Drug Delivery and Translational Research (2023) 13:716–737
https://doi.org/10.1007/s13346-022-01252-0

REVIEW ARTICLE

Cell membrane-coated nanoparticles: a novel multifunctional biomimetic drug delivery system

Hui Liu[1] · Yu-Yan Su[1] · Xin-Chi Jiang[1,2] · Jian-Qing Gao[1,2,3]

Accepted: 16 October 2022 / Published online: 22 November 2022

Abstract

Recently, nanoparticle-based drug delivery systems have been widely used for the treatment, prevention, and detection of diseases. Improving the targeted delivery ability of nanoparticles has emerged as a critical issue that must be addressed as soon as possible. The bionic cell membrane coating technology has become a novel concept for the design of nanoparticles. The diverse biological roles of cell membrane surface proteins endow nanoparticles with several functions, such as immune escape, long circulation time, and targeted delivery; therefore, these proteins are being extensively studied in the fields of drug delivery, detoxification, and cancer treatment. Furthermore, hybrid cell membrane-coated nanoparticles enhance the beneficial effects of monotypic cell membranes, resulting in multifunctional and efficient delivery carriers. This review focuses on the synthesis, development, and application of the cell membrane coating technology and discusses the function and mechanism of monotypic/hybrid cell membrane-modified nanoparticles in detail. Moreover, it summarizes the applications of cell membranes from different sources and discusses the challenges that may be faced during the clinical application of bionic carriers, including their production, mechanism, and quality control. We hope this review will attract more scholars toward bionic cell membrane carriers and provide certain ideas and directions for solving the existing problems.

Keywords Nanoparticle · Drug delivery systems · Cell membrane · Applications · Challenges and prospects

Abbreviations

DDSs	Drug delivery systems
NP	Nanoparticle
EPR	Enhanced permeability and retention
RES	Reticuloendothelial system
ABC	Accelerated blood clearance phenomenon
PEG	Polyethylene glycol
GRAS	Generally recognized as safe
FDA	Food and Drug Administration
CMC-NPs	Cell membrane-coated nanoparticles
RBC	Red blood cell
HCMNs	Hybrid cell membrane-coated nanoparticles
PLGA	Poly(lactic-co-glycolic acid)
PTT	Photothermal therapy
SPIO	Superparamagnetic iron oxide
PDT	Photodynamic therapy
MRI	Magnetic resonance imaging
RBC-MNs	RBC membrane-capped magnetic nanoparticles
NPID	Noninvasive pregnant diagnostics
WB	Western blot
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
TEM	Transmission electron microscopy
FRET	Förster resonance energy transfer
CD47	A cluster of differentiated 47
SIRPα	Signal-regulatory protein alpha
DAF	Decay-accelerating factor
CR1	Complement receptor 1
DOX	Doxorubicin

Hui Liu and Yu-Yan Su contributed equally to this work.

✉ Xin-Chi Jiang
11419014@zju.edu.cn

✉ Jian-Qing Gao
gaojianqing@zju.edu.cn

[1] College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang 310058, People's Republic of China

[2] Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cell and Regenerative Medicine, Zhejiang University, Hangzhou, Zhejiang 310058, People's Republic of China

[3] Jinhua Institute of Zhejiang University, Jinhua, Zhejiang 321299, People's Republic of China

SGNPs	Supramolecular gelatin nanoparticles
Ru–SeNPs	Ru complex-modified selenium nanoparticles
PMNPs	Platelet membrane-coated nanoparticles
ICG	Indocyanine green
CCNPs	Cancer cell membrane-coated nanoparticles
CCAMs	Cancer cell adhesion molecules
TF-Ag	Thomsen–Friedenreich glycoantigen
Ig-SF	Immunoglobulin superfamily
MNPs	Macrophage membrane-coated nanoparticles
LPS	Lipopolysaccharide
PRR	Pattern recognition receptor
ICB	Immune checkpoint blockade
EpCAM	Epithelial cell adhesion molecule
PFTs	Pore-forming toxins
LCM	Leukocyte–cancer cell HCMN
CTCs	Circulating tumor cells
DLS	Dynamic light scattering
GMP	Good manufacturing practice

Introduction

Nanotechnology is defined as a branch of science, engineering, and technology that involves molecules at the nanoscale (1–100 nm). To date, nanotechnology has contributed to several scientific fields, such as chemistry, physics, biology, and medicine. In particular, in biomedicine [1], many novel and promising nanoparticle (NP)-based drug delivery systems (DDSs) have been used for the safe and efficient transport of drugs or therapeutic genes in vivo [2]. Controlled distribution and drug release of NPs due to their nanoscale properties could improve bioavailability in vivo [2]. For example, because of their enhanced permeability and retention (EPR) effect [3–6], NPs can highly accumulate in tumor tissues. Even if NP delivery systems can achieve passive targeting, problems such as interaction with the reticuloendothelial system (RES), formation of a protein crown, accelerated blood clearance (ABC), and poor targeting ability toward specific cells remain unresolved [7–11]. Polyethylene glycol (PEG), designated as generally recognized as safe (GRAS) by the Food and Drug Administration (FDA), is widely used for the surface modification of NPs in order to extend their blood circulation time and enhance their targeting capabilities [12]. The PEG chains form a flexible polymer brush layer and create steric hindrance, which can cover up the NP surface charge [13, 14]. This significantly inhibits the adsorption of serum proteins, thereby reducing the recognition of macrophages and minimizing complement activation [15]. However, recent clinical research has indicated the existence of anti-PEG immunity, suggesting that PEGylation can also lead to the ABC phenomenon [16–19]. Therefore, more modification strategies for NPs should be considered.

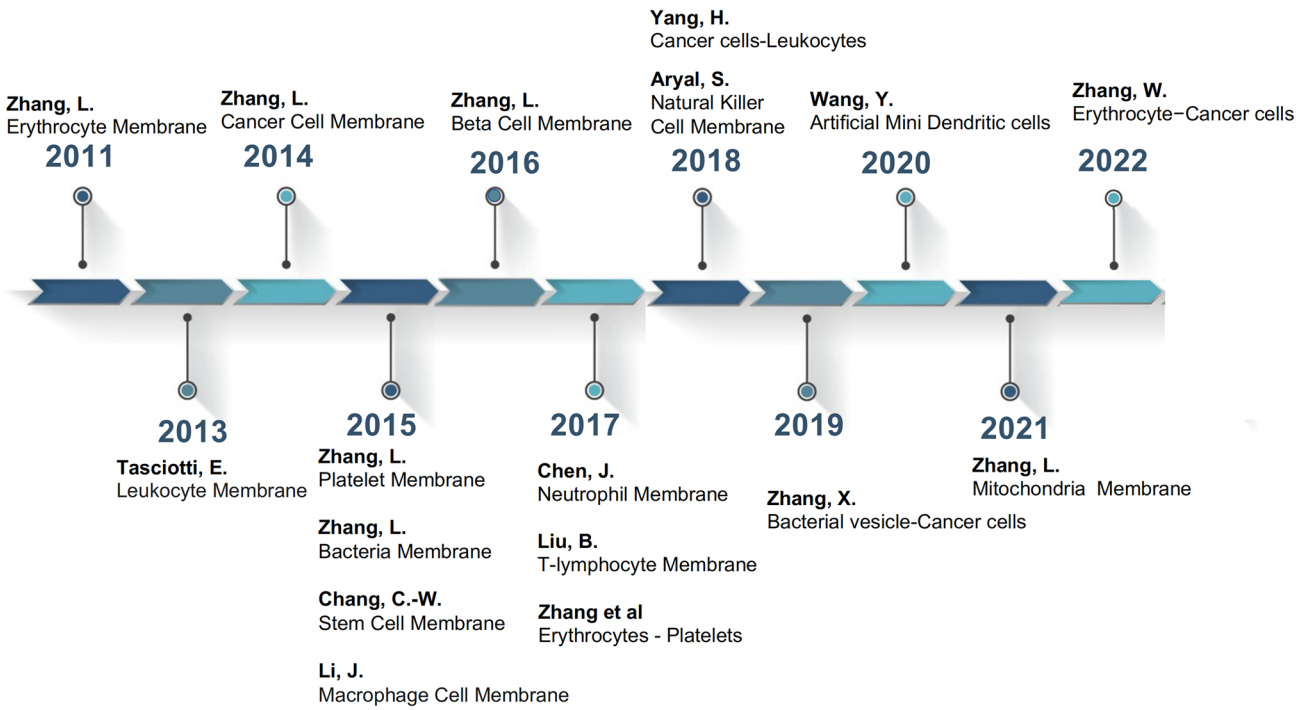

Fig. 1 Timeline of CMC-NPs development

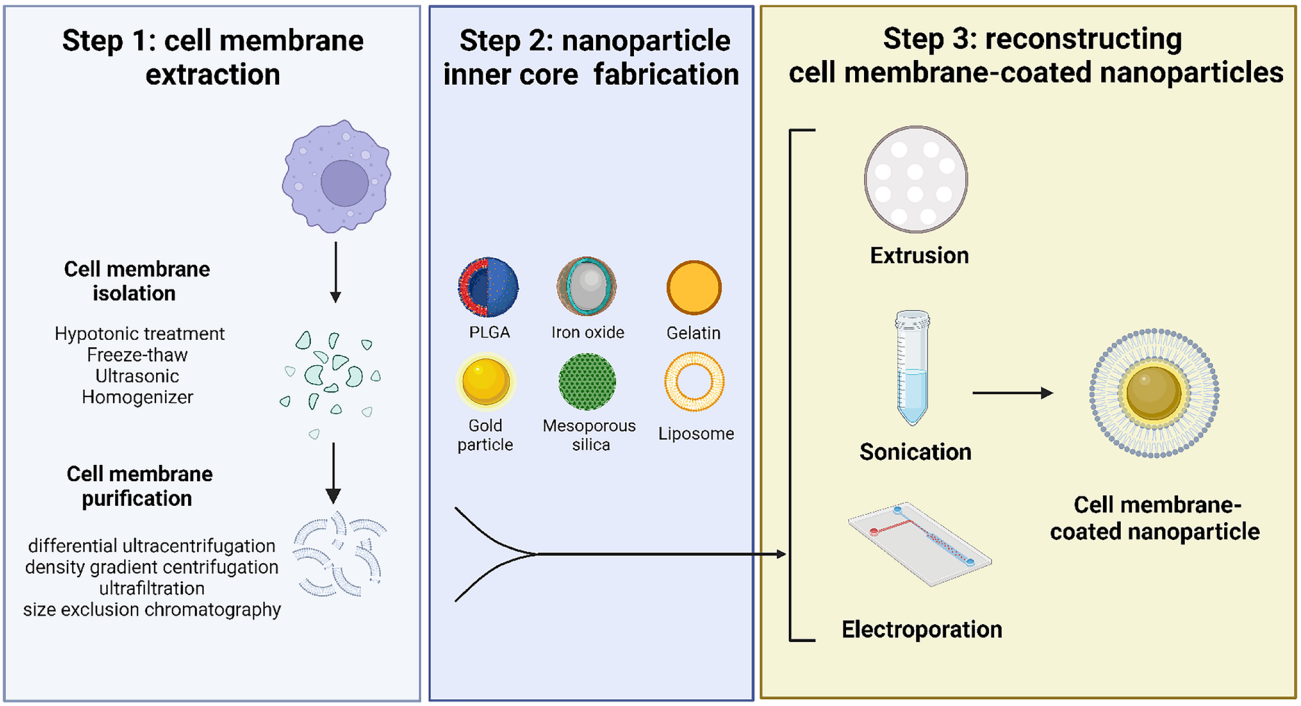

Fig. 2 A schematic diagram of preparing monotypic cell membrane-coated nanoparticles. Step 1 includes two processes of harvesting cell membrane fragments; step 2 requires cautious selection and fabrication of the inner core according to the purpose; step 3 is the final step to coat the cell membrane onto a template. Created with BioRender.com

The membrane coating technology provides a novel solution to the aforementioned problems. The timeline of CMC-NPs development is presented in Fig. 1. In 2011, Zhang et al. developed a top–down biomimetic approach in which they utilized natural erythrocyte membranes to coat polymeric NPs in order to reduce macrophage uptake and systemic clearance for the first time [20]. Later, Tasciotti et al. expanded the selection of membranes from non-nucleated cells to nucleated cells and used leukocytes as the raw material for membrane coating. In 2015, Zhang L et al. enriched the source of membrane material, shifting the focus from human cells to bacterial cells. They again explored the cell membrane biomimetic field and identified mitochondria as a membrane source in 2021. In the past decade, various cell membranes were utilized to design biomimetic systems; these include red blood cells (RBCs) [20], platelets [21], cancer cells [22], and macrophages [23]. Some CMC-NPs are already being considered for clinical application.

To further integrate multiple functions, the hybrid cell membrane-coated nanoparticle (HCMN) strategy has been designed [24–26]. This strategy was first proposed by Zhang et al. in 2017. The RBC–platelet HCMN DDS preserves proteins from RBCs and platelets, combining their unique functions. Subsequently, increasing numbers of differentiated cells are combined to modify NPs, e.g., cancer cells–RBCs [27], macrophages–cancer cells [28], and bacterial vesicles–cancer cells [29]. Double cell membrane NPs are the most common particles in HCMNs. Few studies have used a mixture of three or more membrane

Table 1 Summary of methods used in step 1

Methods	Advantages	Disadvantages	Examples	Ref
Hypotonic lysis	Simple	Low cell fragmentation efficiency	Erythrocyte	[20, 32, 33]
Freeze–thaw	Simple	Partly affect protein activity, influence the recovery of active protein	Platelet	[34, 35]
Ultrasonic	Efficient	Generate a lot of heat, hard to be used in factory-scale	NK-92, cancer cell	[43, 44]
Homogenizer	Efficient and broad scope of application, suitable for large-scale industry	Large energy consumption, require an enormous maintenance workload, not suitable for high viscosity samples as well	Neutrophil, cancer cell, mitochondria	[22, 40–42]

types because the preparation and inspection processes are complex and expensive. Hence, it can be difficult for membrane proteins to function effectively [26, 30].

This review introduces various types of monotypic CMC-NPs and HCMNs with double cell membranes and discusses their manufacturing techniques, benefits, and therapeutic uses. Moreover, it covers the difficulties in clinical application and the advantages of membrane-coated biomimetic NPs.

Methods for preparing cell membrane-coated NPs

Monotypic cell membrane-coated NP preparation methods

The preparation of CMC-NPs usually involves three steps (Fig. 2), namely cell membrane extraction (step 1), NP inner core fabrication (step 2), and cell membrane coating (step 3).

