International Journal of Nanomedicine

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REVIEW

Cell Membrane-Camouflaged Nanoparticles Mediated Nucleic Acids Delivery

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Abstract: Nucleic acids have emerged as promising therapeutic agents for many diseases because of their potential in modulating gene expression. However, the delivery of nucleic acids remains a significant challenge in gene therapy. Although viral vectors have shown high transfection efficiency, concerns regarding teratogenicity or carcinogenicity have been raised. Non-viral vehicles, including cationic polymers, liposomes, and inorganic materials possess advantages in terms of safety, ease of preparation, and low cost. Nevertheless, they also face limitations related to immunogenicity, quick clearance in vivo, and lack of targeting specificity. On the other hand, bioinspired strategies have shown increasing potential in the field of drug delivery, yet there is a lack of comprehensive reviews summarizing the rapid development of bioinspired nanoparticles based on the cell membrane camouflage to construct the nucleic acids vehicles. Herein, we enumerated the current difficulties in nucleic acid delivery with various non-viral vehicles and provided an overview of bioinspired strategies for nucleic acid delivery.

Keywords: nucleic acids, bioinspired nanoparticles, non-viral vehicles, gene therapy, cell membranes

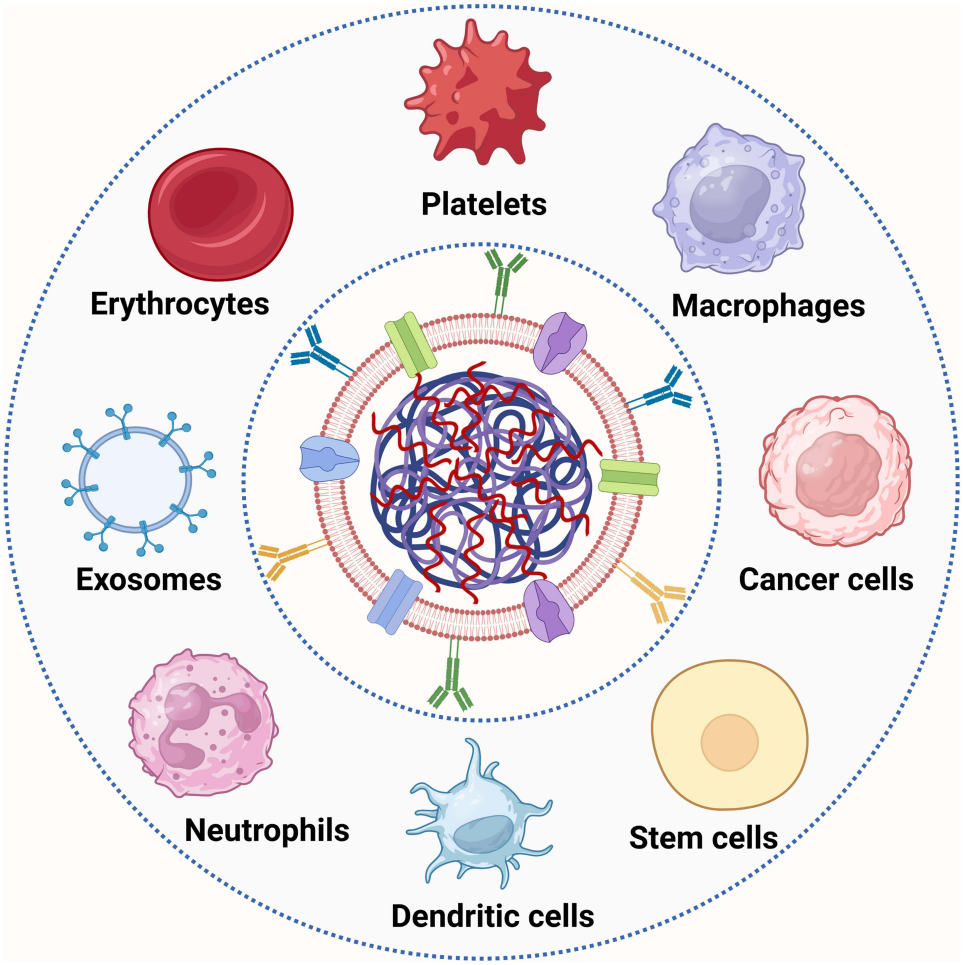
Introduction

Nucleic acids have promising therapeutic potential for the treatment of various diseases including genetic disorders,[1] cancer,[2] cardiovascular diseases,[3] and infectious diseases,[4] as they can target specific genes and modulate their expression. However, the delivery of nucleic acids, such as plasmid DNA (pDNA), small interfering RNA (siRNA), self-amplifying RNA (saRNA), messenger RNA (mRNA), aptamer, and antisense oligonucleotides (ASO) presents significant challenges in gene therapy. Several obstacles need to be overcome before nucleic acids become an effective therapy. First of all, nucleic acids are susceptible to degradation by nucleases in the extracellular environment, which limits their stability and activity. Besides, the lack of tissue or cell selectivity may lead to off-target and other side effects. The negative charge and hydrophilic nature of nucleic acids also pose impediments to crossing cell membranes. And lastly, even if they manage to enter the cells, nucleic acids are hard to escape from lysosomes, which also hamper therapy efficiency.[5,6]

There are three main approaches for delivering nucleic acids: biological methods, physical methods, and chemical methods. Biological methods mainly rely on viral vectors which are the very first used in nucleic acids delivery due to their high efficiency. Some common examples of viral vectors include retrovirus, adeno-associated virus, adenovirus, lentivirus, and virus-like particles.[7] However, the complex compositions of viral vectors remain a problem. Techniques using physical methods then have been developed to deliver nucleic acids into cells both in vitro and in vivo. Electroporation and ultrasonic perforation can transfect nucleic acids into cells by perforating cell membranes.[8,9] Such methods apply mechanical force, which may disrupt the structural integrity and lead to cell death. Microinjection is injecting nucleic

Received: 3 August 2023
Accepted: 16 December 2023
Published: 28 December 2023

Graphical Abstract



acids into cells with the assistance of a micropipette and microscope.[10] But it needs specialized instruments and can only operate one cell at a time. Chemical methods involve the use of composite nanoparticles, including liposomes,[11] polymer,[12] peptides,[13] gold nanoparticle,[14] mesoporous silica,[15] and so on. Compared to viral vectors, nanoparticles offer relatively better biocompatibility, structural stability, and simpler preparation scheme.[16] Nevertheless, nanoparticles also have certain limitations in terms of immunogenicity, quick clearance in vivo, and lack of targeting specificity.[17]

To address these limitations, the bioinspired strategy by producing non-viral vehicles with biomimetic structures and functions has raised the attention of potential clinical applications in the field of drug delivery. One of the most powerful approaches to produce bioinspired nanoparticles was cell membrane coating nanotechnology, which was performed by coating synthetic nanoparticles with natural cell membranes. This technology has been extended to other biomembranes, such as the membranes derived from organelles or extracellular vesicles. The cell membrane camouflaged nanoparticles (CMCNPs) have been considered novel nucleic acid vehicles, which possess biocompatibility, low immunogenicity, and efficient targeting capabilities. The cell membrane coating also acts as a protective layer for the nanoparticles and nucleic acids, promoting gene therapy efficiency.[18–20] The use of CMCNPs is a promising strategy for gene therapy. Herein, we summarized the difficulties in nucleic acid delivery with nanoparticles at present and provided an overview of the applications of CMCNPs in nucleic acid delivery.

