This hybrid membrane enables efficient penetration of tumor

Table 7 Example of NPs Encapsulated Within Hybridized Cells in Cancer Treatment

Source Cells	Core	Loaded Drug	Tumor Type	Application	Ref.
PLT; RBC (hybrid) RBC; cancer cell (hybrid)	PLGA	–	Breast cancer	Tumor-targeted delivery	[231]
	Melanin	ICG	Breast cancer	Enhancing photothermal therapy efficacy in tumors	[70]
	Hollow CuS	DOX	Melanoma	Homotypic tumor-targeted; photothermal therapy	[232]
	Chitosan	DOX	Breast cancer	Enhance the chemotherapy effect of breast cancer	[233]
	Fe ₃ O ₄ NPs	ICG	Ovarian Cancer	Enhanced photothermal immunotherapy	[234]
	AuNCs	DOX	Breast cancer	Achieving efficient and safe photothermal/radiation/chemotherapy combination therapy	[235]
	MSG	DOX	HeLa cell-bearing tumor	Achieving high-performance chemical/photothermal therapy	[236]
PLT; cancer cell (hybrid)	PLGA	β-mangostin	C6 glioma; THP-I leukemia;	Improving the efficacy of targeted chemotherapy	[237]
	Lipid NPs	SFN; TPL	Carcinoma	Improving the efficacy of targeted chemotherapy and synergistic detoxification	[238]
Stromal cell; glioma cell (hybrid)	PLGA	TMZ	Glioma	TME targeted drug delivery for glioma	[239]
PLT; WBC (hybrid)	Fe ₃ O ₄ NPs	PTX	Breast cancer	Targeting CTCs	[240]
Mø; cancer cell (hybrid)	Liposomal	DOX	Melanoma	Tumor-targeted chemotherapy	[241]
	PLGA	DOX	Breast cancer	Tumor-targeted chemotherapy Tumor-targeted chemotherapy	[242]
DCs; cancer cell (hybrid)	MOF (PCN-224)	–	Breast cancer	Targeting homotypic tumors, enhancing immunity and photodynamic therapy	[243]
	–	DTX	Glioma	Tumor-targeted drug delivery combined with immunotherapy for treatment	[244]
SC; cancer cell (hybrid)	Fe ₂ O ₃ NPs	–	Squamous cell carcinoma	Enhanced photothermal therapy	[245]
NE; Mø (hybrid)	PLGA	Rapamycin	Glioma	Effectively cross the blood-brain barrier and target brain tumor chemotherapy	[246]
Cancer cell; bacteria (hybrid)	PLGA	–	Melanoma	Persistent immunosuppression and local photothermal therapy	[247]
	HPDA	ICG	Melanoma	Collaborative immunotherapy and photothermal therapy	[248]
Cancer cell; liposome (hybrid)	LC	DTX; siPGAM1	Non-small cell lung cancer	Collaborative metabolic therapy and chemotherapy	[249]

Abbreviations: SFN, sorafenib; TPL, triptolide; MSG, mesoporous silica gold nanorods; HPDA, hollow polydopamine; TMZ, temozolomide; LC, lipoic acid-modified polypeptides; siPGAM1, phosphoglycerate mutase 1 (PGAM1) siRNA.

cells, delivery of RA, disruption of the Golgi apparatus, interference with PD-L1 synthesis, and inhibition of extracellular vesicle secretion carrying PD-L1. A significantly decreased recurrence rate and prolonged survival were observed in a mouse model of incomplete metastatic melanoma resection. This strategy is a promising treatment for patients insensitive to immune checkpoint inhibitors (Figure 17).²⁵⁰

Besides fusing two types of natural CMs, researchers have used a mixture of natural CMs and engineered membranes as coating materials to enhance the function of BNDDS by artificially imparting satisfactory biological properties to NPs. Zhang et al²⁵¹ developed a comprehensive treatment platform for TME reprogramming and immune cell activation. A mixed membrane composed of a mesenchymal stem CM (MSCm) and a pH-sensitive liposome (pSL) was used to encapsulate manganese oxide (MnO₂) NPs loaded with BPTES, a glutamine metabolism inhibitor. This hybrid synthetic CM endowed the NPs with targeting capability for the TME, as well as the characteristics of internal/lysosomal escape and