Cell membrane extraction

The first step involves cell membrane isolation and membrane purification, both of which need to be performed gently to preserve the structure and composition of the membrane [31]. Pure and intact cell membranes facilitate maximal functional replication on the inner core surface and result in minimal adverse reactions. Methods widely used for membrane isolation are listed in Table 1; these include hypotonic lysis, freeze-thawing, use of ultrasonic waves, and homogenization.

The principle of hypotonic lysis is that cells can become swollen and rupture under low osmotic pressure. Hypotonic lysis is widely used in erythrocyte membrane extraction but is not commonly used in the extraction of other cells because of its low efficiency [20, 32, 33].

In freeze-thawing, cells are frozen at low temperatures and repeatedly thawed at room temperature. This is a relatively simple method commonly used during platelet membrane extraction [34, 35]. However, freezing and thawing can partially affect protein activity.

Ultrasonic waves cause cell breakage as a result of vast shock waves and shear forces. This method is efficient and suitable for crushing most microorganisms but generates large amounts of heat. Hence, the sensitivity of membrane proteins to heat should be considered when choosing this method. Corresponding cooling measures also should be taken. This may restrict the use of ultrasonic waves in large-scale apparatuses [36].

Homogenization can shear cells into smaller pieces and disperse them. Depending on the pressure setting, a homogenizer may function at pressures up to 2000 bar and can accept a variety of sample volumes (0.05–50 L/h) [37, 38]. In a study conducted by Van Hee et al., cell rupture results remained consistent for different biomass concentrations from 0.06 to 115 g/L in high-pressure homogenizers, indicating potential application in large-scale industries [39]. Previous research has revealed that homogenization is suitable for the fragmentation of various cell types, including neutrophils, cancer cells, and even mitochondria [22, 40–42]. A recent report also revealed that homogenization separates mitochondria from the mouse liver and membrane from mitochondria, indicating that it is a practical method for intracellular organelles [42]. However, the use of a homogenizer is energy intensive and causes a heavy maintenance workload. In addition, it is poorly suited for samples with high viscosity.

The combined use of these methods can yield satisfactory results. For example, B16-F10 mouse melanoma cells were first treated by hypotonic lysis and later treated using a Dounce homogenizer. Consequently, the cancer antigens were preserved and the NPs were successfully functionalized [22].

The next stage involves the purification of cell membranes. Several methods have been developed, including differential ultracentrifugation, density gradient centrifugation, and ultrafiltration [24, 45, 46].

Differential ultracentrifugation adopts a gradual increase in centrifugal speed, which is suitable for cell lysates with significantly different sedimentation coefficients. Density gradient centrifugation requires the formation of a continuous or discontinuous density gradient in the centrifuge tube. The cell suspension or homogenate at the top of the medium can be stratified and separated by gravity or centrifugal force fields. This method is suitable for separating materials with different densities [47]. By contrast, ultrafiltration requires no phase change, no heat release, low energy consumption, and no chemical reagents. It is an energy-saving and eco-friendly separation technology; however, it is greatly limited by sample volume [48].

In summary, cell characteristics determine the method of membrane extraction. For non-nuclear cells, simpler extraction methods, such as hypotonic lysis and freeze-thawing, can be used. For nuclear cells, other methods, such as the use of ultrasonic waves and homogenization, are more suitable [24, 49]. In industrial-scale production, homogenization combined with centrifugation is extensively used [37, 38, 49].

Principal types of NP templates

Different inner cores endow CMC-NPs with different properties. There are two main types of inner cores: organic and inorganic. Core selection according to the subsequent application is necessary.

Organic inner cores have better biocompatibility and biodegradability [50, 51]. The US FDA has approved the clinical application of gelatin, liposome, and poly(lactic-co-glycolic

acid) (PLGA). Among all inner cores, PLGA is the most commonly used in the preparation of membrane biomimetic carriers and holds great promise for clinical applications [52]. Various membranes, including platelet membranes [21, 53], cancer cell membranes [22, 54], macrophage membranes [55], and stem cell membranes [56], can be modified on PLGA particles to prevent the formation of agglomerates on NPs and achieve better delivery efficiency. Another widely used inorganic inner core is a liposome, which resembles the cell membrane [57, 58]. Liposomes are biodegradable colloids capable of containing hydrophobic or hydrophilic pharmaceuticals [59, 60]. Moreover, they can penetrate in vivo barriers as they are flexible [60]. Cell membrane coating improves the stability of phospholipid membranes and achieves a longer circulation time without affecting the drug loading capacity [61, 62].

The stability of inorganic NPs and their resistance to enzymatic degradation are unmatched [63]. Moreover, by manipulating the form, size, composition, and surface qualities of inorganic NPs, their inherent electrical, optical, and magnetic capabilities can be enhanced to achieve full therapeutic potential [63]. For example, an innovative class of nanophotothermal transduction agents, Fe_3O_4 NPs, can be designed for use in photothermal therapy (PTT) [28]. Macrophage membrane-coated Fe_3O_4 NPs can specifically target cancer cells and selectively kill cells by increasing the ambient temperature when exposed to laser light [64]. Another example is the use of stem cell membrane-camouflaged superparamagnetic iron oxide (SPIO) NPs for thermomagnetic therapy. SPIO NPs can rapidly change their magnetic moments and thus generate heat under a high-frequency alternating magnetic field for hyperthermia therapy applications [65]. When using inorganic nanocarriers, toxicity and biodistribution continue to be key concerns. Changing the particle size is one solution [66]. For instance, micron-sized CuO could result in safe delivery; however, CuO NPs could cause DNA damage [66–68]. In the case of SiO_2, an increase in particle size (from 30–40 to 100–150 nm) could significantly reduce cytotoxicity [69]. In addition, cell membrane coating is a persuasive strategy. By blending with the cell membrane, NPs achieve higher biocompatibility and avoid direct contact with the internal environment, indicating a high potential for use in safe and effective therapy [8].

In conclusion, different inner cores have different characteristics and perform multiple functions. Organic inner cores are safer carriers with strong loading capacity, while inorganic inner cores have more unique functions in photodynamic therapy (PDT), PTT, fluorescence imaging, and magnetic resonance imaging (MRI), among others.

Construction of cell membrane-coated NPs

Several methods are commonly used to coat the cell membrane onto the inner core; these include physical extrusion, sonication, and microfluidic electroporation. When selecting the coating method, membrane coverage, right-side-out ratio, uniformity, size dispersity, and protein loss are important factors that need to be considered.

Extrusion refers to the production of uniformly sized particles without sacrificing the membranes by pushing the material through nanoporous membranes; it is also known as nonsacrificing template synthesis [70]. The obtained cell membrane fragments can form uniform cell membrane-derived vesicles by extrusion (Fig. 3a). These vesicles are re-extruded with solid NPs (inner core) in the nanopore channel, thereby fusing to form core–shell CMC-NPs [71]. The efficiency of cell membrane coating by extrusion can be determined based on two factors: membrane-to-polymer ratio and surface charge of the inner core. These factors influence the membrane coverage of NPs and the right-side-out ratio [72]. Compared with conventional methods, extrusion results in better uniformity and smaller size dispersity [73]. In addition, extrusion significantly improves the membrane sidedness with a "right-side-out" orientation ratio of over 80% [71]. In 2011, erythrocyte membrane-camouflaged polymeric NPs,

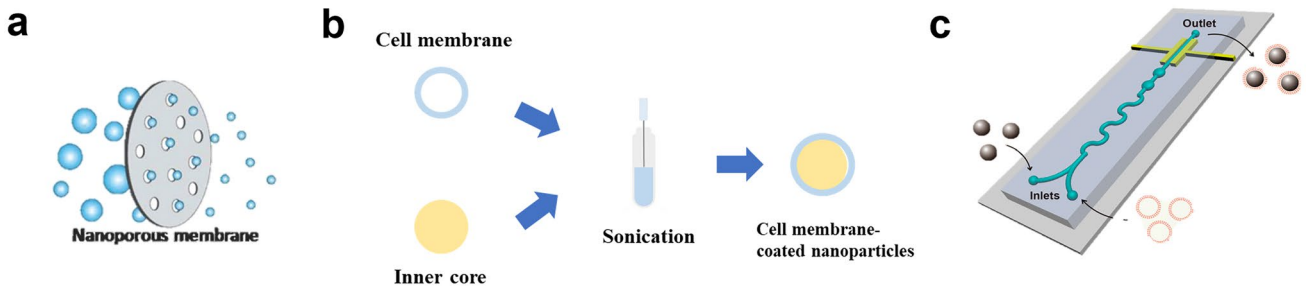

Fig. 3 **a** Schematic illustration of the vesicle extrusion process for liposome preparation. Reproduced with permission [70]. Copyright 2005, Small. **b** Schematic illustration of the camouflage of cell membrane to nanoparticles by sonication. **c** Microfluidic electroporation facilitates the synthesis of RBC membrane-capped magnetic nanoparticles (RBC-MNs). Reproduced with permission [78]. Copyright 2017, ACS Nano

the first membrane-coated NPs, were constructed through extrusion [20]. Since then, extrusion has been one of the most commonly used methods as it is straightforward and can be flexibly applied to coat NPs of different sizes, ranging from 65 to 340 nm [42]. The primary drawback of using this method for mass manufacture is the substantial sample waste resulting from the buildup of material on the porous membrane [24].

The sonication method generates a dispersed cell membrane layer via sonic energy. The cell membrane and template are brought back together to produce a membrane-coated NP through noncovalent interactions (Fig. 3b). This technique has been used for constructing CMC-NPs by several groups. For example, RBC membrane-coated NPs (RBCNPs) were constructed by sonication. Anti-RBC polyclonal IgG was successfully bound and neutralized by these NPs, indicating that the function of membrane protein was not affected by ultrasound waves [74]. In recent research, sonication was used to coat the mitochondrial membrane. Subsequent experiments revealed that mitochondrial membrane-coated NPs exhibited a competitive right-side-out ratio [42]. Unlike extrusion, sonication prevents material loss during the coating process and yields the possibility of a high degree of dispersion [63]. However, this method may cause uniformity and an uneven size [75, 76]. Moreover, limitations on the soft inner core will be imposed because the cavitation caused by ultrasound exposure will shrink and modify the surface of nanomaterials [77].

Microfluidic electroporation successfully enhances the entrance of the inner core into membrane vesicles by generating temporary hydrophilic holes through the cell membrane using quick high-voltage electric field pulses (Fig. 3c) [78]. The feasibility of CMC-NP manufacture using microfluidics was proven in 2017. Rao et al. coated RBC membrane-derived vesicles onto Fe_3O_4 magnetic NPs and constructed RBC-MNs through an S-shaped channel microfluidic chip [78]. The RBC-MNs showed improved colloidal stability, uniform size, and high efficacy in vivo. The benefits of this approach are its high throughput and quantitative format. This method may be used at the industry scale because of its scalability and storage capacity [24, 79]. However, problems such as the lack of specifications and standards for core technologies need to be addressed if industrial production is to be further advanced. To achieve high production efficiency, it is necessary to specify different standards of chip pipes,

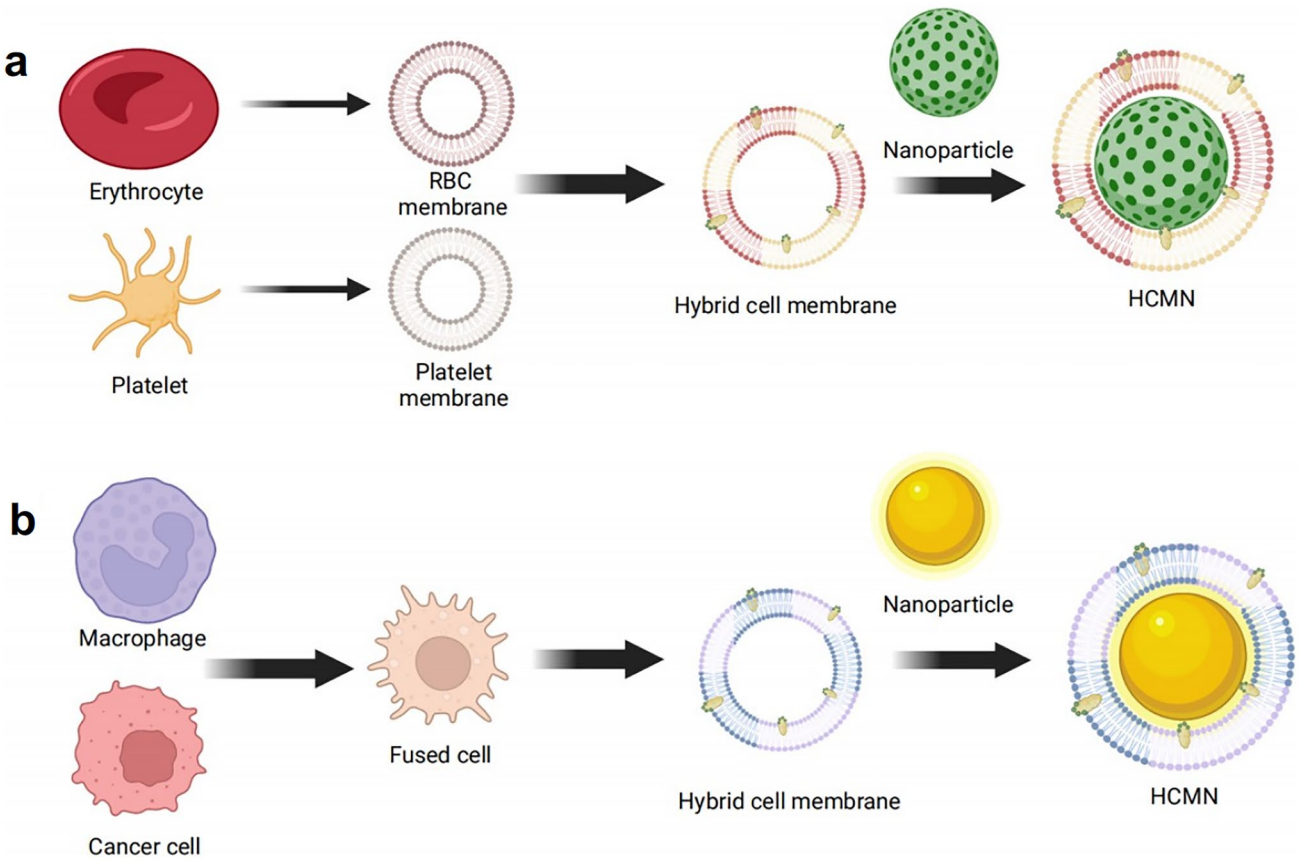

Fig. 4 Schematic of different synthesis methods. **a** Separately extracted cell membranes and then fused two membranes. **b** Cells fused first, and obtain hybrid membrane from the fused cell. Created with BioRender.com

applied voltages, and flow rate ratios for different cell membranes and NPs by reasonable investigation of the product's physical and chemical properties (such as size, PDI, and surface charge) [80]. Moreover, the microfluidic electroporation chip must be manufactured in accordance with good manufacturing practice (GMP) standards while retaining batch-to-batch repeatability to get approved by the FDA [81].