Difficulties in Nucleic Acid Delivery with Nanoparticles at Present

The delivery of nucleic acids with nanoparticles is a complex process that involves several challenges (Figure 1). One of the main challenges is the dissociation of nucleic acids from nanoparticles while circulating. Free nucleic acids are susceptible to nucleases in the blood and extracellular environment, limiting their stabilities and therapeutic potential. To address this issue, CMCNPs provide enhanced protection for nucleic acids, which can reduce dissociation and degradation during delivery.

Another challenge is the immunogenicity of both free nucleic acids and encapsulated nucleic acids by nanoparticles. They can be detected and phagocytosed by the reticuloendothelial system, leading to a short circulation time. While PEGylation can make nanoparticles "stealth", it may also lead to potential tissue toxicity and adverse reactions.[21] CMCNPs, on the other hand, demonstrate good biocompatibility, reduced immune recognition, and prolonged half-life.

The third challenge is the off-target effects of nucleic acid delivery, potentially causing unintended gene silencing or activation. This is often due to the non-specific binding of nanoparticles to non-target tissues or cells. Nanoparticles need to possess certain sizes and specific ligands to achieve targeting, but modifying nanoparticles through complicated chemical reactions may affect their structures and properties. In contrast, CMCNPs facilitate targeting without chemical conjugations. For example, cancer cell membranes camouflaged nanoparticles improved the recognition to the tumor tissues by homologous targeting, while stem cell membranes camouflaged nanoparticles naturally show tumor tropism.

To exert their therapeutic effect, nanoparticles must enter target cells through processes such as pinocytosis or membrane insertion. The cell membranes, which are lipid bilayers, act as barriers that distinguish the intracellular environment from the extracellular environment. CMCNPs often show enhanced cellular uptake through alternative

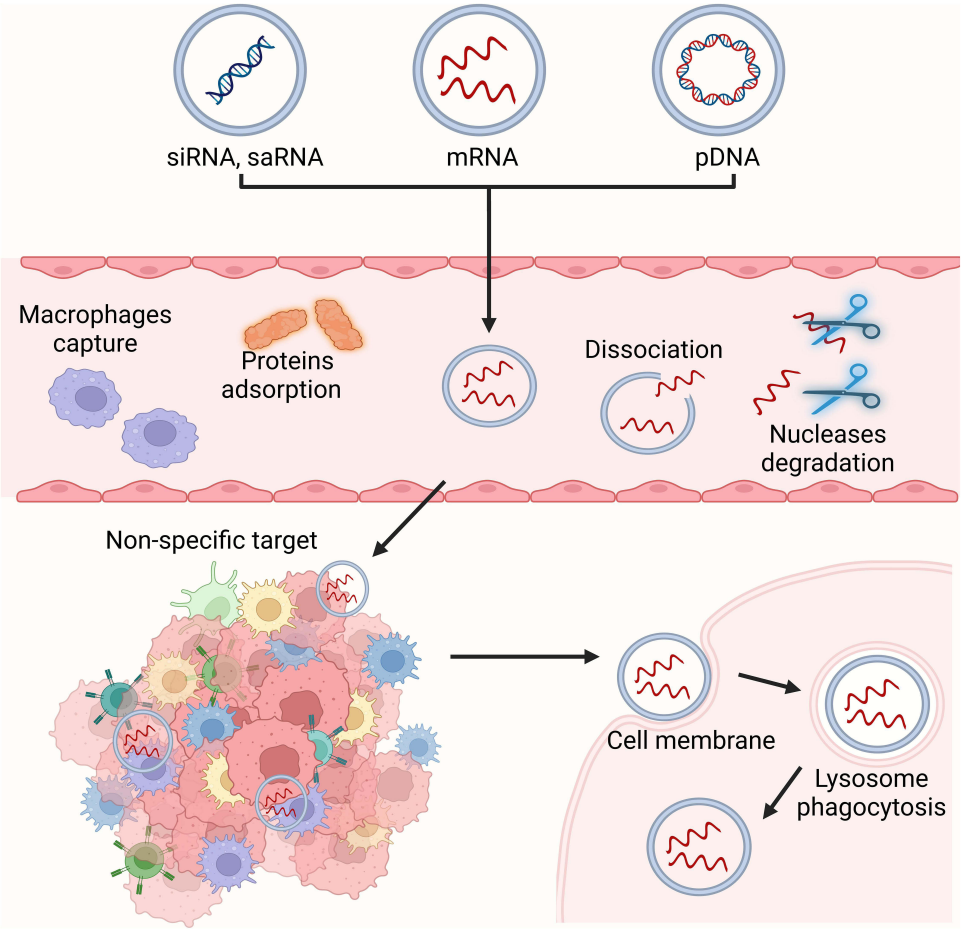


Figure 1 Difficulties in nucleic acid delivery with nanoparticles. Created with BioRender.com.

endocytic pathways such as membrane fusion or receptor-mediated endocytosis. Escaping from endo/lysosomes is a prerequisite for successful gene therapy, and CMCNPs may facilitate this process by fusing with lysosomal membranes.

Preparation of Cell Membranes Camouflaged Nanoparticles for Nucleic Acid Delivery

Cell membranes camouflaged nanoparticles (CMCNPs) have emerged as a promising strategy for the delivery of nucleic acids, offering enhanced targeting ability and efficient intracellular delivery. The preparations of CMCNPs typically involve three key steps: cell membranes extraction, fabrication of nanoparticles for nucleic acids loading, and CMCNPs construction.

Extraction of Cell Membranes

Different methods had been applied to extract cell membranes, including hypotonic lysis, freeze-thaw, ultrasonication, and homogenization. Hypotonic lysis is to swell cells under low osmotic pressure. While this method is widely used in erythrocyte membrane preparation, it is not suitable for other cell types due to relatively low efficiency.[22,23] Freeze-thaw is a universal method where cells are repeatedly frozen at low temperatures and thawed at room temperature.[24,25] During this process, cell membranes are prone to rupture in the presence of ice crystals. Ultrasonication is another efficient method to isolate cancer cell membranes. The shock waves and shear forces generated by the ultrasonic apparatus disrupt cell membranes. Homogenization has been used for a broad scope of applications. Regardless of the method chosen, it is crucial to maintain the integrity of cell membranes and the activity of proteins on cell membranes. The addition of proteinase inhibitors and conducting the procedures at low temperatures are prerequisites for preserving the functionality of cell membranes. We compared the advantages and disadvantages of cell membranes extraction methods in Table 1.

Fabrication of Nanoparticles for Nucleic Acid Loading

The second step is fabricating the nanoparticles to load nucleic acids. Various materials, such as liposome,[35] metal-organic frameworks (MOF),[36] poly(β-amino ester) (PBAE),[37] poly(ethylene imine) (PEI),[38] chitosan,[39] poly(lactic-co-glycolic acid) (PLGA),[40] mesoporous silica nanoparticles[41] have been used for gene delivery. Lipids like N, N, N-trimethyl-2,3-bis (octadec-9-en-1-yloxy) propan-1-aminium chloride (DOTMA),[42] 2,3-Dioleoyloxy-propyl-trimethylammonium-chloride (DOTAP),[43] 1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE)[44] are commonly used in cationic liposome, in which nucleic acid encapsulated in the inner hydrophilic phase or complexed on the surface because of the electrostatic adsorption (Figure 2). Composed by ionizable or cationic lipids, phospholipids, and cholesterol, the lipid nanoparticles (LNP) exhibit better stability than liposomes. PLGA, a biodegradable polymer approved by Food and Drug Administration, shows low nucleic acid delivery capacity due to its negative charge. Zhang et al developed a PLGA/DOTAP core to ensure high loading efficiency of siRNA.[45] DOTAP was positively charged and thus can interact with the negatively charged siRNA inside the aqueous core and enhance encapsulation. Moreover, DOTAP improves the endo/lysosomal escape by its fusogenic property or proton sponge effect. Nucleic acid loading can be performed during or after the nanoparticle fabrication. For example, Qiu et al used a microfluidic system to mix synthetic active lipidoid, cholesterol, 1.2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and 1.2-dimyristoyl-rac-