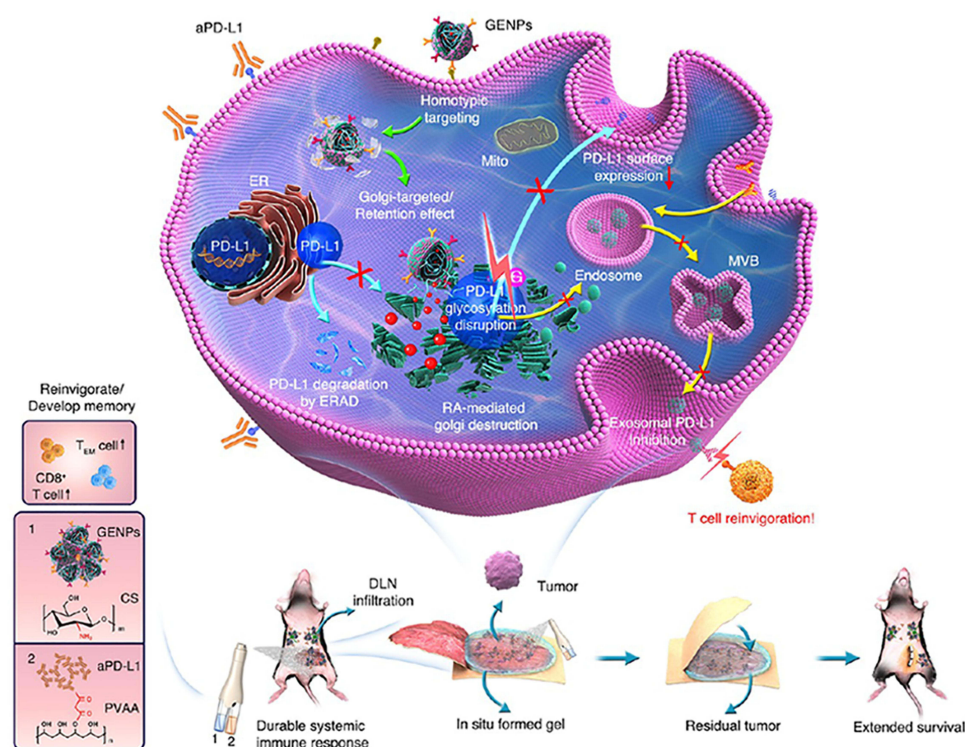


Figure 17 Schematic diagram of exosomes-Golgi apparatus HCM-NPs in tumor treatment.

Notes: Reprinted with permission from Ye H, Wang K, Zhao J, et al. In Situ Sprayed Nanovaccine Suppressing Exosomal PD-L1 by Golgi Apparatus Disorganization for Postsurgical Melanoma Immunotherapy. *ACS Nano*. 2023;17(11):10,637–10,650. Copyright (2023) American Chemistry Society.²⁵⁰

sensitive release. The combination of red blood CMs with pH-responsive liposomes not only optimized the pharmacokinetics and tumor accumulation of nanomedicine but also addressed the limitations of DNA carriers in terms of packaging capacity and interception by the reticuloendothelial system. Mouse experiments demonstrated that a mixed membrane-camouflaged HER2-targeted DNA-aptamer-modified DNA tetrahedron combined with maytansine (DM1) was potent in the treatment of HER2 positive breast cancer.²⁵² Hybrid membrane vesicles have also been studied and showed enhanced anti-tumor effects. Chen et al²⁴⁷ designed and constructed a eukaryotic-prokaryotic vesicle nanoplateform with strong immunotherapeutic effects by fusing melanoma CM vesicles and attenuated *Salmonella* OMVs. In another study, Rao et al²⁵³ developed a ternary hybrid NV (hNV) integrating the functions of platelet-derived NVs (P-NV), cancer cell-derived NVs overexpressing SIRPα variants (Sα V-C-NV), and M1-type macrophage-derived NVs (M1-NV). These findings provide valuable insights into the development of novel anti-tumor immune response strategies (Figure 18).

Novel NDDS Based on Simulated Viruses or CMs

Virus-based immunotherapy has shown potential for overcoming resistance to immune checkpoint blockade, which is a promising method for cancer treatment.^{254,255} Recently, simulating the infection mechanism of natural viruses within cells has become an attractive concept for anti-tumor immunotherapy. For example, Zhao et al²⁵⁶ used the herpes simplex virus (HSV) to trigger a natural immune response as an entry point to construct novel mimics of HSV-NPs applied in cancer-targeted therapy. In this system, DNase-loaded Mn-ZIF-90 NPs (ZM@TD) were designed to mimic the viral nucleocapsid containing the genome, whereas the erythrocyte membrane was modified with RGD and HA2 functional peptides to simulate the viral envelope. This biomimetic platform not only effectively evades rapid elimination in blood circulation but also mimics the various infection processes of HSV. It successfully activated innate immunity through the cGAS-STING pathway, resulting in 68% regression of primary tumors and a 32-day increase in the median survival time of 4T1 tumor-bearing mice.