HCMN preparation methods

Membranes from different cells can be fused to prepare HCMN before covering the NPs (Fig. 4a). Fusing two source cells by centrifugation or electrofusion is another method of obtaining hybrid membrane-derived vesicles (Fig. 4b) [26, 82, 83].

These two methods exhibit slight differences in terms of the stability of HCMNs, degree of membrane fusion, and expression of characteristic proteins. The second method may result in uncontrollable protein expression on the fused cells [26, 84]. More importantly, its preparation process is far more complex. Generating sufficient self-recognition markers on dendritic cells and 4T1 cells requires at least 6 days for fusion [84, 85]. Therefore, the first approach is more widely used to prepare a hybrid membrane [28, 52, 86].

Both ultrasound waves and extrusion can be used to mix already extracted membranes. Monodispersed uniform-sized membrane vesicles can be successfully prepared after sonication or extrusion through a polycarbonate membrane [25, 26]. Furthermore, numerous experiments have indicated that this fusion approach is applicable to both nucleated and nucleus-free cells (e.g., bacterial vesicle–cancer cell hybrid membranes [29] and macrophage–cancer cell hybrid membranes [87]). Most existing studies on HCMNs have utilized different membrane proportions and ultrasonic parameters to optimize the process ratio for hybrid membrane preparation, and most experimental results have indicated that 1:1 (w/w) is the preferable ratio to obtain the desired fusion effect.

Sonication, extrusion, PEG modification, and electrofusion are widely used for hybrid cell membrane synthesis [88]. These methods are quite different from those used to obtain monotypic membranes. In this section, the unique steps of preparing hybrid membrane-derived vesicles are described (Table 2).

Morphology, thickness, and biomarker characterization are key attributes for determining whether HCMNs are successfully fused. Most studies have performed western blot (WB) analysis and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) to detect surface marker proteins in order to determine whether cell membranes are successfully mixed and wrapped to the inner core. As shown in Fig. 5, CD235a (an important RBC sialoglycoprotein), CD41 (a surface glycoprotein on platelets), and the cluster of differentiation 47 (CD47, a "do not eat me" marker on RBCs and platelets) appeared on RBC–platelet membrane-coated NPs (RBC–PMNPs) [52, 91], verifying that the membranes of RBCs and platelets were successfully modified on NPs. Furthermore, transmission electron microscopy (TEM) allowed a more intuitive observation of a thicker layer of film structure outside the NPs and a larger particle size in HCMNs.

The uniformity of encapsulation is a significant factor when evaluating a hybrid cell membrane. Förster resonance energy transfer (FRET) can visualize the fusion process and uniformity [27, 92, 93]. For instance, during the preparation of RBC–platelet hybrid membranes [52, 91], the intensity of dye on platelets interacting with RBCs would increase on increasing the RBC input, whereas the intensity of dye interacting with platelets would decrease, indicating the dispersion and fusion of the two membrane materials.

Mechanisms and functions of monotypic CMC-NPs

RBCNPs

Most circulating blood cells are RBCs. They have several biological characteristics, including long-circulating half-life, biocompatibility, and biodegradability. The utilization of RBC membranes has gained considerable research interest since the initial attempt to isolate RBC vesicles by Gaudreault et al. in 1994 [94]. In 2011, Zhang et al. pioneered the use of erythrocyte membrane-camouflaged polymeric NPs as a bioinspired delivery system [20]. The past decade has witnessed the rapid progress of RBCNPs for various biomedical applications, including anticancer [95–97], antibacterial [98, 99], antiviral [100], imaging, and photoactivatable therapies [78, 101, 102], as well as their transition from preclinical to clinical stages.

RBCs have a long circulation time of approximately 120 days [103]. CD47 significantly contributes to the in vivo circulation of RBC membranes [104]. CD47 can interact with signal-regulatory protein alpha (SIRPα) glycoprotein, which is expressed on phagocytic cells [104]. When CD47 interacts with macrophage-expressed SIRP, SH2 domain-containing tyrosine phosphatases are activated. This prevents myosin IIA from accumulating in phagocytic synapses and promotes the release of "do not eat me" signals that block macrophage-related phagocytosis [105, 106]. Other RBC membrane proteins contribute to defense against complement system attacks; these include C8-binding protein (C8bp), complement receptor 1 (CR1), decay-accelerating factor (DAF), and CD59

Table 2 Synthesis, composition, and merits of different types of HCMN

Membrane compositions	Synthesis ways	Membrane proportion	Nanoparticles	Advantages	Usage	Ref
Erythrocyte–leukocyte	Ultrasonication and extrusion	1:1 (w/w)	Magnetic nanoparticles	Biocompatibility, significant efficiency, and purity	Noninvasive pregnant diagnostics (NIPD)	[89]
Leukocytes–tumor cells	Sonication and extrusion	1:1 (w/w)	Paclitaxel-loaded liposomal nanoparticles	Prolonging circulation time, minimizing the MPS uptake, enhancing solid tumor targeting	B16 melanoma	[28]
Erythrocyte–melanoma cells	Sonication	5:1, 3:1, 1:1 (w/w)	Doxorubicin-loaded hollow copper sulfide nanoparticles	B16-F10 cell self-recognition capability, high photothermal conversion efficiency	Photothermal/chemotherapy of melanoma	[27]
Erythrocyte–4T1 cancer cells	Dialyzed, ultrasound and coextruding	1:10 (w/w)	Dextran-poly (histidine) copolymer incorporated BLZ-945	Biocompatible and nonimmunogenic, tumor targeting capability	Cancer immunotherapy	[90]
Erythrocyte–MCF-7 cells	Magnetically stirring, centrifuging, wash buffer	1:1 (w/w)	Melanin nanoparticles	Adding flexibility and controllability in nano-drug functionality, enhancing PTT efficacy, homotypic targeting, reducing the cellular uptake by macrophages	Tumor photothermal therapy	[86]
Erythrocyte–platelet	Sonicating, repeatedly extruding	1:1, 2:1, 1:2 (w/w)	Polypyrrole nanoparticles	Evading immune system attacks, extending blood retention times, improving the photothermal killing ability	Tumor photothermal therapy	[91]
Macrophage–cancer cells	Sonication	5:1, 4:1, 3:1, 2:1, 1:1 (w/w)	Doxorubicin-loaded PLGA nanoparticles	Specific targeting 4T1 cell, enhancing anticancer effects, long-term survival, without overt cardiotoxicity	Lung metastasis in breast cancer therapy	[87]

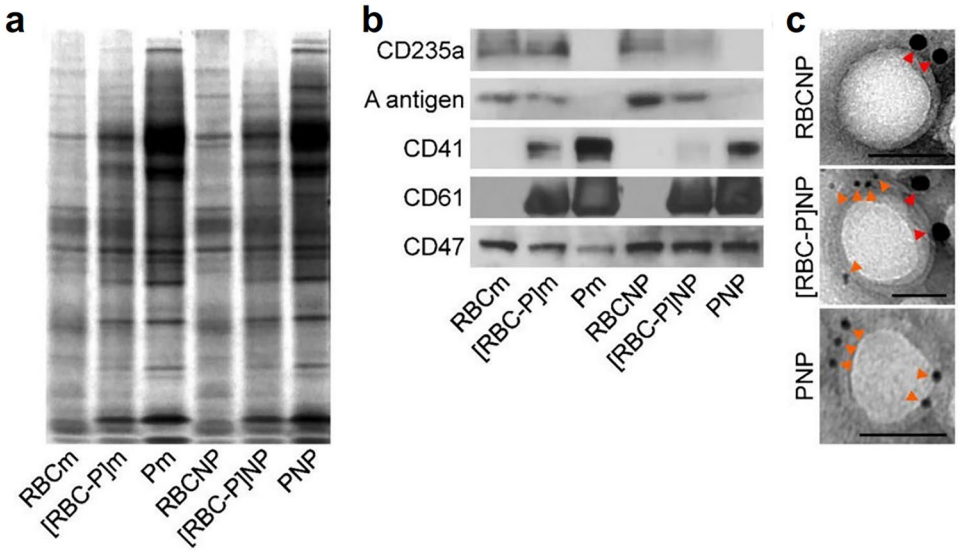

Fig. 5 Characterization of HCMN. **a** SDS-PAGE protein analysis of HCMN. **b** Western blot analysis for HCMN. **c** Immunogold TEM images of HCMN (scale bars = 50 nm). Reproduced with permission [52]. RBCm, RBC membrane; [RBC-P]m, RBC–platelet hybrid membrane; Pm, platelet membrane; RBCNP, RBC membrane-coated nanoparticle; [RBC-P]NP, RBC–platelet hybrid membrane-coated nanoparticle; PNP, platelet membrane-coated nanoparticle Copyright 2017, Advanced Materials

[107–109]. In vivo experiments by Hu et al. on male ICR mice suggested that the elimination half-life was 39.6 h for RBCNPs, being much longer than that for PEG-modified NPs (15.8 h) [20]. Another in vivo experiment revealed that RBCNPs had a longer half-life than uncoated particles (2.63-fold increase) [110]. These results indicate that the membrane coating technique outperforms PEG modification in extending the circulation time. Furthermore, as a natural substance, RBC membranes are highly biocompatible and biodegradable. These attributes are crucial for resolving material toxicity on bare materials, such as carbon nanotubes and iron NPs [111]. RBCNPs loaded with doxorubicin (DOX) could deliver toxic chemotherapy drugs to target sites and have a significantly prolonged survival time without eliciting immune reactions [96].

In addition, RBCs take part in the innate immune response. RBC membranes can neutralize bacterial exotoxins and be effective against resistant bacteria. For example, compared with bare SGNPs, RBC membrane-coated supramolecular gelatin NPs (SGNPs) showed exceptional exotoxin clearance capacity and antihemolytic activity, indicating the detoxification property of RBC membranes [112]. Lin constructed a Ru–Se@GNP-RBCM nanosystem using RBC membranes and gelatin NPs (GNPs) to effectively deliver Ru complex-modified selenium NPs (Ru–SeNPs) [98]. On the one hand, the RBC membrane acted as an invisible cloak, assisting the Ru–Se@GNP-RBCM nanosystem in evading immune cells and thus extending the circulation time. On the other hand, Ru–Se@GNP-RBCM could remove exotoxins because of the RBC membrane coating. Hence, Ru–Se@GNP-RBCM had better accumulation efficiency at the infection site and improved antibacterial effects [98].

Notably, RBCs are quite suitable for low-cost mass production. In addition, the preparation process of RBCNPs is relatively simple [8, 113–115]. As mammalian erythrocytes are anucleate at maturity, the process of extracting cell membranes is much easier than that from nucleated cells. Moreover, given the prevalence of blood transfusions, there is a possibility of using type-matched RBCs as membrane sources to maximize biocompatibility [116].

In conclusion, RBCNPs have long-term circulation and detoxification properties and have the potential to be used for mass production. All these advantages jointly support the clinical application of RBCNPs and open a window for advanced therapeutic use.

PMNPs

Platelets are derived from cytoplasmic lysis of mature megakaryocytes. The plasma membrane of platelets contains multifunctional membrane proteins and provides an essential biological basis for platelets to perform their physiological functions in blood hemostasis [117]. PMNPs inherit the natural properties of platelets and possess functionalized characteristics of immunocompatibility and selective adherence [21].

The ability of PMNPs to evade macrophage detection is also thought to be related to the CD47 receptor. Therefore, platelet membrane cloaking counteracts cellular uptake (approximately 0.55 times less cellular uptake by human THP-1 and macrophage-like cells) and prolongs circulation time, which are vital for more efficient drug delivery [21].

PMNPs can also selectively adhere to pathogens. Bacteria can attach to platelets via bacterial surface proteins or plasma-bridging molecules that join bacterial and platelet surface receptors [118]. Both in vivo and in vitro experiments have shown that PMNPs can utilize selective adhesion

mechanisms for more effective targeting delivery and higher antimicrobial efficacy than bare NPs or RBCNPs [21].

Furthermore, platelets can selectively aggregate and adhere to damaged vasculatures and the inflamed endothelium via surface membrane proteins [119] such as GPIbα [120], GPIa/IIa, GPVI [121, 122], GPIIb/IIIa (αIIbβ3 integrin) [123, 124], P-selectin, and GVPI integrin [125, 126]. In addition, the membrane proteins α6β1, αIIbβ3, and P-selectin are proposed to be involved in platelet–tumor cell interaction and tumor metastasis [127]. Hence, PMNPs have the potential to adhere to damaged vasculatures, inflamed endothelia, and tumor tissues. Compared with free drug treatment, drug-loaded PMNP-directed delivery to diseased vasculatures was found to significantly reduce the intima-to-media ratio and luminal obliteration by more than four times [21]. PMNPs also adhere to intercellular collagen IV in vitro by interacting with collagen through GPVI. They have been reported to exhibit a satisfactory treatment effect in DBA/1 mice with collagen-induced arthritis [125]. Moreover, PMNPs can better deliver DOX and indocyanine green (ICG) to cancer cells and significantly inhibit breast cancer cells [128].

In summary, PMNPs specifically bind to pathogens and damaged vasculatures. Moreover, they can evade macrophage detection. All these characteristics offer fresh perspectives on the therapeutic uses of PMNPs in patients with cardiovascular disorders, ischemic stroke, cancers, autoimmune diseases, and infectious diseases. Although increasing PMNPs are being explored and developed, the challenges are still non-negligible. Pressing issues, such as maintaining the bioactivity of PMNPs and meeting the supplementation of platelet membranes during large-scale production in the event of blood donor shortage, remain unresolved [122, 129].

Cancer cell membrane-coated NPs (CCNPs)

CCNPs inherit natural immune escape and cancer-homing features from cancer cells [22, 130], providing fresh perspectives on the clinical application of DDSs for anticancer therapy and cancer immunotherapy.

The overexpression of CD47 on the cell membrane is regarded as the cause of immune escape [131]. The mechanism of homotypic response is highly dependent on cancer cell adhesion molecules (CCAMs) [132]. Membrane receptors, such as selectins, cadherins, integrins, the immunoglobulin superfamily (Ig-SF), and lymphocyte-homing receptors (such as CD44), are included in CCAMs [133]. The details are summarized in Table 3. Cell–cell adhesion, cell signaling, cell migration, and gene regulation are significantly influenced by cadherin [134]. Integrins play a role in both cell–cell and cell-extracellular membrane interactions, and they are required for cell proliferation, differentiation, and migration [135–137]. Apart from these CCAM proteins, tumor-associated Thomsen–Friedenreich glycoantigen (TF-Ag) with galectin-3 can mediate metastatic cell homotypic aggregation [137]. Thus, CCNPs use the innate homotypic targeting ability of cancer cell membranes to provide a special cancer targeting technique that may be used for anticancer drug delivery [138]. Compared with RBCNPs and bare PLGA cores, MDA–MB-435 membrane-coated NPs showed approximately 40-fold and 20-fold higher homologous cellular uptake in vitro, respectively [22]. In addition, compared with bare NPs, SGC7901 cell membrane-coated silica NPs showed reduced accumulation in the liver and kidney and increased homing to tumor tissues [139].