Table 1 Comparation of Cell Membranes Extraction Methods

Methods	Advantages	Disadvantages	Samples	References
Hypotonic lysis	Maneuverable	Low efficiency	Erythrocytes, macrophages	[26–28]
Freeze-thaw	Maneuverable	Affect protein activity	B16-OVA cells, platelets, mBMSCs	[24,29,30]
Ultrasonication	Efficient	Generate heat	Macrophages, 4T1 cells	[31,32]
Homogenization	Efficient, wide application range	Require specific instrument, large energy consumption	4T1 cells, B16F10 cells, macrophages	[33,34]

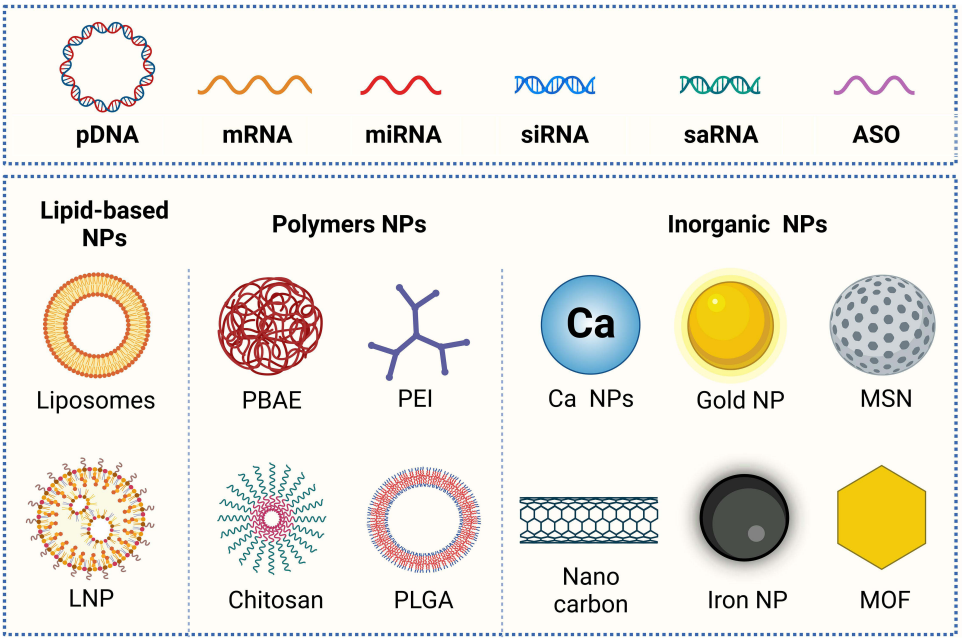


Figure 2 Classification of nanoparticles for nucleic acid delivery. Nanoparticles including lipid-based nanoparticles (NPs), polymers nanoparticles and inorganic nanoparticles have been used to deliver plasmid DNA (pDNA), messenger RNA (mRNA), microRNA (miRNA), small interfering RNA (siRNA), self-amplifying RNA (saRNA), or antisense oligonucleotides (ASO). Created with BioRender.com.

glycero-3-methoxypolyethylene glycol-2000 (DMG-PEG2000) (50: 38.5: 10: 1.5) in ethanol solution with sodium acetate buffer containing mRNA.[46] By doing so, mRNA was encapsulated in the internal hydrophilic cavity. Polymers such as PEI, PBAE, and chitosan which are positively charged, can form complexes with negatively charged nucleic acids spontaneously (Figure 2). Calcium phosphate nanoparticles possess biocompatibility and biodegradability, which load nucleic acids by charge neutralization. Carbon nanocages and mesoporous silicas demonstrate specific surface area, which load nucleic acids by absorbing. Metallic nanoparticles, such as gold nanoparticles, metal-organic frameworks (MOF), and Iron nanoparticles benefit from the advantages of small size and stable morphologies. The optimized materials can not only complex the nucleic acids, but possess the characteristics, such as biodegradability, selective distribution, environmental responsiveness, and controlled release within the cells.

Construction of CMCNPs

The camouflage with cell membranes is one of the most important procedures that significantly affects the fabrication and performance of CMCNPs. The source of cell membranes can vary, such as erythrocytes,[47] platelets,[48] stem cells,[49] macrophage,[50] or cancer cells[51] depending on the desired properties and targeting ability. The approaches mainly include vortex, extrusion, sonication, and microfluidic electroporation. Cell membranes with negative charge because of the glycosylation domain of membrane protein and phospholipids can roughly coat positively charged nanoparticles such as PBAE and MOF through the mutual attraction of positive and negative charges by means of vortex. The extrusion of cell membranes and nanoparticles through polycarbonate film in different apertures are commonly employed to consolidate the core-shell CMCNPs and standardize the particle size based on the mobility of cell membranes (Figure 3).[52] Sonication also has been used in several works to construct CMCNPs.[53,54] Unlike extrusion, sonication minimizes material loss during the process and gets CMCNPs in good dispersion. The power, frequency, and duration of sonication influence the coating efficiency (Figure 3). Both extrusion and sonication are by virtue of external force. However, it should be noted that sonication can disrupt electrostatic interaction and thus may not be suitable for nanoparticles complexed with nucleic acids on their surface. Microfluidic electroporation is a newly emerging technology by generating temporary hydrophilic holes through the cell membranes using quick high-voltage electric field pulses (Figure 3), which offers the advantages of high throughput and quantitative format.[55,56]

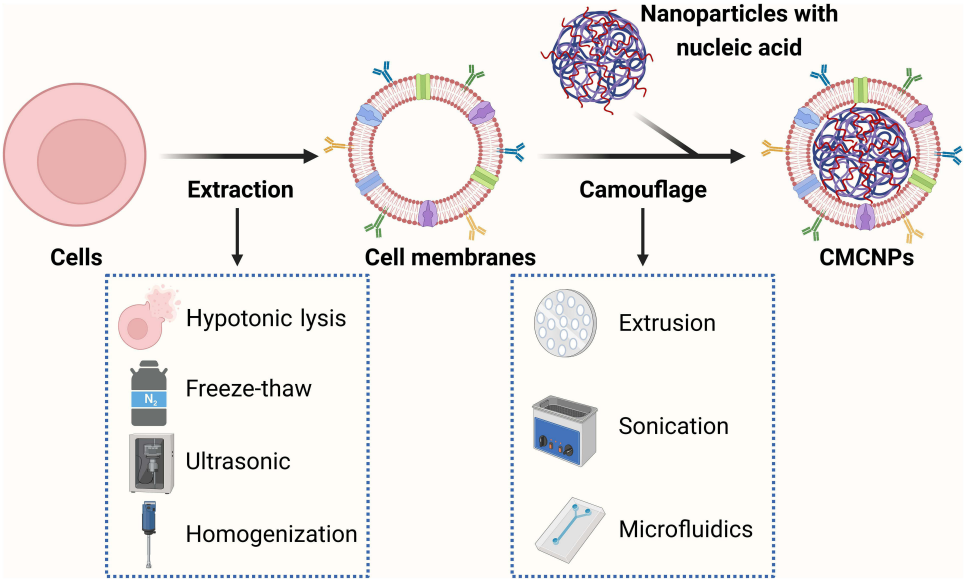


Figure 3 Preparation of cell membranes camouflaged nanoparticles for nucleic acid delivery. Firstly, extracting cell membranes through hypotonic lysis, freeze-thaw, ultrasonic or homogenization. Secondly, fabricating nanoparticles and load nucleic acid. At the last, camouflaging the nanoparticles with cell membranes by extrusion, sonication, or microfluidics to form cell membranes camouflaged nanoparticles (CMCNPs). Created with BioRender.com.