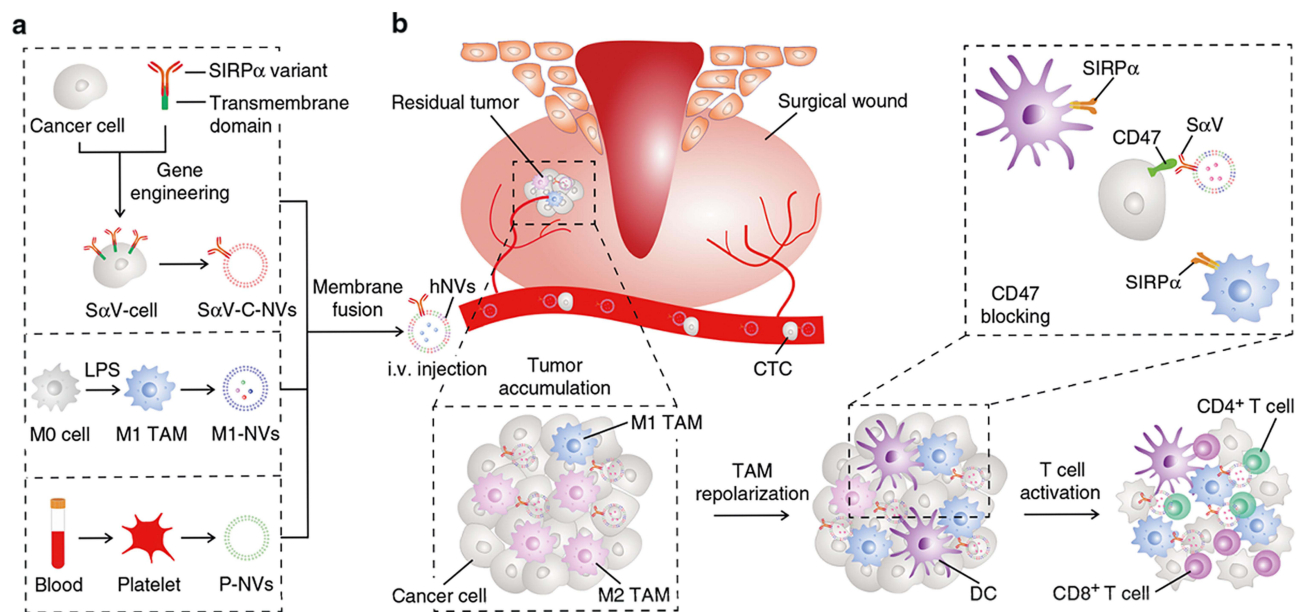


Figure 18 Schematic diagram of (a) the composition of hybrid cell membrane nanovesicles (hNVs) and (b) the mechanism by which hnv effectively enhances the immune response of macrophages.

Notes: (a and b) reprinted with permission from Rao L, Wu L, Liu Z, et al. Hybrid cellular membrane nanovesicles amplify macrophage immune responses against cancer recurrence and metastasis. *Nat Commun.* 2020;11(1):4909. Copyright © 2020, This is a US government work and not under copyright protection in the US; foreign copyright protection may apply. <http://creativecommons.org/licenses/by/4.0/> License.²⁵³

Coating particles with engineered simulated CMs is another way to achieve a functionalized NDDS. Han et al²⁵⁷ prepared CpG-OD-adsorbed PLGA NPs loaded with berberine and melanoma antigen-Hgp peptide fragments. The NP surfaces were then coupled with M2pep (an m2-like macrophage-binding peptide) and a receptor-scavenging B-type 1 targeted peptide to prepare m2-like tumor-associated macrophage (TAM)-targeted nanocomposites. These nanocomposites promote the delivery of baicalin, antigens, and immune stimulators to TAMs, polarizing and reversing M2-like TAM phenotypes. This dual action successfully transforms the TME while eliminating tumor cells. Formulations featuring core-shell structures similar to those of CM-NPs have also been studied for constructing intelligent delivery systems. Xue et al²⁵⁸ programmatically attached an anti-degradable Y-shaped skeleton rigid triangular DNA brick (sticky YTDB) with a sticky end onto Au-NPs loaded with siRNA, forming a multifunctional three-dimensional DNA shell with active tumor-targeting capabilities. This shell protects the siRNA from enzymatic degradation, provides serum stability, and enables cancer-specific cell internalization of the siRNA-encapsulated formula.