Moreover, CCNPs efficiently present tumor antigens and can thus be used for cancer immunotherapy [22, 130, 140]. Fontana et al. constructed CCNP-loaded acetylated dextran for cancer immunotherapy, resulting in decreased expression of co-stimulatory signals in the immortal cell lines and increased secretion of inflammatory factors [141].

In summary, CCNPs effectively induce phagocytosis and increase tumor-specific accumulation. By camouflaging the cancer membrane, these NPs prevent medications from being released into the bloodstream too soon and enable precision distribution, thereby reducing side effects and achieving precise delivery [142]. Thus, they provide a potential strategy for synergistic anticancer therapies [132]. Notably, CCNPs target both primary cancer cells and metastatic cancer cells [143]. Hence, this biomimetic site-specific delivery

Table 3 Selective key cancer cell membrane proteins in the adhesion of cancer cells [132]

Cancer cell membrane adhesion-related proteins	Selective proteins
Cadherins, catenin	Cadherin-1, 2, 19; protocadherin; catenins-α, β, γ; desmoglein DSG2, DSG3; desmocollin DSC2, DSC3
Integrins	αvβ3, αvβ5, α5β1, α6β4, α4β1, αvβ6
Ig-SF CAMs	ALCAM, contactin, ICAM, MCAM, NCAM
Tetraspanins	CD9, CD151, CD44
Integrin-associated proteins	CD47
G proteins and GPCRs	CXCR4, CD97

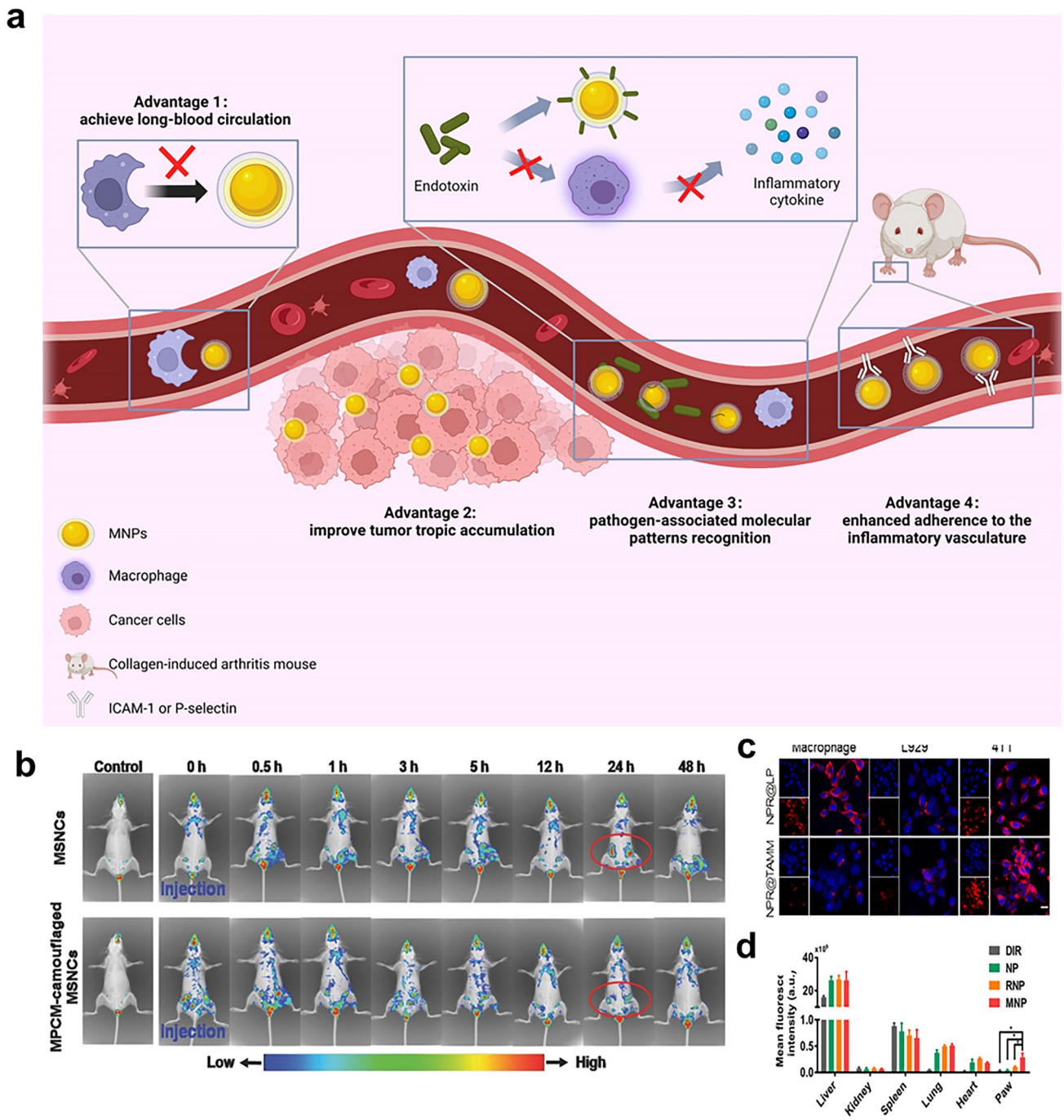

Fig. 6 **a** A schematic illustration of the advantages of MNPs. Created with BioRender.com. **b** Fluorescence imaging of mice after in vivo injection of Rhd B-labeled MPCM-camouflaged MSNCs or bare MSNCs through the tail vein of mice in 48 h. Reproduced with permission [23]. Copyright 2015, Advanced Healthcare Materials. **c** Representative fluorescence images of cellular uptake of tumor-associated macrophage membrane-coated nanoparticles or liposome-coated nanoparticles (red fluorescence) in 4T1, L929, or primary macrophages. Reproduced with permission [150]. Copyright 2021, Nano Letters. **d** Fluorescence intensity of MNP in different organs. $n = 3$, $^{*}p < 0.05$. Reproduced with permission [154]. Copyright 2019, Nano Letters

tool provides a potential treatment strategy for metastatic cancer cells, which is a great challenge at present [143]. Although the manufacturing costs, scale-up logistics, and quality control methods remain critical barriers [142, 144], CCNPs offer new insights into precise cancer treatment in the future [145, 146].

Macrophage membrane-coated NPs (MNPs)

Recently, MNPs have gained increased attention as they mimic the natural properties of macrophages, namely non-immunogenicity, tumor cell targeting, inflammatory site targeting, and pathogen adhesion [23, 147, 148].

MNPs can inhibit macrophage uptake and have a long circulation time (Fig. 6a). In a previous study, after 24 h of treatment, more than 30% of MNPs remained free, whereas uncoated NPs were almost phagocytosed (Fig. 6b) [23]. Consequently, tumor growth was successfully reduced by MNPs loaded with low doses of DOX in 4T1 tumor model mice [23].

MNPs also inherit the tumor endothelium recognition property [147] and can therefore lead to better tumor tropic accumulation than bare NPs, RBCNPs [149], or PEGylated NPs (Fig. 6a) [23]. In another recent study, MNP-mediated PDT therapy reduced the amount of CSF1 that tumor cells released and gathered specifically in the tumor microenvironment (Fig. 6c) [150]. This therapy also converted the protumoral M2-like phenotype to an antitumoral M1-like state, eliminating primary tumor growth and producing an abscopal effect to inhibit distant tumor growth. Thus, MNPs provide a solid foundation that could be used for several anticancer treatments following the inner cores [151, 152].

Macrophages can bind to and recognize pathogen-associated molecular patterns (Fig. 6a). During infection, macrophages release potent proinflammatory cytokines that help eliminate invading pathogens when the pathogen-associated molecular pattern CD14 recognizes lipopolysaccharide (LPS)-binding protein. All these important membrane proteins required for endotoxin binding are maintained by MNPs. A previous study revealed that MNPs could neutralize LPS and sequester cytokines by interacting with proinflammatory factors via the pattern recognition receptor (PRR) and cytokine receptor [55]. Thus, MNPs can serve as fake cytokine binders without triggering downstream inflammation cascades (pathological cytokine storm) [55], thereby avoiding pathological consequences, such as septic shock. In addition, inflammation often occurs during the recruitment of monocyte-derived macrophages because of the membrane proteins Mac-1 and CD44 [153]. Compared with bare NPs and RBCNPs, macrophage-derived microvesicle-coated NPs exhibited enhanced binding to inflamed vessels in a mouse model of collagen-induced arthritis (Fig. 6a, d) [154]. All these results suggest that MNPs are promising vehicles for anti-infectious and anti-inflammatory treatments.

In summary, macrophage membrane coating confers MNPs with properties of inflammatory tissues, cancer site targeting, and pathogen and inflammatory cytokine adhesion, providing exciting opportunities for advanced applications in anticancer therapies, anti-inflammatory therapies, and detoxification strategies.

The mechanism, benefits, and applications of four types of cell membrane carriers are introduced in this section. Researchers have used various membranes to treat various diseases as they have unique biological roles. The following Table 4 summarizes the types of cell membranes that can be selected for some common disease application scenarios, in addition to their advantages and mechanisms.

Different combinations and biomimetic applications of HCMNs

Some studies have incorporated ligand targeting and biomarker auxiliary modification in the multiple functions of CMC-NPs [30, 170], inspiring research on HCMN DDSs. RBCs were first used in the preparation of HCMNs because of their biocompatibility and immune clearance escape ability. Subsequently, increasing numbers of biological membranes were involved in the preparation and application of HCMNs.

RBC–platelet HCMNs

The combination of RBC and platelet cell membranes has distinct advantages in the field of DDSs as they both avoid immune clearance and target the inflammatory area [21, 52, 171]. The circulation half-life of RBC–platelet HCMNs was found to be 51.8 h, which was much longer than that of RBCNPs (42.4 h) and PMNPs (38.3 h) [52]. After the induction of multiple microthrombosis and inflammatory factors in tumor regions, RBC–platelet hybrid membranes coated with polypyrrole showed the longest circulation time and significantly better tumor targeting ability in vivo. These membranes resulted in higher temperatures during PTT than monotypic cell membrane-coated NPs and bare NPs, suggesting that RBC–platelet HCMNs can improve photothermal conversion efficiency and achieve better curative effects [81].

RBC membranes can also target bacteria and absorb PFTs [164] that are normally released in gram-positive bacterial infections. Meanwhile, platelet membrane proteins can interact with bacterial pathogens and adhere to them. Hence, several researchers have combined RBC and platelet membranes to remove toxins and pathogenic bacteria (e.g., *Staphylococcus aureus*) from the bloodstream [172].

In summary, RBC–platelet HCMNs enable the integration of cell membrane surface proteins, resulting in advantages, such as increased circulation time, payload accumulation in diseased tissues, and detoxification [52, 91, 172].

Table 4 Different cell membranes can be chosen in various diseases

Disease conditions	Mechanism	Cell membrane type	Advantages	Ref
Endotoxemia (LPS-related diseases such as obesity and diabetes)	The high affinity between membrane receptors (CD14, TLR-4) and LPS block the immune response and decrease the release of cytokines.	Macrophage, extracellular vesicles from immune cell	Avoid antibiotic resistance, biocompatible and efficient	[155–158]
Cancer treatment	Immune evasion ability through CD47, the innate inflammation directed chemotactic ability, activating anti-tumor immune response, intercellular homologous binding capability.	Immune cell, stem cell, cancer cell, platelet, RBC	Escaping the immune system and long circulation time, cancer targeting, or homologous targeting ability	[159–163]
Cancer detection	Achieving highly specific self-recognition of source cancer cell lines.	Cancer cell	Display the diversity of antigens on the source cell surface to realize keen detection	[137]
Bacterial infection	Pore-forming toxins (PFTs) attack or LPS-induced activation of the immune system is the main virulence mechanism. Cell membranes can absorb various PFTs and reduce toxicity. Some cell membranes can capture LPS to block immune response.	Bacterial cell, platelet, RBC, macrophage	Improve detoxification ability and biosafety, and reduce antibiotic resistance	[164–166]
Inflammatory arthritis (Autoimmune diseases)	Combine with immunomodulatory molecules to exert anti-inflammatory effects. Stimulate the production of neutrophil chemokines in the region, and repair tissue damage.	Neutrophil	High efficiency, low toxicity, and safety. Overcome the complexity and heterogeneity of the inflammatory network of autoimmune diseases	[167]
Vaccination	The bio-membrane exerts its own function by activating the autoimmune system to effectively inhibit the disease process such as cancer and bacterial/viral infection.	Cancer cell, bacterial cell	Targeting delivery, good biocompatibility, immunomodulation ability, long circulation time and avoiding antibiotic resistance	[22, 168, 169]

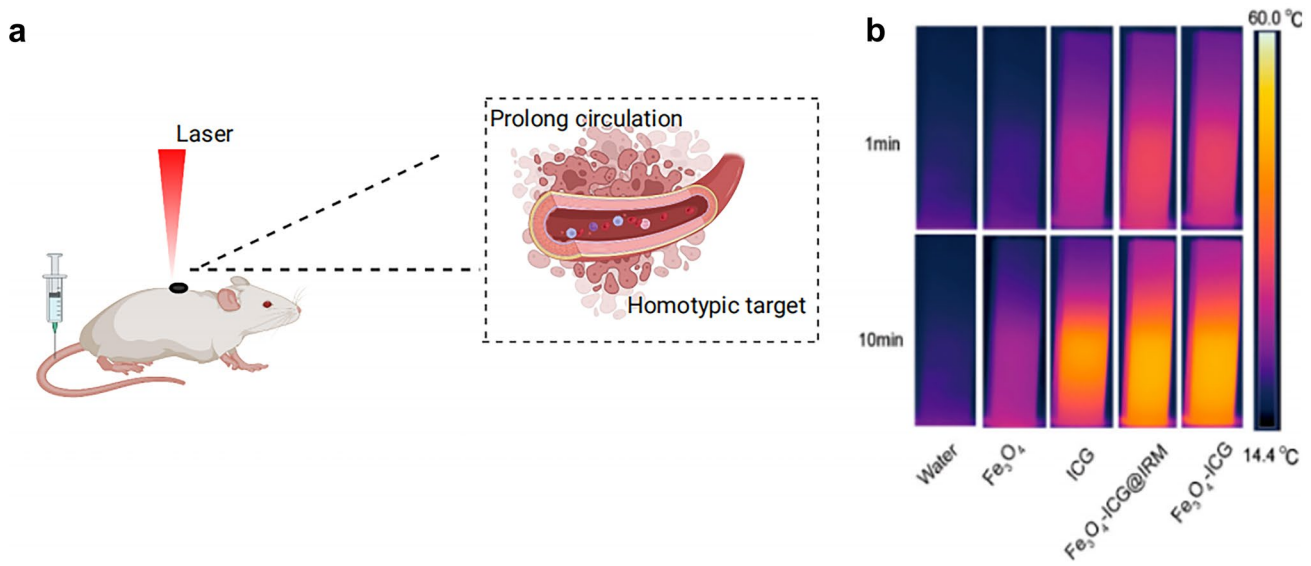

Fig. 7 **a** Synergistic photothermal of cancer. Created with BioRender.com. **b** Temperature increases of water, Fe_3O_4, ICG, Fe_3O_4-ICG, and Fe_3O_4-ICG@IRM with NIR irradiation (808 nm, 1.0 W/cm^2, 10 min). Reproduced with permission [176]. Fe_3O_4-ICG@IRM, IRM (ID8 ovarian cancer cell membrane-RBC membrane) camouflaged ICG-loaded magnetic nanoparticles; Fe_3O_4-ICG, ICG-loaded magnetic nanoparticles. Copyright 2021, ACS Nano

Erythrocyte–cancer cell HCMNs

Adhesion molecules on the surface of tumor cell membranes share homologous recognition and homing characteristics [173]. The preparation of monotypic cancer cell membrane vesicles may result in a loss of membrane protein integrity and fail to avoid immune surveillance completely [26]. However, combination with RBC membranes could realize the complementarity of long-term circulation. Hence, several studies have used erythrocyte–cancer cell HCMNs as an effective DDS in cancer therapy [27, 163, 164].