Applications for Nucleic Acid Delivery by Cell Membranes Camouflaged Nanoparticles

Nanoparticles can be camouflaged with different cell membranes from erythrocytes,[57–60] platelets,[61–63] macrophages,[64–67] cancer cells,[68–74] stem cells,[75–78] dendritic cells,[79–81] neutrophil,[82–84] exosomes,[85–87] or other membranes depend on desired applications (Figure 4). Blood cells likes erythrocytes and platelets could reduce endothelial reticular system clearance and prolong half-time. Immune cells such as macrophages and neutrophil as well as stem cells are capable of targeting to inflammatory site. Cancer cells camouflaged nanoparticles already used in cancer gene therapy for homologous targeting ability.

Erythrocytes Membranes Camouflaged Nanoparticles (EMCNPs)

Erythrocytes, also known as red blood cells, are the most abundant cell type in mammals, circulating in the bloodstream for approximately 120 days.[88] Erythrocytes membranes express markers such as CD47, CD59, and complement factor 1, which send out a "don't eat me" signal to evade clearance by the reticuloendothelial system.[89–91] Mature erythrocytes have no nucleus and organelles, which make membrane extraction relatively straightforward. Erythrocyte membranes demonstrate excellent endurance and tensile strength, allowing them to coat anisotropic nanoparticles.[92] Erythrocytes membranes camouflaged nanoparticles (EMCNPs) exhibit good biocompatibility, low immunogenicity, favorable biodegradability, and prolonged circulation time.[93–95] Hu et al prepared erythrocyte membranes camouflaged PLGA nanoparticles which demonstrated a longer elimination half-life of 39.6 h compared to 15.8 h of PEG-coated nanoparticles.[96] Liang et al used erythrocytes membranes to camouflage matrix metalloproteinase 2 (MMP2)-activated nanoparticles to prepared EMCNPs named REMAIN by incubation after sonication (Figure 5A).[97] REMAIN showed a ~20 nm increase in the size than uncoated nanoparticles (Figure 5B). Moreover, REMAIN possessed protein components similar to the ones on the erythrocyte membranes, indicating the successfully camouflage with erythrocytes membranes (Figure 5C). REMAIN remained about 50% in blood after 24 h, exhibiting extended circulation time and effectively inhibiting lung cancer growth in vivo (Figure 5D and E). However, erythrocyte membranes lack adhesion peptides, which limits their targeting capabilities. To address this, several studies have modified erythrocyte membranes to achieve different affinities.[98–100] Gao et al camouflaged siRNA-loaded nanogel with erythrocyte membranes and modified them with

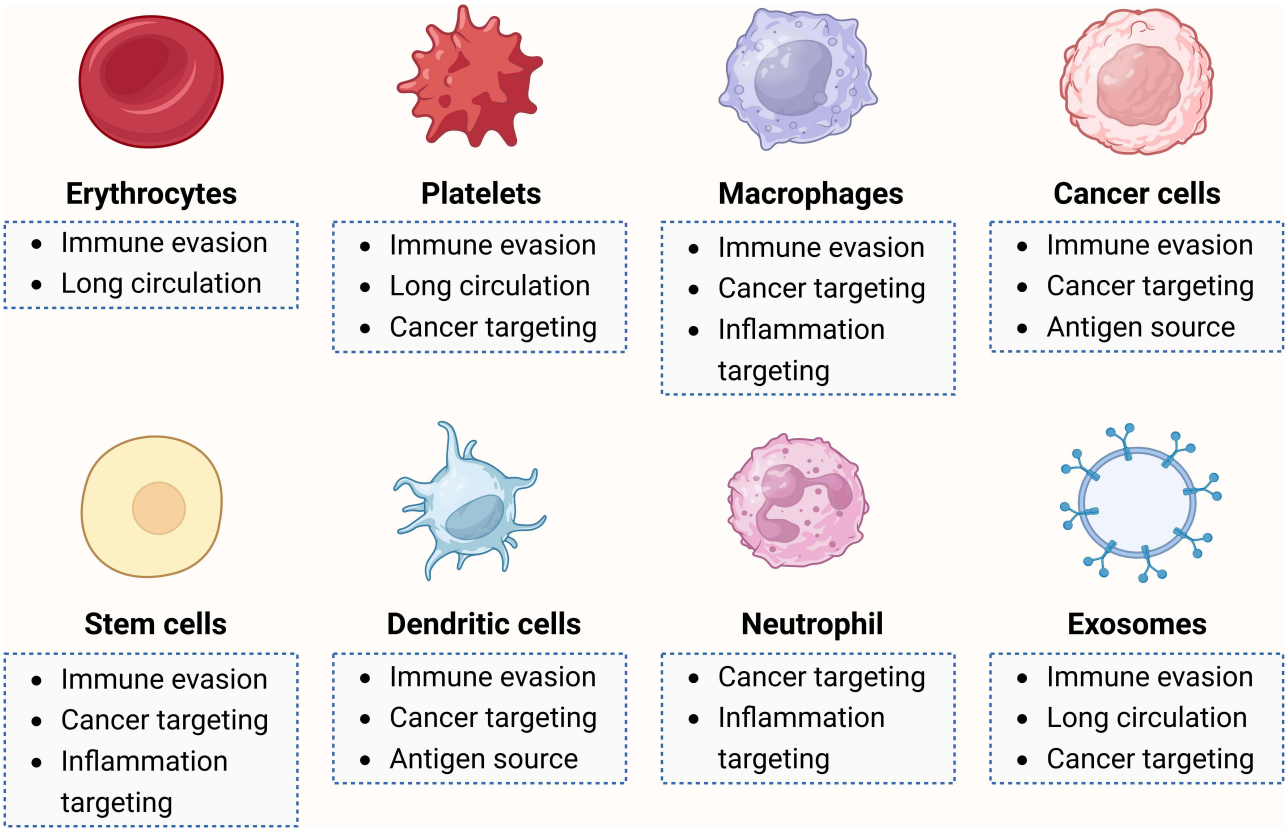


Figure 4 The sources and functions of cell membranes. Created with BioRender.com.

M2pep and HA2 peptides (Vir-gel).[101] The Vir-gel not only had a longer half-life than nanogel alone but also showed stronger fluorescence intensity in the brain, colocalizing with macrophages with the assistance of M2pep and HA2.

Platelet Membranes Camouflaged Nanoparticles (PMCNPs)

Platelets are the smallest cells in the bloodstream, with an average lifespan of 7~10 days. Platelet membranes camouflaged nanoparticles (PMCMPs) can serve as a biomimetic delivery system, mimicking platelets in the blood.[102] Similar to EMCNPs, PMCNPs demonstrate excellent biocompatibility, reduced immunogenicity, and prolonged circulation time.[103,104] Hu et al reported a type of PMCNPs called PNP by enclosing polymeric nanoparticles with human platelets membranes through sonication.[105] PNP featured right-side-out unilamellar membrane coating functionalized with immunomodulatory and adhesion antigens associated with platelets. The platelet membranes camouflaging reduced the uptake of polymeric nanoparticles by macrophages and prevented particle-induced complement activation in autologous human plasma. Likewise, our previous work found that platelet membranes camouflaged PLAG/DOTAP nanoparticles showed a much longer half-life in mice (36.44 ± 4.33 h) compared to the non-camouflaged nanoparticles (11 ± 4.65 h).[45] The camouflage with platelet membranes ameliorated the surface functions significantly, which reduced immunogenicity and enhanced the circulation lifetime. This approach is beneficial for the nucleic acids to accumulate in the targeted sites.