Conclusion

This review summarizes BNDDS and the recent advancements in cancer treatment. As a nature-inspired drug delivery system, BNDDS is expected to be a promising platform for tumor therapy. Compared to synthetic nano-drug delivery system, the innovative composite platform can achieve targeted drug delivery and overcome biological barriers by mimicking natural cells. Firstly, the biomimetic membrane shell can avoid the drug being cleared by the immune system, thus improving the stability and durability of the drug. Second, the bionic membrane shell-encapsulated nanocarriers can preferentially target the therapeutic dose to tumor tissues, reducing damage to healthy tissues. In addition, by utilizing the supportive role of the nanoparticle core, the bionic membrane shell can maintain a stable morphological structure, ensuring the accuracy and controllability of drug delivery. Most importantly, BNDDS possesses the ability to load multiple types of therapeutic drugs, which is significant in multi-drug combination therapy. Researchers can select or synthesize specific biomimetic membrane shells tailored to their intended applications, allowing for customized formulations. Based on these advantages, BNDDS have been extensively studied in preclinical models to evaluate their potential for drug delivery, photothermal therapy, and immunotherapy, as well as multimodal theranostic treatment.

Despite progress made by BNDDS, challenges and security issues still need to be addressed. Currently, research is primarily conducted in laboratory settings; however, it is important to consider the species differences between animal models and humans, as they have a significant impact on CM-NPs. In addition, research on the impact of tumor behavior and function is limited. Given the high heterogeneity of the physiological and pathological characteristics among different tumors, it is crucial to develop models that can better simulate tumors and formulate treatment strategies tailored to the specific heterogeneity of each tumor. However, CM-NPs have several limitations that hinder their clinical application. First, research on CM-NPs is still in its early stages and the production technology is not fully developed, making it challenging to achieve large-scale preparation. Second, the characterization methods for CM-NPs are limited, and the effectiveness of the membrane coating can be confirmed only through particle size detection and morphological observation. Third, CM-NPs still pose potential safety risks, such as uncontrolled differentiation and proliferation, cell embolism, autoimmune reactions, and specific storage requirements. Therefore, extensive fine-tuning is necessary to ensure a successful clinical translation. Furthermore, most current studies have primarily focused on the accumulation of CM-NPs at the tumor site, neglecting how the physical and chemical properties of CM-NPs, including size, surface charge, shape, and elasticity, influence the interactions between biomimetic nanocarriers and organisms.²⁵⁹ In addition, limited attention has been paid to the overall lifespan and quality of life.

The use of NDDS based on CMs or engineered CM encapsulation has demonstrated notable advantages in tumor treatment and diagnosis. As biomimetic nanotechnology continues to be researched, the development of membrane-biomimetically modified NPs is anticipated to become a crucial approach in tumor treatment, with the potential to greatly affect human cancer treatment and enhance patient prognosis.

Abbreviations

AAD, anti-angiogenic drug; AF, activated fibroblast; BEV, bacterial extracellular vesicle; BM, bacterial membrane; BMSC, bone marrow hematopoietic stem cell; BNDDS, biomimetic nano-drug delivery system; CAR, chimeric antigen receptor; CCM, cancer cell membrane; CM, cell membrane; EV, extracellular vesicle; GASC, glioma-associated stromal cell; HSV, herpes simplex virus; ICD, immunogenic cell death; LSC, leukemia stem cell; MOF, metal organic framework; MSC, mesenchymal stem cell; MSN, mesoporous silica nanoparticle; NK, natural killer; OMV, outer membrane vesicle; RA, retinoic acid; RBC, red blood cell; RBCM, red blood cell membrane; SC, stem cell; SWE, shear-wave elasticity; TAM, tumor-associated macrophage; VDA, vascular disrupting agent; WBC, white blood cell.

Acknowledgments

This study was supported by the Shanghai Natural Science Foundation (23ZR1453400).

Disclosure

The authors report no conflicts of interest in this work.

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