Compared with other types of HCMNs, erythrocyte–cancer cell HCMNs are more frequently combined with various cancer treatment methods, such as ICB therapy, PTT, and PDT. The latter two methods belong to phototherapy [175]. Phototherapy combined with erythrocyte–cancer cell HCMNs could greatly tackle the disadvantages of phototherapy agents, such as easy recognition, clearance by the immune system after injection, and less accumulation at the target location. ID8 ovarian cancer cell–erythrocyte HCMNs combined with PTT showed the highest photothermal conversion efficiency (Fig. 7) [176], tumor elimination rate, and tumor growth inhibition rate by prolonging the blood circulation time and improving cancer homotypic targeting. Thus, erythrocyte–cancer cell HCMNs are beneficial for cancer therapy.

Erythrocyte–cancer cell HCMNs also exhibit great advantages in the field of drug delivery. They mainly evade elimination, prolong the systemic circulation time in vivo, and exhibit a high degree of homologous tumor targeting. After 24 h post-administration, erythrocyte–cancer cell HCMNs get highly aggregated in tumor tissues, become less targeted to the liver, and exhibit reduced removal; these findings are attributed to the synergistic effect of homotypic binding and immune camouflaging abilities of the hybrid cell membrane [90].

In recent years, erythrocyte–cancer cell HCMNs have also been used in tumor vaccines. Tumor vaccines introduce different forms of tumor-derived antigens into patients, thus creating an adequate and long-lasting immunogenic context for effective treatments [166]. However, several trials have indicated that autologous tumor vaccines cannot totally suppress tumor recurrence because of their weak immunogenicity [177]. Senescent RBCs have the ability to target the splenic antigen-presenting cell; therefore, erythrocytes and cancer cell membrane-associated antigens are coated onto NPs [174]. They can successfully interact with splenic APCs and trigger T-cell immune responses, ensuring biosecurity without any unwanted by-products.

In summary, erythrocyte–cancer cell HCMNs exhibit the advantages of both cell membranes and can be widely used in multiple scenarios.

Leukocyte–cancer cell HCMNs (LCMs)

Various types of research have been conducted on LCMs to combine the immune escaping ability of leukocytes with tumor targeting ability. Compared with other hybrid membranes, LCMs were found to exhibit synergistic effects of cancer cells and leukocyte membranes on tumor targets in vivo. The tumor targeting ability could achieve therapeutic drug accumulation in tumor tissues, high tumor clearance

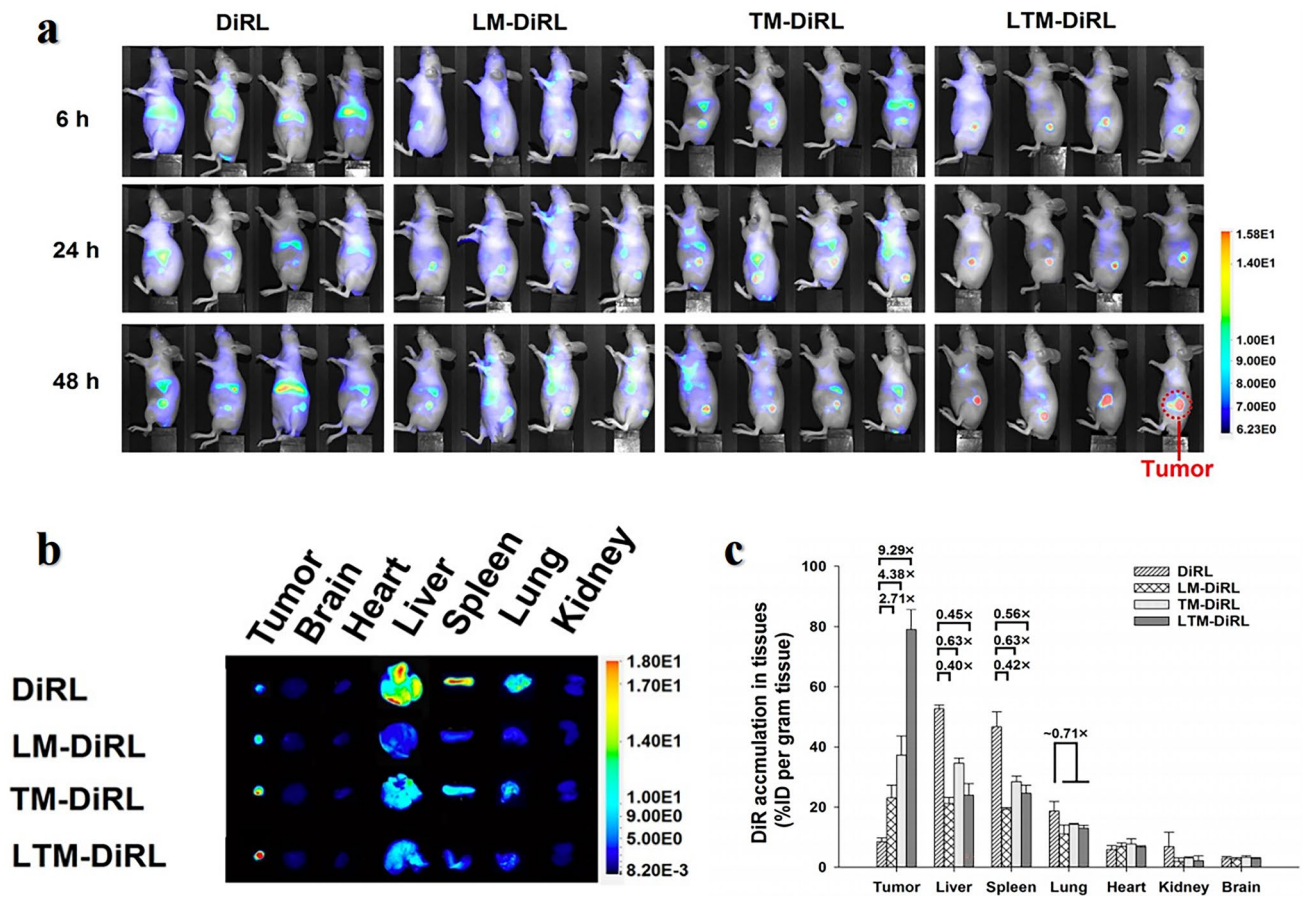

Fig. 8 DiRL labeled liposomal nanoparticles (DiRL, LM-DiRL, TM-DiRL, and LTM-DiRL) ($n=4$). **a** In vivo biodistribution of different groups after intravenous injection. **b** Quantitative analysis of fluorescence accumulation in the main organs. **c** Histogram of quantitative analysis of fluorescence accumulation in the main organs. Reproduced with permission [28]. DiRL, DiR-labeled liposomal nanoparticles; LM-DiRL, leukocyte membrane-coated DiRL; TM-DiRL, tumor cell membrane-coated DiRL; LTM-DiRL, leukocyte-tumor cell membrane-coated DiRL. Copyright 2018, Nano Letter

rates, and positive therapeutic effects. To enhance solid tumor homing, Yang et al. composited leukocyte and cancer cell membranes. At 48 h post-administration, the biodistribution result of LCMs in tumor-bearing mice revealed that the fluorescence intensity was highly aggregated in the tumor region, being approximately 9.3-fold higher than that in the control group (Fig. 8) [28].

LCMs can also be used for cancer detection, playing an important role in cancer monitoring and diagnosis. Some existing detection methods are not sensitive and accurate enough for capturing and detecting circulating tumor cells (CTCs). They fail to predict tumor metastasis in advance because of the low concentration of CTCs and interference from leukocytes [178]. However, LCMs can reduce interference from homologous leukocytes and have the ability of tumor region targeting, which can improve CTC isolation and detection. For instance, Ding et al. successfully built a nanoplatform with LCMs for highly efficient cancer detection [171]. The purity of captured CTCs in the LCM-coated NPs group was 96.96%, which was much higher than that in the bare NPs and monotypic cell membrane-coated NPs groups.

In conclusion, LCMs can be extensively used for disease treatment, particularly in cancer therapy. Leukocytes have also been confirmed to be a precursor of tumor metastasis in human bodies. Therefore, some studies have focused on the regulation of epigenetic expression of the parent cell by LCMs and expression of a specific antigen profile for performing immunotherapy in order to enable efficient removal of tumor cells and cancer treatment [89].

This section reviews the characteristics and advantages of various types of HCMNs. More applications and experiments of HCMNs are presented in Table 2 for better understanding. In summary, several reports have indicated that different cell membrane combinations play unique roles in the treatment of specific diseases. HCMNs can have multiple applications, use in liquid biopsy and cancer vaccines, targeting disease regions, use in combination with other treatments, and detoxification.

Prospects and challenges

Cell membrane coating utilizes natural components at the source to directly transfer natural properties displayed by source cells, thereby recreating complex biological functions and integrating functions that cannot be achieved through synthesis. In this review, the drug delivery capabilities of CMC-NPs are highlighted. Biologically derived raw materials offer a longer blood circulation time, better immune escape, and stronger targeting ability than bare NPs. Undeniably, CMC-NPs still have drawbacks and pose obstacles. Their prospects and challenges will be the main topics of this section.

Quality control

As CMC-NP is a novel drug delivery platform, its quality control needs to be further explored. By referring to the existing standards and quality control specifications for cellular medicines [179, 180], the quality control of CMC-NPs can be divided into three parts.

Cell collection and isolation process control

In the case of cellular raw materials used for preparing CMC-NPs, cell identification, survival and growth activity assessment, foreign pathogen detection, and basic cell characteristic assessment are necessary. Cell characteristics include specific populations of cell surface markers, expression products, and differentiation potentials.

In addition, standard operation and management procedures for the collection and separation of different cells should be formulated and strictly implemented based on GMP requirements. Moreover, each cell type requires standardized and well-established cell culture protocols so that its phenotype and purity can be maintained during passaging [181].

Manufacturing process and storage ability

More consideration needs to be given to the fusion process. Careful calculation and control of the membrane-to-NP ratio are essential to ensure complete coverage and reduce loss of cell membrane. Moreover, the preparation of HCMNs is complex (e.g., determination of the ratio of the two cell membranes and the membrane mixing type), making it difficult to determine an optimal HCMN preparation method suitable for a particular disease [25]. Furthermore, producers are required to use standard biotechnological production and purification techniques. The entire production process should not lead to further impurities other than those originating from the active substance.

Sterilization is another important part of manufacturing process control. The currently accepted sterility assurance level (SAL) is 10^{-6} [182]. Quality control systems need to guarantee that pyrogens, bacteria, virus endotoxins, or LPS do not contaminate CMC-NPs. Filter sterilization is a widely used technique for sterilizing nanoformulations [183, 184]. Specific standards for sterility and endotoxin testing can be formulated according to national quality control regulations.

During the storage process, biological sample storage is usually performed using the freeze–drying method [185]. The potential influence of the lyophilization process on finished product quality results in product-derived impurities, which need to be controlled using the established analytical methods. In addition, the purity and coverage of the preparation process can impact the storage stability of different cell membrane coating systems [24, 31]. Therefore, numerous pre-experiments on screening conditions in the early stage of mass production are required to improve the storage stability of certain CMC-NPs.

Product control, batch analysis, and product stability

For analyzing the active substance quality in CMC-NPs, therapeutic activity, encapsulation rate, and drug release rate are assessed. The precise ingredients in each CMC-NP primarily vary in two areas: safety and efficacy.

To ensure batch-to-batch repeatability during mass production, process parameters must be examined to determine the variables that could harm the product. Process variables include ambient conditions (temperature, pH, and pressure), formulation variables (cell types, component ratios, and solvents utilized), and formulation processes (time, speed, flow conditions, and power) [186]. Short-, medium-, and long-term stability must also be assessed.

Consideration for clinical applications

Although massive studies have resulted in different membrane-coated NP formulations, little research has progressed to clinical practice. This section focuses on the challenges in the clinical translation of CMC-NPs and tries to provide reliable solutions.

First, the in vivo mechanisms of both hybrid and monotypic CMC-NPs remain unknown. One of the main reasons why it is challenging to perform clinical trials for membrane biomimetic carriers is the intricacy and unpredictability of the intermediate process results in vivo. It is risky to assume that the CMC or HCMN would deliver drugs via the theoretical route after entering the human body. To apply membrane coatings beyond the current black box approach [8], researchers need to elucidate more physiological mechanisms, such as internalized mechanisms, intracellular release mechanisms, and subcellular-level actions. This requires a more

fundamental understanding of cell biology, which is becoming more prevalent. Therefore, it is imperative to study the in vivo mechanism of membrane biomimetic carrier DDSs, their route of delivery, and their process as soon as possible.

Second, there are issues related to actual benefits. In vivo and in vitro experiments on various types of HCMNs have revealed that HCMNs can indeed exhibit the functional advantages of both types of CMC-NPs. Several experiments, however, have revealed that the mixed benefits of HCMNs are not as high as the unique benefits of monotypic cell membranes in terms of certain functions, such as targeting ability [86, 87] or prolonged blood circulation time [8, 27]. In other words, while the new HCMN DDS verifies and realizes the possibility of $1+1$, this does not make it >2.