In addition, platelet membranes possess specific receptors such as P-selectin and CLEC-2, which specifically recognize the CD44 and podoplanin on the cancer cell membranes, respectively.[106,107] PMCNPs also can be applied to cancer gene therapy. Zhuang et al reported platelet membranes camouflaged metal-organic framework nanoplatform (P-MOF-siRNA) for the targeted delivery of siRNA in vivo.[108] P-MOF-siRNA expressed CD41, CD61 and P-selectin as platelet membranes (Figure 6A). A layer film could be seen outside the P-MOF-siRNA nanoparticles (Figure 6B). The above results indicated that successfully platelet membranes camouflage on MOF. Zhuang also compared P-MOF-siRNA with erythrocytes membrane-camouflaged MOF (R-MOF-siRNA) and found similar gene down-regulation (Figure 6C),

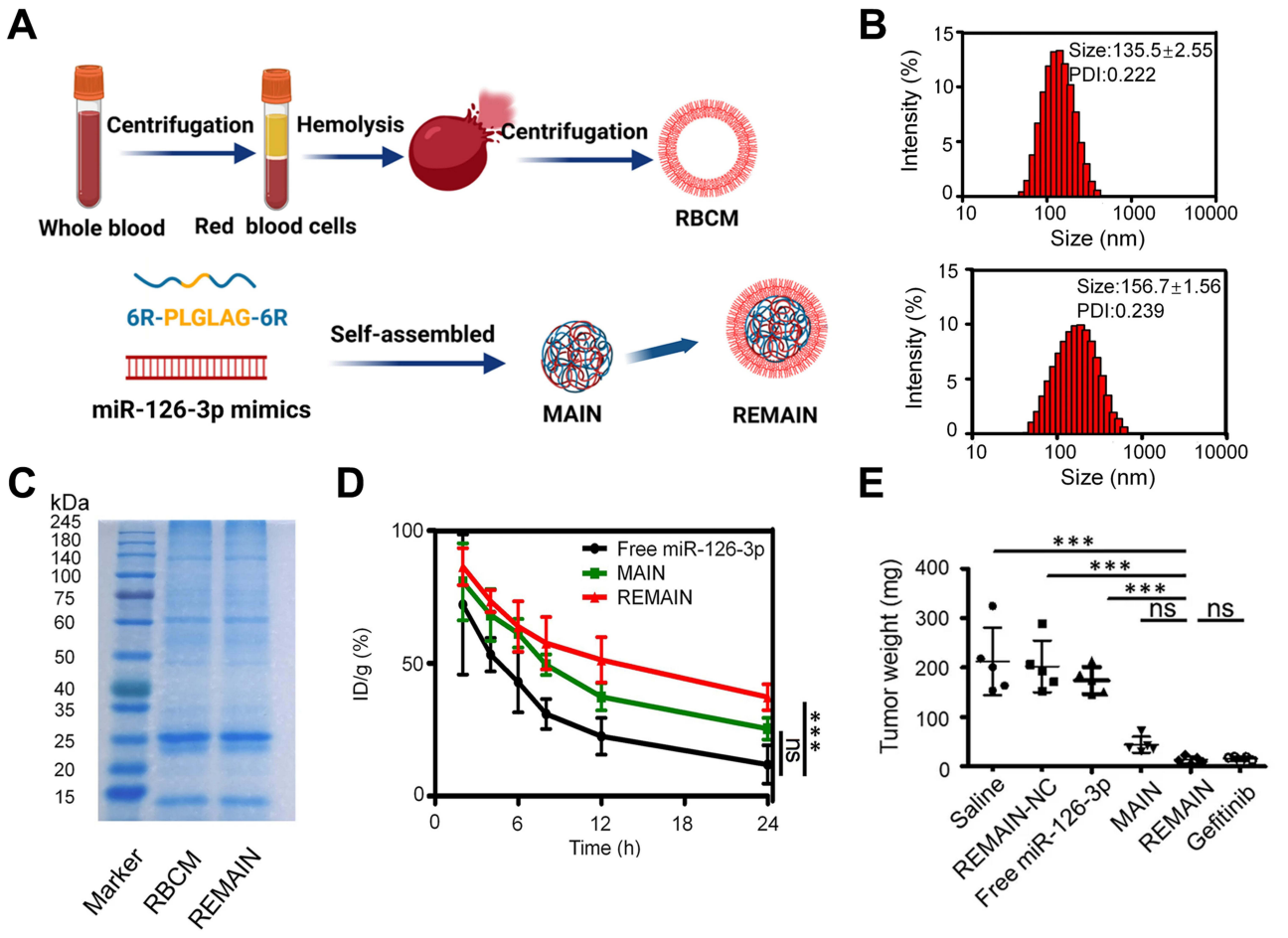


Figure 5 Preparation, characteristics and biodistribution of REMAIN. (**A**) Preparation scheme of REMAIN preparation. (**B**) Size distribution of MAIN and RAMAIN. (**C**) Coomassie blue staining of REAMIN. (**D**) Circulation lifetime of REMAIN in vivo. ns, no significance; ***, $P < 0.001$. (**E**) Tumor weight of different treatment. Adapted with permission from Liang L, Cen H, Huang J et al. The reversion of DNA methylation-induced miRNA silence via biomimetic nanoparticles-mediated gene delivery for efficient lung adenocarcinoma therapy. *Mol Cancer*. 2022;21(1):186.[97]

as well as reduced binding to macrophages in vitro (Figure 6D). Interestingly, P-MOF-siRNA showed higher accumulation in tumors than R-MOF-siRNA, resulting better tumor inhibition capability and longer lifetime when encapsulated siRNA^{Sur} (Figure 6D and F). Receptors on platelet membranes like integrin α2β1 and Glycoprotein VI have an affinity for collagen IV and GPIa-IIa, respectively.[109,110] PMCNPs can also be utilized in the treatment of autoimmune diseases and atherosclerosis.[111,112]

Macrophages Membranes Camouflaged Nanoparticles (MMCNPs)

Macrophages, as natural immune and antigen presenting cells, have long half-life. Macrophages membranes camouflaged nanoparticles (MMCNPs) not only can evade the clearance of reticuloendothelial system and prolong the circulation time in vivo, but also actively identify to inflammation tissue and penetrate in solid tumors.[113,114] MMCNPs are capable to homologous target to macrophages in inflammation tissue to treat atherosclerosis,[115,116] arthritis,[117,118] colitis,[65,119] hepatitis,[120] and other inflammatory disease. Cao et al developed a bone marrow mesenchymal macrophage membrane camouflaged metal-organic framework (MOF) system for plasmid DNA delivery (Macrophages membranes/MOF/pDNA, abbreviated as MMD) in the treatment of sepsis.[121] The membranes coating conferred negative charge (Figure 7A) and increased the size of MD, with an average size of 160 ± 5 nm (Figure 7B). MMD remained key membrane antigens including TLR4, TNFR2, CD36, CCR2 and CD47, implying MOF/pDNA nanoparticles were camouflaged by macrophage membranes (Figure 7C). Both confocal laser scanning microscopy, flow cytometry, and quantitative analysis of zinc that revealed MMD uptake by RAW 264.7 cells more than in other cell lines indicating good

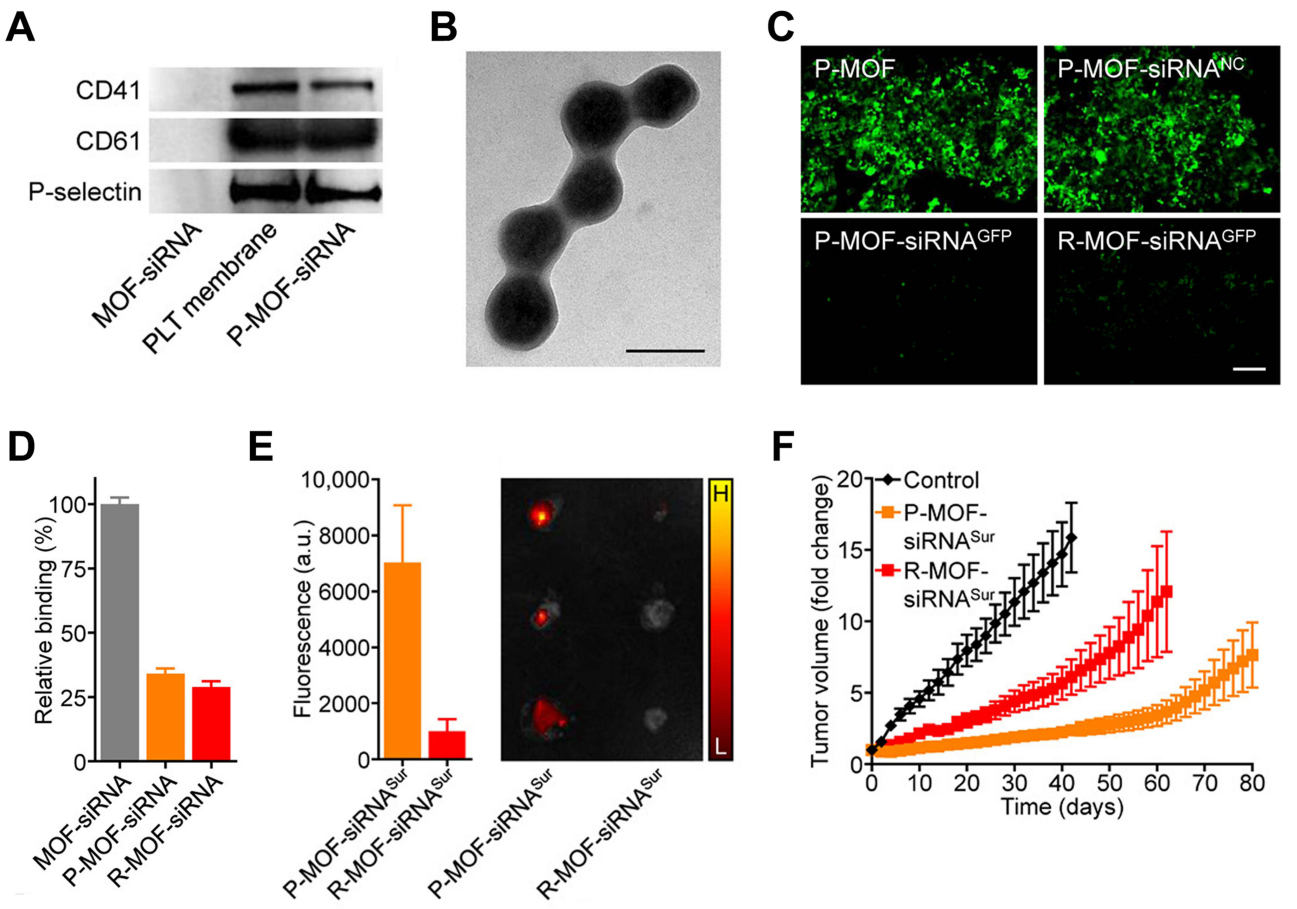


Figure 6 Characteristics and siRNA deliver efficiency of P-MOF-siRNA. (**A**) Western blot of CD41, CD61, and P-selectin of P-MOF-siRNA. (**B**) TEM of P-MOF-siRNA. (**C**) Visualization of gene knockdown in GFP-transduced cells after incubation with P-MOF, P-MOF-siRNA^{NC}, P-MOF-siRNA^{GFP}, or R-MOF-siRNA^{GFP} for 48 h. (**D**) Uptake of MOF-siRNA, P-MOF-siRNA, or R-MOF-siRNA by macrophages after 24 h of incubation. (**E**) Fluorescent of P-MOF-siRNA and R-MOF-siRNA within the tumor 1 hour after intravenous administration. (**F**) Growth kinetics of tumors implanted subcutaneously into nu/nu mice and treated intravenously with P-MOF-siRNA^{Sur} or R-MOF-siRNA^{Sur}. Adapted with permission from Zhuang J, Gong H, Zhou J et al. Targeted gene silencing in vivo by platelet membrane-coated metal-organic framework nanoparticles. *Sci Adv.* 2020;6(13):eaaz6108.[108] Copyright 2020 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science.

homotypic targeting (Figure 7D-7F). Macrophages are abundant in tumor microenvironment and closely associated with tumor development, also called tumor associated macrophages.[122]

Likewise, MMCNPs promote tumor targeting by homing to tumor associated macrophages. Nai et al applied macrophage membranes to camouflaged thermosensitive liposomes (C-siRNA/MTSLR).[123] After administration, the fluorescence of C-siRNA/MTSL in tumor site was stronger than nanoparticles without macrophages membranes. The surface receptors like integrin α4, integrin β1 facilitate MMCNPs penetrate in solid tumors by recognizing vascular cell adhesion molecule 1(VCAM-1).[113] MMCNPs also can be used for cancer targeting gene therapy. Yang et al applied M1 macrophages membranes to coat nanoparticles encapsulating short-hairpin RNA and doxorubicin.[52] The prepared MMCNPs evaded from the reticuloendothelial system and enriched in tumor sites, effectively phagocytosing by B16F10 cells and M1 macrophages. Nevertheless, the cellular uptake of MMD and C-siRNA/MTSL in cancer cells were less than in macrophages (Figure 7D-7F).[121,123] Since macrophages membranes coating lacks of tumor targeting peptides and exists repels electricity with cancer cells, prohibiting nanoparticle uptake. With the modification of cRGD on macrophages membranes, C-siRNA/MTSL possessed increased cancer accumulation and inhibition effect.[123]

Mesenchymal Stem Cells Membranes Camouflaged Nanoparticles (MSCMCNPs)

Mesenchymal stem cells (MSCs) are plastic multifunctional fibroblast-like cells with self-renewal capacity and multi-differentiation potential.[124] MSCs derived from sources including bone marrow, umbilical cord, and adipose tissues have