Third, technical difficulties in acquiring source materials still exist. While cell membranes can be autologous, it may be more practical to obtain and store materials from types of matched donors [24]. However, heterologous cells may have toxicity, biological incompatibility, and immunogenicity. The optimization of protocols to remove unnecessary proteins and retain necessary ones remains to be explored. In addition, changes in membrane protein contents during storage remain another challenge [187, 188]. However, we believe that once a patient-specific cell membrane becomes available, precision medicine will dramatically advance. Addressing disease heterogeneity and establishing personalized therapeutics will then become an achievable goal.

Furthermore, cell membrane-coated platforms will encounter greater developmental opportunities through the integration of newer branches of science and biotechnology (e.g., synthetic biology and biomaterial science), leading to richer therapeutic possibilities. For instance, the use of CMC-NPs to develop vaccines is a novel method for the prevention and treatment of COVID-19, which has been continuously developed and transformed in recent years [189]. Moreover, a few studies have used the membrane from genetically engineered source cells. In these studies, the expression of specific surface markers has been induced or upregulated, optimizing the functionality for a given application [41, 190]. Although cell membranes are by far the main source of membrane coatings, more consideration could be given to other membrane sources, like organelle membranes [42].

Conclusion

Monotypic cell membrane coating or hybrid cell membrane coating confers unique biological properties to NPs, including immune escape, long circulation time, and targeted delivery, thereby enabling more efficient drug delivery. Consequently, cell membrane-coated DDSs have gradually become a novel research hotspot. However, more efforts are needed for the clinical transformation and application of CMC-NPs. Obstacles to the standard protocol, quality control, and large-scale production need to be overcome. Assessment of the mechanism and in vivo process will also guide further improvements in the design and preparation of biomimetic carriers.

Author contribution All authors contributed to the study conception and design. Xin-Chi Jiang and Jian-Qing Gao planned and structured the review. The first draft and all the illustrations were created by Hui Liu and Yu-Yan Su. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by the National Natural Science Foundation of China (U22A20383, 81620108028), the Natural Science Foundation of Zhejiang Province (LD22H300002), and the Fundamental Research Funds for the Central Universities (2021QNA7021).

Availability of data and materials Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical–physical applications to nanomedicine. Molecules. 2019;25:112.
2. Gao Z, Zhang L, Sun Y. Nanotechnology applied to overcome tumor drug resistance. J Controlled Release. 2012;162:45–55.
3. Cao H, Dan Z, He X, Zhang Z, Yu H, Yin Q, et al. Liposomes coated with isolated macrophage membrane can target lung metastasis of breast cancer. ACS Nano. 2016;10:7738–48.
4. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17:613–20.
5. Sindhwani S, Syed AM, Ngai J, Kingston BR, Maiorino L, Rothschild J, et al. The entry of nanoparticles into solid tumours. Nat Mater. 2020;19:566–75.
6. Kalyane D, Raval N, Maheshwari R, Tambe V, Kalia K, Tekade RK. Employment of enhanced permeability and retention effect (EPR): nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. Mater Sci Eng C. 2019;98:1252–76.
7. Wu H, Jiang X, Li Y, Zhou Y, Zhang T, Zhi P, et al. Engineering stem cell derived biomimetic vesicles for versatility and effective targeted delivery. Adv Funct Mater. 2020;30:2006169.
8. Fang RH, Kroll AV, Gao W. Zhang L. c. Adv Mater. 2018;30:1706759.
9. Chen L, Hong W, Ren W, Xu T, Qian Z, He Z. Recent progress in targeted delivery vectors based on biomimetic nanoparticles. Signal Transduct Target Ther. 2021;6:225.

10. Karmali PP, Simberg D. Interactions of nanoparticles with plasma proteins: implication on clearance and toxicity of drug delivery systems. Expert Opin Drug Deliv. 2011;8:343–57.
11. Tsoi KM, MacParland SA, Ma X-Z, Spetzler VN, Echeverri J, Ouyang B, et al. Mechanism of hard-nanomaterial clearance by the liver. Nat Mater. 2016;15:1212–21.
12. Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Adv Drug Deliv Rev. 2016;99:28–51.
13. Yu H, Tang Z, Zhang D, Song W, Zhang Y, Yang Y, et al. Pharmacokinetics, biodistribution and in vivo efficacy of cisplatin loaded poly(l-glutamic acid)-g-methoxy poly(ethylene glycol) complex nanoparticles for tumor therapy. J Controlled Release. 2015;205:89–97.
14. Zhou H, Fan Z, Deng J, Lemons PK, Arhontoulis DC, Bowne WB, et al. Hyaluronidase embedded in nanocarrier PEG shell for enhanced tumor penetration and highly efficient antitumor efficacy. Nano Lett. 2016;16:3268–77.
15. Pannuzzo M, Esposito S, Wu L-P, Key J, Aryal S, Celia C, et al. Overcoming nanoparticle-mediated complement activation by surface PEG pairing. Nano Lett. 2020;20:4312–21.
16. Zhang P, Sun F, Liu S, Jiang S. Anti-PEG antibodies in the clinic: current issues and beyond PEGylation. J Controlled Release. 2016;244:184–93.
17. Mohamed M, Abu Lila AS, Shimizu T, Alaaeldin E, Hussein A, Sarhan HA, et al. PEGylated liposomes: immunological responses. Sci Technol Adv Mater. 2019;20:710–24.
18. Wang M, Xin Y, Cao H, Li W, Hua Y, Webster TJ, et al. Recent advances in mesenchymal stem cell membrane-coated nanoparticles for enhanced drug delivery. Biomater Sci. 2021;9:1088–103.
19. Dams ET, Laverman P, Oyen WJ, Storm G, Scherphof GL, van Der Meer JW, et al. Accelerated blood clearance and altered biodistribution of repeated injections of sterically stabilized liposomes. J Pharmacol Exp Ther. 2000;292:1071–9.
20. Hu C-MJ, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proc Natl Acad Sci. 2011;108:10980–5.
21. Hu C-MJ, Fang RH, Wang K-C, Luk BT, Thamphiwatana S, Dehaini D, et al. Nanoparticle biointerfacing by platelet membrane cloaking. Nature. 2015;526:118–21.
22. Fang RH, Hu C-MJ, Luk BT, Gao W, Copp JA, Tai Y, et al. Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery. Nano Lett. 2014;14:2181–8.
23. Xuan M, Shao J, Dai L, He Q, Li J. Macrophage cell membrane camouflaged mesoporous silica nanocapsules for in vivo cancer therapy. Adv Healthc Mater. 2015;4:1645–52.
24. Chugh V, Vijaya Krishna K, Pandit A. Cell membrane-coated mimics: a methodological approach for fabrication, characterization for therapeutic applications, and challenges for clinical translation. ACS Nano. 2021;15:17080–123.
25. Chen H-Y, Deng J, Wang Y, Wu C-Q, Li X, Dai H-W. Hybrid cell membrane-coated nanoparticles: a multifunctional biomimetic platform for cancer diagnosis and therapy. Acta Biomater. 2020;112:1–13.
26. Liao Y, Zhang Y, Blum NT, Lin J, Huang P. Biomimetic hybrid membrane-based nanoplatforms: synthesis, properties and biomedical applications. Nanoscale Horiz. 2020;5:1293–302.
27. Wang D, Dong H, Li M, Cao Y, Yang F, Zhang K, et al. Erythrocyte–cancer hybrid membrane camouflaged hollow copper sulfide nanoparticles for prolonged circulation life and homotypic-targeting photothermal/chemotherapy of melanoma. ACS Nano. 2018;12:5241–52.
28. He H, Guo C, Wang J, Korzun WJ, Wang X-Y, Ghosh S, et al. Leutusome: a biomimetic nanoplatform integrating plasma membrane components of leukocytes and tumor cells for remarkably enhanced solid tumor homing. Nano Lett. 2018;18:6164–74.
29. Wang D, Liu C, You S, Zhang K, Li M, Cao Y, et al. Bacterial vesicle-cancer cell hybrid membrane-coated nanoparticles for tumor specific immune activation and photothermal therapy. ACS Appl Mater Interfaces. 2020;12:41138–47.
30. Li Y, Che J, Chang L, Guo M, Bao X, Mu D, et al. CD47- and Integrin α 4/ β 1-comodified-macrophage-membrane-coated nanoparticles enable delivery of colchicine to atherosclerotic plaque. Adv Healthc Mater. 2022;11:2101788.
31. Liu Y, Luo J, Chen X, Liu W, Chen T. Cell membrane coating technology: a promising strategy for biomedical applications. Nano-Micro Lett. 2019;11:100.
32. Rao L, Bu L-L, Xu J-H, Cai B, Yu G-T, Yu X, et al. Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance. Small. 2015;11:6225–36.
33. Wang Y, Zhang K, Qin X, Li T, Qiu J, Yin T, et al. Biomimetic nanotherapies: red blood cell based core–shell structured nanocomplexes for atherosclerosis management. Adv Sci. 2019;6:1900172.
34. Wei X, Gao J, Fang RH, Luk BT, Kroll AV, Dehaini D, et al. Nanoparticles camouflaged in platelet membrane coating as an antibody decoy for the treatment of immune thrombocytopenia. Biomaterials. 2016;111:116–23.
35. Li J, Ai Y, Wang L, Bu P, Sharkey CC, Wu Q, et al. Targeted drug delivery to circulating tumor cells via platelet membrane-functionalized particles. Biomaterials. 2016;76:52–65.
36. McMillan JR, Watson IA, Ali M, Jaafar W. Evaluation and comparison of algal cell disruption methods: microwave, waterbath, blender, ultrasonic and laser treatment. Appl Energy. 2013;103:128–34.
37. Kuznetsov VI, Haws SA, Fox CA, Denu JM. General method for rapid purification of native chromatin fragments. J Biol Chem. 2018;293:12271–82.
38. Tam YJ, Allaudin ZN, Lila MAM, Bahaman AR, Tan JS, Rezaei MA. Enhanced cell disruption strategy in the release of recombinant hepatitis B surface antigen from Pichia pastoris using response surface methodology. BMC Biotechnol. 2012;12:70.
39. van Hee P, Middelberg APJ, van der Lans RGJM, van der Wielen LAM. Relation between cell disruption conditions, cell debris particle size, and inclusion body release. Biotechnol Bioeng. 2004;88:100–10.
40. Kang T, Zhu Q, Wei D, Feng J, Yao J, Jiang T, et al. Nanoparticles coated with neutrophil membranes can effectively treat cancer metastasis. ACS Nano. 2017;11:1397–411.
41. Park JH, Jiang Y, Zhou J, Gong H, Mohapatra A, Heo J, et al. Genetically engineered cell membrane–coated nanoparticles for targeted delivery of dexamethasone to inflamed lungs. Sci Adv. 2021;7:eabf7820.
42. Gong H, Zhang Q, Komarla A, Wang S, Duan Y, Zhou Z, et al. Nanomaterial biointerfacing via mitochondrial membrane coating for targeted detoxification and molecular detection. Nano Lett. 2021;21:2603–9.
43. Deng G, Sun Z, Li S, Peng X, Li W, Zhou L, 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;12:12096–108.
44. Nie D, Dai Z, Li J, Yang Y, Xi Z, Wang J, et al. Cancer-cell-membrane-coated nanoparticles with a yolk–shell structure augment cancer chemotherapy. Nano Lett. 2020;20:936–46.
45. Franke WW, Lüder MR, Kartenbeck J, Zerban H, Keenan TW. Involvement of vesicle coat material in casein secretion and surface regeneration. J Cell Biol. 1976;69:173–95.
46. Javed S, Alshehri S, Shoaib A, Ahsan W, Sultan MH, Alqahtani SS, et al. Chronicles of nanoerythrosomes: an erythrocyte-based