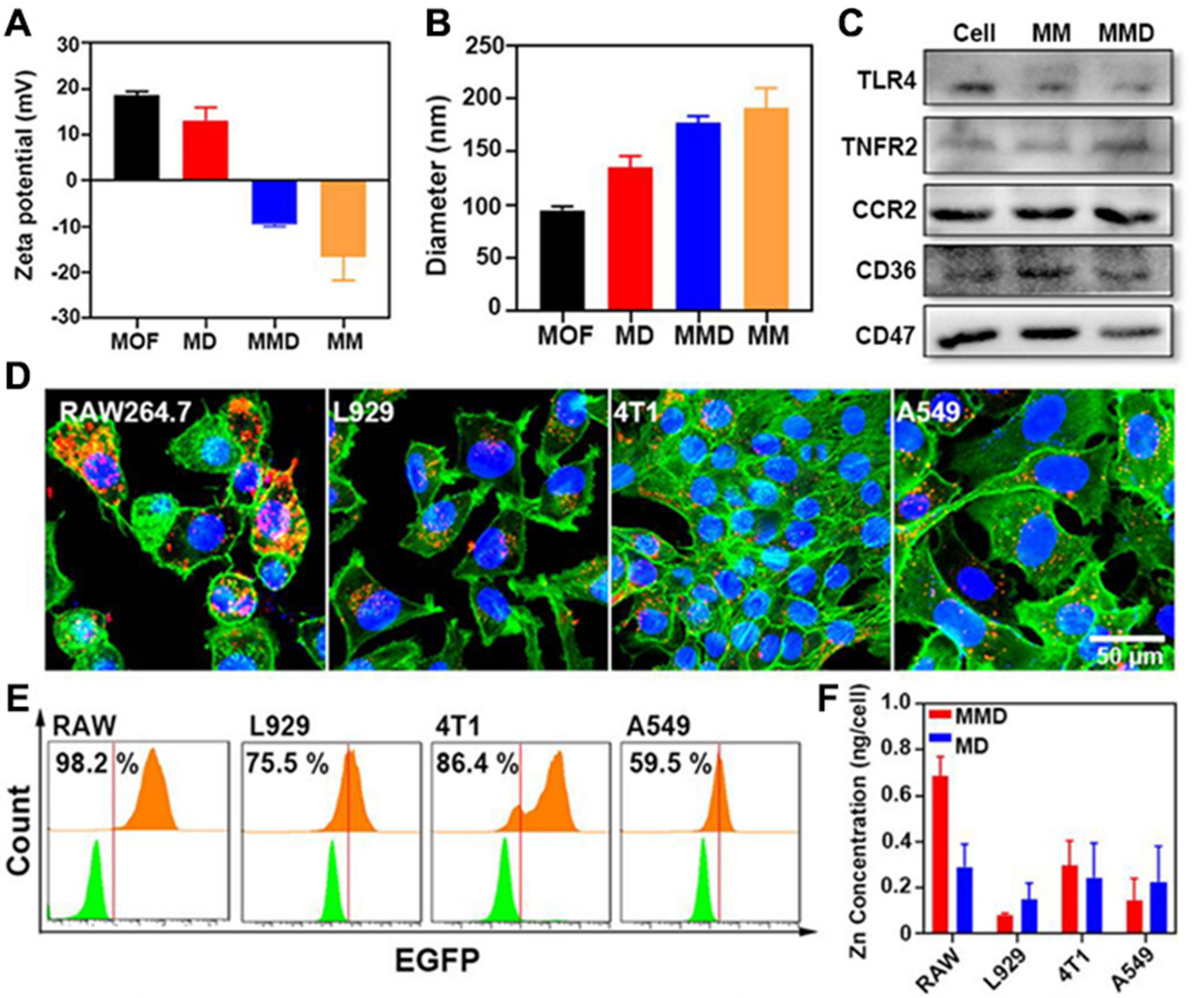


Figure 7 Characteristics and cellular uptake of MMD. (**A**) Zeta potential of MOF, MD, MMD, and MM. (**B**) Size of MOF, MD, MMD, and MM. (**C**) Western blot analysis of the expression of characteristic proteins in macrophages, MM, and MMD. (**D**) CLSM images of RAW 264.7, L929, 4T1, and A549 cells after MMD treatment for 4 h. MMD, red; phalloidin immunostaining, green; DAPI, blue. (**E**) Flow cytometric profiles of the MMD-treated cells for 4 h. (**F**) ICP-MS analysis of zinc (Zn) after MMD or MD co-incubation with RAW 264.7, L929, 4T1, or A549 cells for 4 h. MM, Macrophages membranes; MD, MOF/pDNA; MMD, Macrophages membranes/MOF/pDNA. Reprinted with permission from Cao H, Gao Y, Jia H et al. Macrophage-membrane-camouflaged nonviral gene vectors for the treatment of multidrug-resistant bacterial sepsis. *Nano Lett.* 2022;22(19):7882–7891.[121] Copyright 2022 American Chemical Society.

been widely utilized in cell membranes camouflaged nanoparticles.[125,126] MSCs express a variety of chemokine and cytokine receptors such as CXCR1, CXCR2, CCR1, CCR2, thereby mesenchymal stem cells membranes camouflaged nanoparticles (MSCMCNPs) trend to the inflammatory site.[127] Hitherto, MSCMCNPs have been applied in acute myocardial infarction,[128] hematological diseases[129] and bone tissue repair.[130] Yao et al assembled a stem cell membranes camouflaged nanocomplex to deliver miRNA.[131] They first loaded miRNA with mesoporous silica nanoparticles and then wrapped them with mesenchymal stem cell membranes. This approach enabled efficient loading of miRNA and protected miRNA from degradation. The MSCMCNPs can evade the clearance of the immunologic system, and target ischemic injured cardiomyocytes as well.

MSCs demonstrate strong affinity for the tumor tissue through the binding of chemokine receptors and endothelial adhesion molecules, such as CXCR4.[132] Leveraging this natural tumor-targeting ability, MSCs have been used to fabricate cell membranes camouflaged nanoparticles in cancer gene therapy. Yang et al developed a style of biomimetic zeolitic imidazolate framework-8 based on mesenchymal stem cell membranes camouflaged nanoparticles which can deliver so-called "biological bombs" carrying HSV-I thymidine kinase-encoded plasmids and ganciclovir to treat lung

Table 2 Applications of MSCMCNPs in Nucleic Acid Delivery

Nanoparticles	Nucleic Acid	Disease	References
Lipidoid	Cas9/sgIL1 complex	Acute myeloid leukemia	[129]
MSN	miRNA-21	Myocardial infarction injury	[131]
PDA	PD-L1 siRNA	Prostatic cancer	[49]
PLGA	SUR siRNA	Osteosarcoma	[75]
MOF	HSVtK pDNA	Lung cancer	[133]
Fe_3O_4@PDA	PLK1 siRNA	Prostatic cancer	[134]

cancer.[133] The biomimetic MSCMNPs showed enhanced circulation time and drug accumulation in the tumor tissues thus significantly inhibited the tumors. Inspired by the multifunction of MSCs, MSCMCNPs had deliver nucleic acid for diseases therapy (Table 2).

Cancer Cell Membranes Camouflaged Nanoparticles (CCMCNPs)

Tumor cells utilize various adhesion molecules such as N-cadherin, epithelial cell adhesion molecules, and galactoagglutinin-3 to promote cell aggregation.[135,136] Tumor cells can proliferate indefinitely, and their biomimetic nanoparticles have homologous targeting.[137] Many works proved that the cell membrane derived from the cancer cells could be used to camouflage the nucleic acid-loaded nanoparticles, which improved the stability, circulation lifetime, and specificity of the nanoparticles for the effective and precise delivery of nucleic acids.[138–140] Fang et al found that cancer cell camouflaged nanoparticles had approximately 40-fold and 20-fold increases in uptake compared with erythrocytes camouflaged nanoparticles and bare nanoparticles cores, respectively.[141] Zhang et al designed cancer cell membranes camouflaged nanoparticles (CCMNPs) for homotypic siRNA targeting delivery.[142] In their study, a core composed of polymer poly (β-amino ester) loaded with siRNA targeting PLK1 was camouflaged with NCI-H1299 lung cancer cell membranes by extrusion. Owing to the homologous binding adhesion molecules on cancer cell membranes, the CCMNPs showed effective targeting of cancer cells and knocked down PLK1 expression of cancer cells, thereby inhibiting cancer.