biomimetic smart drug delivery system as a therapeutic and diagnostic tool in cancer therapy. Pharmaceutics. 2021;13:368.
47. Harrison STL. Cell disruption. Compr Biotechnol. Elsevier; 2011 [cited 2022 Jun 28]. p. 619–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780080885049001276
48. Hankins NP, Singhv R. Emerging membrane technology for sustainable water treatment. Elsevier Science 2016.
49. Danaeifar M. New horizons in developing cell lysis methods: a review. Biotechnol Bioeng. 2022;bit.28198.
50. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol. 1965;13:238-IN27.
51. Rao L, Bu L-L, Cai B, Xu J-H, Li A, Zhang W-F, et al. Cancer cell membrane-coated upconversion nanoprobes for highly specific tumor imaging. Adv Mater. 2016;28:3460–6.
52. Dehaini D, Wei X, Fang RH, Masson S, Angsantikul P, Luk BT, et al. Erythrocyte-platelet hybrid membrane coating for enhanced nanoparticle functionalization. Adv Mater. 2017;29:1606209.
53. Zhou M, Lai W, Li G, Wang F, Liu W, Liao J, et al. Platelet membrane-coated and VAR2CSA malaria protein-functionalized nanoparticles for targeted treatment of primary and metastatic cancer. ACS Appl Mater Interfaces. 2021;13:25635–48.
54. Chen Z, Zhao P, Luo Z, Zheng M, Tian H, Gong P, et al. Cancer cell membrane–biomimetic nanoparticles for homologous-targeting dual-modal imaging and photothermal therapy. ACS Nano. 2016;10:10049–57.
55. Thamphiwatana S, Angsantikul P, Escajadillo T, Zhang Q, Olson J, Luk BT, et al. Macrophage-like nanoparticles concurrently absorbing endotoxins and proinflammatory cytokines for sepsis management. Proc Natl Acad Sci. 2017;114:11488–93.
56. Tang J, Shen D, Caranasos TG, Wang Z, Vandergriff AC, Allen TA, et al. Therapeutic microparticles functionalized with biomimetic cardiac stem cell membranes and secretome. Nat Commun. 2017;8:13724.
57. Pitchaimani A, Nguyen TDT, Aryal S. Natural killer cell membrane infused biomimetic liposomes for targeted tumor therapy. Biomaterials. 2018;160:124–37.
58. Jiang L, Zhu Y, Luan P, Xu J, Ru G, Fu J-G, et al. Bacteria - anchoring hybrid liposome capable of absorbing multiple toxins for antivirulence therapy of *Escherichia coli* infection. ACS Nano. 2021;15:4173–85.
59. Johnston MJW, Semple SC, Klimuk SK, Ansell S, Maurer N, Cullis PR. Characterization of the drug retention and pharmacokinetic properties of liposomal nanoparticles containing dihydrosphingomyelin. Biochim Biophys Acta BBA - Biomembr. 2007;1768:1121–7.
60. Niu X, Chen J, Gao J. Nanocarriers as a powerful vehicle to overcome blood-brain barrier in treating neurodegenerative diseases: focus on recent advances. Asian J Pharm Sci. 2019;14:480–96.
61. Chen Z-J, Yang S-C, Liu X-L, Gao Y, Dong X, Lai X, et al. Nanobowl-supported liposomes improve drug loading and delivery. Nano Lett. 2020;20:4177–87.
62. Anwekar H, Patel S, Singhai AK. Liposome-as drug carriers. Int J Pharm Life Sci. 2011.
63. Chen G, Roy I, Yang C, Prasad PN. Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy. Chem Rev. 2016;116:2826–85.
64. Meng Q-F, Rao L, Zan M, Chen M, Yu G-T, Wei X, et al. Macrophage membrane-coated iron oxide nanoparticles for enhanced photothermal tumor therapy. Nanotechnology. 2018;29: 134004.
65. Lai P-Y, Huang R-Y, Lin S-Y, Lin Y-H, Chang C-W. Biomimetic stem cell membrane-camouflaged iron oxide nanoparticles for theranostic applications. RSC Adv. 2015;5:98222–30.
66. Karlsson HL, Gustafsson J, Cronholm P, Möller L. Size-dependent toxicity of metal oxide particles—a comparison between nano- and micrometer size. Toxicol Lett. 2009;188:112–8.
67. Ahamed M, Siddiqui MA, Akhtar MJ, Ahmad I, Pant AB, Alhadlaq HA. Genotoxic potential of copper oxide nanoparticles in human lung epithelial cells. Biochem Biophys Res Commun. 2010;396:578–83.
68. Naz S, Gul A, Zia M. Toxicity of copper oxide nanoparticles: a review study. IET Nanobiotechnol. 2020;14:1–13.
69. Sun D, Gong L, Xie J, Gu X, Li Y, Cao Q, et al. Toxicity of silicon dioxide nanoparticles with varying sizes on the cornea and protein corona as a strategy for therapy. Sci Bull. 2018;63:907–16.
70. Guo P, Huang J, Zhao Y, Martin CR, Zare RN, Moses MA. Nanomaterial preparation by extrusion through nanoporous membranes. Small. 2018;14:1703493.
71. Palmgren MG, Askerlund P, Fredrikson K, Widell S, Sommarin M, Larsson C. Sealed inside-out and right-side-out plasma membrane vesicles: optimal conditions for formation and separation. Plant Physiol. 1990;92:871–80.
72. Luk BT, Jack Hu C-M, Fang RH, Dehaini D, Carpenter C, Gao W, et al. Interfacial interactions between natural RBC membranes and synthetic polymeric nanoparticles. Nanoscale. 2013;6:2730–7.
73. György B, Szabó TG, Pásztói M, Pál Z, Misják P, Aradi B, et al. Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. Cell Mol Life Sci. 2011;68:2667–88.
74. Copp JA, Fang RH, Luk BT, Hu C-MJ, Gao W, Zhang K, et al. Clearance of pathological antibodies using biomimetic nanoparticles. Proc Natl Acad Sci. 2014;111:13481–6.
75. He W, Frueh J, Wu Z, He Q. Leucocyte membrane-coated janus microcapsules for enhanced photothermal cancer treatment. langmuir. 2016;32:3637–44.
76. Arrigo R, Teresi R, Gambarotti C, Parisi F, Lazzara G, Dintcheva N. Sonication-induced modification of carbon nanotubes: effect on the rheological and thermo-oxidative behaviour of polymer-based nanocomposites. Materials. 2018;11:383.
77. Rennhofer H, Zanghellini B. Dispersion state and damage of carbon nanotubes and carbon nanofibers by ultrasonic dispersion: a review. Nanomaterials. 2021;11:1469.
78. Rao L, Cai B, Bu L-L, Liao Q-Q, Guo S-S, Zhao X-Z, et al. Microfluidic electroporation-facilitated synthesis of erythrocyte membrane-coated magnetic nanoparticles for enhanced imaging-guided cancer therapy. ACS Nano. 2017;11:3496–505.
79. Kim K, Lee WG. Electroporation for nanomedicine: a review. J Mater Chem B. 2017;5:2726–38.
80. Ottonelli I, Duskey JT, Rinaldi A, Grazioli MV, Parmeggiani I, Vandelli MA, et al. Microfluidic technology for the production of hybrid nanomedicines. Pharmaceutics. 2021;13:1495.
81. Holtze C. Large-scale droplet production in microfluidic devices—an industrial perspective. J Phys Appl Phys. 2013;46:114008.
82. Scott-Taylor TH, Pettengell R, Clarke I, Stuhler G, La Barthe MC, Walden P, et al. Human tumour and dendritic cell hybrids generated by electrofusion: potential for cancer vaccines. Biochim Biophys Acta BBA - Mol Basis Dis. 2000;1500:265–79.
83. Ramos C, Bonenfant D, Teissie J. Cell hybridization by electrofusion on filters. Anal Biochem. 2002;302:213–9.
84. Liu W-L, Zou M-Z, Liu T, Zeng J-Y, Li X, Yu W-Y, et al. Cytomembrane nanovaccines show therapeutic effects by mimicking tumor cells and antigen presenting cells. Nat Commun. 2019;10:3199.
85. Koido S, Homma S, Okamoto M, Namiki Y, Takakura K, Takahara A, et al. Combined TLR2/4-activated dendritic/tumor cell fusions induce augmented cytotoxic T lymphocytes. Arens R, editor. PLoS One. 2013;8:e59280.
86. Jiang Q, Liu Y, Guo R, Yao X, Sung S, Pang Z, et al. Erythrocyte-cancer hybrid membrane-camouflaged melanin nanoparticles for enhancing photothermal therapy efficacy in tumors. Biomaterials. 2019;192:292–308.

87. Gong C, Yu X, You B, Wu Y, Wang R, Han L, et al. Macrophage-cancer hybrid membrane-coated nanoparticles for targeting lung metastasis in breast cancer therapy. J Nanobiotechnology. 2020;18:92.
88. Lawrie WC, Desmond JA, Spence D, Anderson S, Edmondson C. Determination of radium-226 in environmental and personal monitoring samples. Appl Radiat Isot. 2000;53:133–7.
89. Wang Z, Cheng L, Sun Y, Wei X, Cai B, Liao L, et al. Enhanced isolation of fetal nucleated red blood cells by enythrocyte-leukocyte hybrid membrane-coated magnetic nanoparticles for noninvasive pregnant diagnostics. Anal Chem. 2021;93:1033–42.
90. Wang Y, Luan Z, Zhao C, Bai C, Yang K. Target delivery selective CSF-1R inhibitor to tumor-associated macrophages via erythrocyte-cancer cell hybrid membrane camouflaged pH-responsive copolymer micelle for cancer immunotherapy. Eur J Pharm Sci. 2020;142: 105136.
91. Liu Y, Wang X, Ouyang B, Liu X, Du Y, Cai X, et al. Erythrocyte–platelet hybrid membranes coating polypyrrol nanoparticles for enhanced delivery and photothermal therapy. J Mater Chem B. 2018;6:7033–41.
92. Li M, Xu Z, Zhang L, Cui M, Zhu M, Guo Y, et al. Targeted noninvasive treatment of choroidal neovascularization by hybrid cell-membrane-cloaked biomimetic nanoparticles. ACS Nano. 2021;15:9808–19.
93. Hou W, Ma D, He X, Han W, Ma J, Wang H, et al. Subnanometer-precision measurements of transmembrane motions of biomolecules in plasma membranes using quenchers in extracellular environment. Nano Lett. 2021;21:485–91.
94. Lejeune A, Moorjani M, Gicquaud C, Lacroix J, Poyet P, Gaudreault R. Nanoerythrosome, a new derivative of erythrocyte ghost: preparation and antineoplastic potential as drug carrier for daunorubicin. Anticancer Res. 1994;14:915–9.
95. Fu Q, Lv P, Chen Z, Ni D, Zhang L, Yue H, et al. Programmed co-delivery of paclitaxel and doxorubicin boosted by camouflaging with erythrocyte membrane. Nanoscale. 2015;7:4020–30.
96. Luk BT, Fang RH, Hu C-MJ, Copp JA, Thamphiwatana S, Dehaini D, et al. Safe and immunocompatible nanocarriers cloaked in RBC membranes for drug delivery to treat solid tumors. Theranostics. 2016;6:1004–11.
97. Chai Z, Hu X, Wei X, Zhan C, Lu L, Jiang K, et al. A facile approach to functionalizing cell membrane-coated nanoparticles with neurotoxin-derived peptide for brain-targeted drug delivery. J Controlled Release. 2017;264:102–11.
98. Lin A, Liu Y, Zhu X, Chen X, Liu J, Zhou Y, et al. Bacteria-responsive biomimetic selenium nanosystem for multidrug-resistant bacterial infection detection and inhibition. ACS Nano. 2019;13:13965–84.
99. Zhang Y, Gao W, Chen Y, Escajadillo T, Ungerleider J, Fang RH, et al. Self-assembled colloidal gel using cell membrane-coated nanosponges as building blocks. ACS Nano. 2017;11:11923–30.
100. Zhang C, Zhang P-Q, Guo S, Chen G, Zhao Z, Wang G-X, et al. Application of biomimetic cell-derived nanoparticles with mannose modification as a novel vaccine delivery platform against teleost fish viral disease. ACS Biomater Sci Eng. 2020;6:6770–7.
101. Gao W, Hu C-MJ, Fang RH, Luk BT, Su J, Zhang L. Surface functionalization of gold nanoparticles with red blood cell membranes. Adv Mater. 2013;25:3549–53.
102. Piao J-G, Wang L, Gao F, You Y-Z, Xiong Y, Yang L. Erythrocyte membrane is an alternative coating to polyethylene glycol for prolonging the circulation lifetime of gold nanocages for photothermal therapy. ACS Nano. 2014;8:10414–25.
103. Bosman GJCGM. Survival of red blood cells after transfusion: processes and consequences. Front Physiol [Internet]. 2013 [cited 2022 Jun 28];4. Available from: http://journal.frontiersin.org/article/10.3389/fphys.2013.00376/abstract
104. Oldenborg P-A, Zheleznyak A, Fang Y-F, Lagenaur CF, Gresham HD, Lindberg FP. Role of CD47 as a marker of self on red blood cells. Science. 2000;288:2051–4.
105. Zhang W, Huang Q, Xiao W, Zhao Y, Pi J, Xu H, et al. Advances in anti-tumor treatments targeting the CD47/SIRPα axis. Front Immunol. 2020;11:18.
106. McCracken MN, Cha AC, Weissman IL. Molecular pathways: activating T cells after cancer cell phagocytosis from blockade of CD47 "Don't Eat Me" signals. Clin Cancer Res. 2015;21:3597–601.
107. First Pavlov State Medical University of St. Peterburg, Galkin M. Application of cellular and artificial membranes in nanomedicine. Vestn St Petersburg Univ Med. 2020;15:290–9.
108. Fang RH, Hu C-MJ, Zhang L. Nanoparticles disguised as red blood cells to evade the immune system. Expert Opin Biol Ther. 2012;12:385–9.
109. Xia Q, Zhang Y, Li Z, Hou X, Feng N. Red blood cell membrane-camouflaged nanoparticles: a novel drug delivery system for antitumor application. Acta Pharm Sin B. 2019;9:675–89.
110. Ben-Akiva E, Meyer RA, Yu H, Smith JT, Pardoll DM, Green JJ. Biomimetic anisotropic polymeric nanoparticles coated with red blood cell membranes for enhanced circulation and toxin removal. Sci Adv. 2020;6:eaay9035.
111. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. Science. 2006;311:622–7.
112. Li L-L, Xu J-H, Qi G-B, Zhao X, Yu F, Wang H. Core–shell supramolecular gelatin nanoparticles for adaptive and "on-demand" antibiotic delivery. ACS Nano. 2014;8:4975–83.
113. Godfrin Y, Horand F, Franco R, Dufour E, Kosenko E, Bax BE, et al. International seminar on the red blood cells as vehicles for drugs. Expert Opin Biol Ther. 2012;12:127–33.
114. Vincy A, Mazumder S, Amrita null, Banerjee I, Hwang KC, Vankayala R. Recent progress in red blood cells-derived particles as novel bioinspired drug delivery systems: challenges and strategies for clinical translation. Front Chem. 2022;10:905256.
115. Magnani M. Erythrocytes as carriers for drugs: the transition from the laboratory to the clinic is approaching. Expert Opin Biol Ther. 2012;12:137–8.
116. Gao W, Zhang L. Engineering red-blood-cell-membrane-coated nanoparticles for broad biomedical applications. AIChE J. 2015;61:738–46.
117. Anselmo AC, Modery-Pawlowski CL, Menegatti S, Kumar S, Vogus DR, Tian LL, et al. Platelet-like nanoparticles: mimicking shape, flexibility, and surface biology of platelets to target vascular injuries. ACS Nano. 2014;8:11243–53.
118. Fitzgerald JR, Foster TJ, Cox D. The interaction of bacterial pathogens with platelets. Nat Rev Microbiol. 2006;4:445–57.
119. Kieffer N, Phillips DR. Platelet membrane glycoproteins: functions in cellular interactions. Annu Rev Cell Biol. 1990;6:329–57.
120. Modery-Pawlowski CL, Tian LL, Ravikumar M, Wong TL, Gupta AS. In vitro and in vivo hemostatic capabilities of a functionally integrated platelet-mimetic liposomal nanoconstruct. Biomaterials. 2013;34:3031–41.
121. Broos K, De Meyer SF, Feys HB, Vanhoorelbeke K, Deckmyn H. Blood platelet biochemistry. Thromb Res. 2012;129:245–9.
122. Sekhon UDS, Swingle K, Girish A, Luc N, de la Fuente M, Alvikas J, et al. Platelet-mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding. Sci Transl Med. 2022;14:eabb8975.
123. Jurk K, Kehrel BE. Platelets: physiology and biochemistry. Semin Thromb Hemost. 2005;31:381–92.
124. Payrastre B, Missy K, Trumel C, Bodin S, Plantavid M, Chap H. The integrin αIIb/β3 in human platelet signal transduction. Biochem Pharmacol. 2000;60:1069–74.
125. He Y, Li R, Liang J, Zhu Y, Zhang S, Zheng Z, et al. Drug targeting through platelet membrane-coated nanoparticles for the treatment of rheumatoid arthritis. Nano Res. 2018;11:6086–101.

126. Hamilos M, Petousis S, Parthenakis F. Interaction between platelets and endothelium: from pathophysiology to new therapeutic options. Cardiovasc Diagn Ther. 2018;8:568–80.
127. Lavergne M, Janus-Bell E, Schaff M, Gachet C, Mangin P. Platelet integrins in tumor metastasis: do they represent a therapeutic target? Cancers. 2017;9:133.
128. Ye H, Wang K, Wang M, Liu R, Song H, Li N, et al. Bioinspired nanoplatelets for chemo-photothermal therapy of breast cancer metastasis inhibition. Biomaterials. 2019;206:1–12.
129. Han H, Bártolo R, Li J, Shahbazi M-A, Santos HA. Biomimetic platelet membrane-coated nanoparticles for targeted therapy. Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV. 2022;172:1–15.
130. Zhu J-Y, Zheng D-W, Zhang M-K, Yu W-Y, Qiu W-X, Hu J-J, et al. Preferential cancer cell self-recognition and tumor self-targeting by coating nanoparticles with homotypic cancer cell membranes. Nano Lett. 2016;16:5895–901.
131. Sick E, Jeanne A, Schneider C, Dedieu S, Takeda K, Martiny L. CD47 update: a multifaceted actor in the tumour microenvironment of potential therapeutic interest: CD47 in the tumour microenvironment. Br J Pharmacol. 2012;167:1415–30.
132. Bose RJ, Paulmurugan R, Moon J, Lee S-H, Park H. Cell membrane-coated nanocarriers: the emerging targeted delivery system for cancer theranostics. Drug Discov Today. 2018;23:891–9.
133. Bellone S, Siegel ER, Cocco E, Cargnelutti M, Silasi D-A, Azodi M, et al. Overexpression of epithelial cell adhesion molecule in primary, metastatic, and recurrent/chemotherapy-resistant epithelial ovarian cancer: implications for epithelial cell adhesion molecule-specific immunotherapy. Int J Gynecol Cancer. 2009;19:860–6.
134. Parodi A, Quattrocchi N, van de Ven AL, Chiappini C, Evangelopoulos M, Martinez JO, et al. Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions. Nat Nanotechnol. 2013;8:61–8.
135. Rabiee N, Yaraki MT, Garakani SM, Garakani SM, Ahmadi S, Lajevardi A, et al. Recent advances in porphyrin-based nanocomposites for effective targeted imaging and therapy. Biomaterials. 2020;232: 119707.
136. McDonald PC, Fielding AB, Dedhar S. Integrin-linked kinase – essential roles in physiology and cancer biology. J Cell Sci. 2008;121:3121–32.
137. Lian M, Shao S, Liu M, Shi Y, Zhang H, Chen D. Cell membrane-coated nanoparticles as peroxidase mimetics for cancer cell targeted detection and therapy. Talanta. 2022;238: 123071.
138. Sun H, Su J, Meng Q, Yin Q, Chen L, Gu W, et al. Cancer-cell-biomimetic nanoparticles for targeted therapy of homotypic tumors. Adv Mater. 2016;28:9581–8.
139. Yang J, Teng Y, Fu Y, Zhang C. Chlorins e6 loaded silica nanoparticles coated with gastric cancer cell membrane for tumor specific photodynamic therapy of gastric cancer. Int J Nanomedicine. 2019;14:5061–71.
140. Jin J, Krishnamachary B, Barnett JD, Chatterjee S, Chang D, Mironchik Y, et al. Human cancer cell membrane-coated biomimetic nanoparticles reduce fibroblast-mediated invasion and metastasis and induce T-cells. ACS Appl Mater Interfaces. 2019;11:7850–61.
141. Fontana F, Shahbazi M-A, Liu D, Zhang H, Mäkilä E, Salonen J, et al. Multistaged nanovaccines based on porous silicon@acetalated dextran@cancer cell membrane for cancer immunotherapy. Adv Mater. 2017;29:1603239.
142. Pereira-Silva M, Santos AC, Conde J, Hoskins C, Concheiro A, Alvarez-Lorenzo C, et al. Biomimetic cancer cell membrane-coated nanosystems as next-generation cancer therapies. Expert Opin Drug Deliv. 2020;17:1515–8.
143. Gong X, Li J, Tan T, Wang Z, Wang H, Wang Y, et al. Emerging approaches of cell-based nanosystems to target cancer metastasis. Adv Funct Mater. 2019;29:1903441.
144. Harris JC, Scully MA, Day ES. Cancer cell membrane-coated nanoparticles for cancer management. Cancers. 2019;11:1836.
145. Zou M-Z, Li Z-H, Bai X-F, Liu C-J, Zhang X-Z. Hybrid vesicles based on autologous tumor cell membrane and bacterial outer membrane to enhance innate immune response and personalized tumor immunotherapy. Nano Lett. 2021;21:8609–18.
146. Xiong X, Zhao J, Pan J, Liu C, Guo X, Zhou S. Personalized nanovaccine coated with calcinetin-expressed cancer cell membrane antigen for cancer immunotherapy. Nano lett. 2021;21:8418–25.
147. Si J, Shao S, Shen Y, Wang K. Macrophages as active nanocarriers for targeted early and adjuvant cancer chemotherapy. Small. 2016;12:5108–19.
148. Cai H, Wang R, Guo X, Song M, Yan F, Ji B, et al. Combining gemcitabine-loaded macrophage-like nanoparticles and erlotinib for pancreatic cancer therapy. Mol Pharm. 2021;18:2495–506.
149. Xuan M, Shao J, Dai L, Li J, He Q. Macrophage cell membrane camouflaged Au nanoshells for in vivo prolonged circulation life and enhanced cancer photothermal therapy. ACS Appl Mater Interfaces. 2016;8:9610–8.
150. Chen C, Song M, Du Y, Yu Y, Li C, Han Y, et al. Tumor-associated-macrophage-membrane-coated nanoparticles for improved photodynamic immunotherapy. Nano Lett. 2021;21:5522–31.
151. Rao L, He Z, Meng Q-F, Zhou Z, Bu L-L, Guo S-S, et al. Effective cancer targeting and imaging using macrophage membrane-camouflaged upconversion nanoparticles: Effective cancer targeting and imaging. J Biomed Mater Res A. 2017;105:521–30.
152. Poudel K, Banstola A, Gautam M, Soe Z, Phung CD, Pham LM, et al. Macrophage-membrane-camouflaged disintegrable and excretable nanoconstruct for deep tumor penetration. ACS Appl Mater Interfaces. 2020;12:56767–81.
153. Louwe PA, Badiola Gomez L, Webster H, Perona-Wright G, Bain CC, Forbes SJ, et al. Recruited macrophages that colonize the post-inflammatory peritoneal niche convert into functionally divergent resident cells. Nat Commun. 2021;12:1770.
154. Li R, He Y, Zhu Y, Jiang L, Zhang S, Qin J, et al. Route to rheumatoid arthritis by macrophage-derived microvesicle-coated nanoparticles. Nano Lett. 2019;19:124–34.
155. Shen S, Han F, Yuan A, Wu L, Cao J, Qian J, et al. Engineered nanoparticles disguised as macrophages for trapping lipopolysaccharide and preventing endotoxemia. Biomaterials. 2019;189:60–8.
156. Pussinen PJ, Havulinna AS, Lehto M, Sundvall J, Salomaa V. Endotoxemia is associated with an increased risk of incident diabetes. Diabetes Care. 2011;34:392–7.
157. Jahromi LP, Shahbazi M, Maleki A, Azadi A, Santos HA. Chemically engineered immune cell-derived microrobots and biomimetic nanoparticles: emerging biodiagnostic and therapeutic tools. Adv Sci. 2021;8:2002499.
158. Lassenius MI, Pietiläinen KH, Kaartinen K, Pussinen PJ, Syrjänen J, Forsblom C, et al. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. Diabetes Care. 2011;34:1809–15.
159. Cao B, Yang M, Zhu Y, Qu X, Mao C. Stem cells loaded with nanoparticles as a drug carrier for in vivo breast cancer therapy. Adv Mater. 2014;26:4627–31.
160. Wu M, Le W, Mei T, Wang Y, Chen B, Liu Z, et al. Cell membrane camouflaged nanoparticles: a new biomimetic platform for cancer photothermal therapy. Int J Nanomedicine. 2019;14:4431–48.
161. Huang Y, Gao X, Chen J. Leukocyte-derived biomimetic nanoparticulate drug delivery systems for cancer therapy. Acta Pharm Sin B. 2018;8:4–13.

162. Zhang L, Li R, Chen H, Wei J, Qian H, Su S, 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;12:2129–42.
163. Tang H, Xue Y, Li B, Xu X, Zhang F, Guo J, et al. Membrane-camouflaged supramolecular nanoparticles for co-delivery of chemotherapeutic and molecular-targeted drugs with siRNA against patient-derived pancreatic carcinoma. Acta Pharm Sin B. 2022;12:3410–26.
164. Hu C-MJ, Fang RH, Copp J, Luk BT, Zhang L. A biomimetic nanosponge that absorbs pore-forming toxins. Nat Nanotechnol. 2013;8:336–40.
165. Ma J, Jiang L, Liu G. Cell membrane-coated nanoparticles for the treatment of bacterial infection. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2022;e1825.
166. Chen Y, Chen M, Zhang Y, Lee JH, Escajadillo T, Gong H, et al. Broad-spectrum neutralization of pore-forming toxins with human erythrocyte membrane-coated nanosponges. Adv Healthc Mater. 2018;7: e1701366.
167. Zhang Q, Dehaini D, Zhang Y, Zhou J, Chen X, Zhang L, et al. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. Nat Nanotechnol. 2018;13:1182–90.
168. Zeng Y, Li S, Zhang S, Wang L, Yuan H, Hu F. Cell membrane coated-nanoparticles for cancer immunotherapy. Acta Pharm Sin B. 2022;12:3233–54.
169. Anwar M, Muhammad F, Akhtar B, Anwar MI, Raza A, Aleem A. Outer membrane protein-coated nanoparticles as antibacterial vaccine candidates. Int J Pept Res Ther. 2021;27:1689–97.
170. Fang RH, Hu C-MJ, Chen KNH, Luk BT, Carpenter CW, Gao W, et al. Lipid-insertion enables targeting functionalization of erythrocyte membrane-cloaked nanoparticles. Nanoscale. 2013;5:8884.
171. Ding C, Zhang C, Cheng S, Xian Y. Multivalent aptamer functionalized Ag_2S nanodots/hybrid cell membrane-coated magnetic nanobioprobe for the ultrasensitive isolation and detection of circulating tumor cells. Adv Funct Mater. 2020;30:1909781.
172. Esteban-Fernández de Ávila B, Angsantikul P, Ramírez-Herrera DE, Soto F, Teymourian H, Dehaini D, et al. Hybrid biomembrane–functionalized nanorobots for concurrent removal of pathogenic bacteria and toxins. Sci Robot. 2018;3:eaat0485.
173. Wang G, Chen X, Liu S, Wong C, Chu S. Mechanical chameleon through dynamic real-time plasmonic tuning. ACS Nano. 2016;10:1788–94.
174. Han X, Shen S, Fan Q, Chen G, Archibong E, Dotti G, et al. Red blood cell–derived nanoerythrosome for antigen delivery with enhanced cancer immunotherapy. Sci Adv. 2019;5:eaaw6870.
175. Cheng L, Wang C, Feng L, Yang K, Liu Z. Functional nanomaterials for phototherapies of cancer. Chem Rev. 2014;114:10869–939.
176. Xiong J, Wu M, Chen J, Liu Y, Chen Y, Fan G, et al. Cancer-erythrocyte hybrid membrane-camouflaged magnetic nanoparticles with enhanced photothermal-immunotherapy for ovarian cancer. ACS Nano. 2021;15:19756–70.
177. Chen Long, Qin Hao, Zhao Ruifang, Zhao Xiao, Lin Liangru, Chen Yang, et al. Bacterial cytoplasmic membranes synergistically enhance the antitumor activity of autologous cancer vaccines. Sci Transl Med. American Association for the Advancement of Science; 2021;13:eabc2816.
178. Wang L, Asghar W, Demirci U, Wan Y. Nanostructured substrates for isolation of circulating tumor cells. Nano Today. 2013;8:374–87.
179. Committee on Standards, and American Association of Blood Banks. Standards Program Committee. FACT-JACIE international standards for hematopoietic cellular therapy product collection, processing, and administration. Stand. Blood Banks Transfus. Serv. 1974.
180. Guidelines for Quality Control and Preclinical Research of Stem Cell Preparations (Trial). 2015.
181. Xu W-J, Cai J-X, Li Y-J, Wu J-Y, Xiang D. Recent progress of macrophage vesicle-based drug delivery systems. Drug Deliv Transl Res [Internet]. 2022 [cited 2022 Jun 28]; Available from: https://link.springer.com/10.1007/s13346-021-01110-5.
182. Malhotra S, Dumoga S, Singh N. Red blood cells membrane-derived nanoparticles: applications and key challenges in their clinical translation. WIREs Nanomed Nanobiotechnol. 2022 [cited 2022 Sep 14];14. Available from: https://onlinelibrary.wiley.com/doi/10.1002/wnan.1776.
183. Vetten MA, Yah CS, Singh T, Gulumian M. Challenges facing sterilization and depyrogenation of nanoparticles: effects on structural stability and biomedical applications. Nanomedicine Nanotechnol Biol Med. 2014;10:1391–9.
184. Alphandéry E. A discussion on existing nanomedicine regulation: progress and pitfalls. Appl Mater Today. 2019;17:193–205.
185. Merivaara A, Zini J, Koivunotko E, Valkonen S, Korhonen O, Fernandes FM, et al. Preservation of biomaterials and cells by freeze-drying: change of paradigm. J Controlled Release. 2021;336:480–98.
186. Ragelle H, Danhier F, Préat V, Langer R, Anderson DG. Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opin Drug Deliv. 2017;14:851–64.
187. Stewart A, Urbaniak S, Turner M, Bessos H. The application of a new quantitative assay for the monitoring of integrin-associated protein CD47 on red blood cells during storage and comparison with the expression of CD47 and phosphatidylserine with flow cytometry. Transfusion (Paris). 2005;45:1496–503.
188. Kriebardis AG, Antonelou MH, Stamoulis KE, Economou-Petersen E, Margaritis LH, Papassideri IS. RBC-derived vesicles during storage: ultrastructure, protein composition, oxidation, and signaling components. Transfusion (Paris). 2008;48:1943–53.
189. Pereira-Silva M, Chauhan G, Shin MD, Hoskins C, Madou MJ, Martinez-Chapa SO, et al. Unleashing the potential of cell membrane-based nanoparticles for COVID-19 treatment and vaccination. Expert Opin Drug Deliv. 2021;18:1395–414.
190. Jiang Y, Krishnan N, Zhou J, Chekuri S, Wei X, Kroll AV, et al. Engineered cell-membrane-coated nanoparticles directly present tumor antigens to promote anticancer immunity. Adv Mater. 2020;32:2001808.