The researchers have also explored modification strategies on cancer cell membranes to achieve co-targeting or better cellular uptake. Ding et al used plasma membrane extracted from the genetically engineered cells overexpressing PD1 to coat siRNA loading lipid nanoparticle for purpose of blocking the PD1/PDL1 immune inhibitory axis.[143] Liu et al coated mRNA loading nanoparticles with ApoE modified erythrocyte membranes which target to the endothelial cell of blood-brain barrier and cancer cells after evading immunocapture.[144] Park et al coated nanoparticles with engineered B16 cell membranes that express hemagglutinin (HA) protein on the surface (named HA-mRNA-NP, Figure 8A).[145] At 24 h incubation, HA-mRNA-NP permeated the cytosol, and escaped from endo/lysosomal indicated by attenuated LysoTracker signal (Figure 8B). HA binded to the sialic acid on the lysosome membranes, facilitating escaping from lysosome through membrane fusion. This approach led to high CLuc fluorescence in cells and tumor-bearing mice (Figure 8C and D). Besides, the camouflage with cancer cell-derived membranes endows the nanoparticles with improved stability and enhanced specificity in vitro and in vivo, which not only protects the nucleic acids, but also improves the cellular uptake in the homogeneous cancer cell lines.

Hybrid Membranes Camouflaged Nanoparticles (HMCNPs)

Most of cell membranes camouflaged nanoparticles have utilized a single type of cell membrane, but sometimes this is challenging to meet the complex therapeutic needs. Researchers have developed innovatively biomimetic nanoparticles by mixing two different types of cell membranes to achieve diverse characteristics (Table 3). Gong et al isolated membranes from RAW264.7 macrophage and 4T1 cancer cells, and then fused them by sonication.[146] After further camouflaged with the siRNA-loaded nanoparticles using a water bath sonicator, the hybrid membranes camouflaged

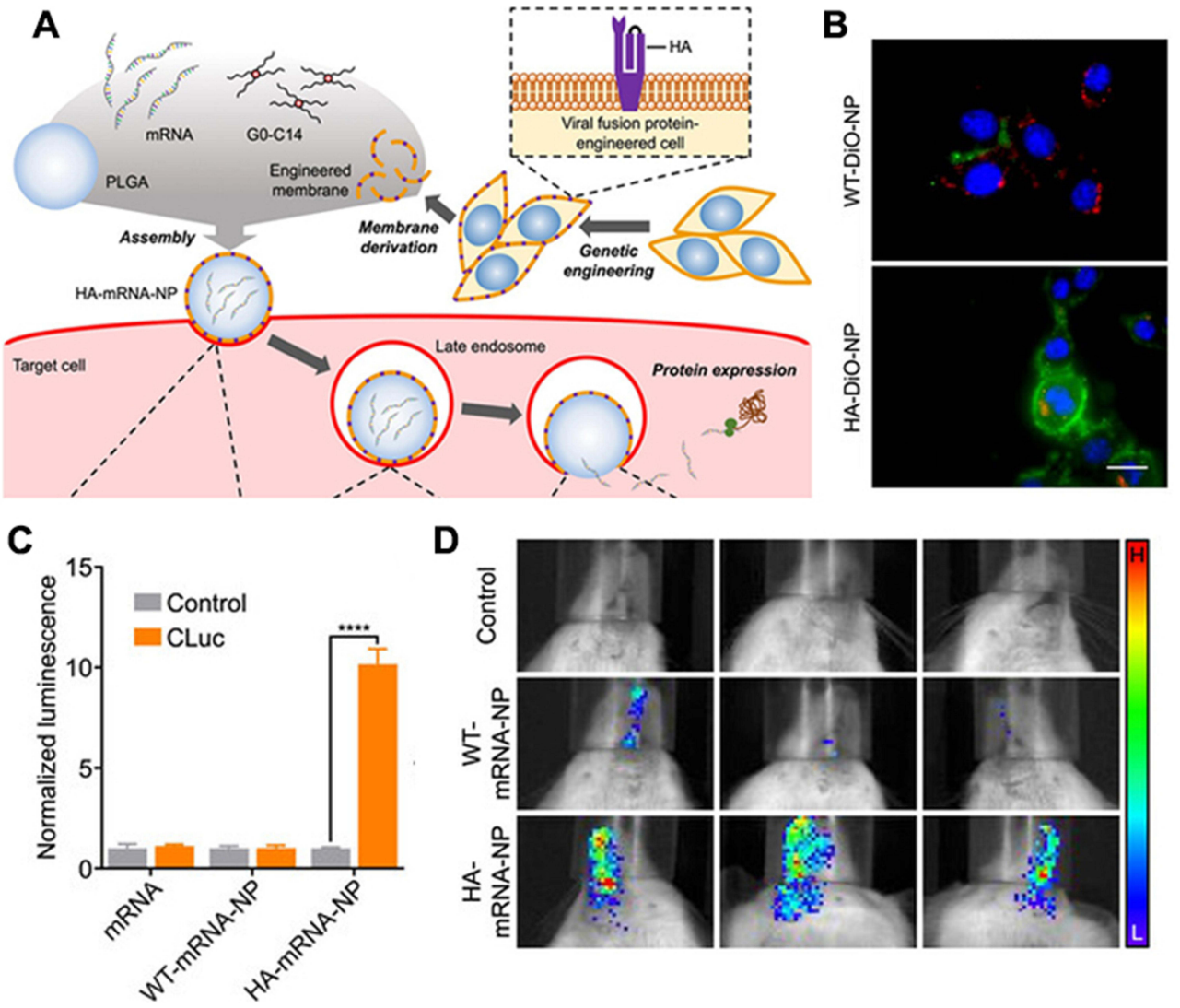


Figure 8 Targeting ability of HA-mRNA-NP in vitro and vivo. (**A**) Preparation and intracellular activity of HA-mRNA-NP. (**B**) Fluorescent visualization of B16-WT cells incubated with WT-DiO-NP and HA-DiO-NP for 24 h (blue: nuclei, red: endosomes, green: nanoparticles). (**C**) CLuc fluorescence of B16-WT cells after incubated with WT-mRNA-NP or HA-mRNA-NP. ****P < 0.0001. (**D**) Visualization of bioluminescent signal from mice intranasally administered with WT-mRNA-NP or HA-mRNA-NP loaded with CLuc mRNA. Reprinted with permission from Park JH, Mohapatra A, Zhou J et al. Virus-mimicking cell membrane-coated nanoparticles for cytosolic delivery of mRNA. *Angew Chem Int Ed*. 2022;61(2):e202113671. doi:10.1002/anie.202113671.[145] Copyright 2023 John Wiley & Sons, Inc.

nanoparticles (HMCNPs) exhibited multi-targeting capability towards both cancer cells and tumor-associated macrophages in vivo.

Exosome Membranes Camouflaged Nanoparticles (EMCNPs)

Exosomes are extracellular vesicles secreted by cells, existing in various body fluids such as blood, urine, and amniotic fluid.[154] Exosomes not only share similar proteins with source cells, but also express markers such as CD9, CD63, TSG101, ALIX.[155] Exosome membranes contain a variety of transmembrane proteins, lipid anchoring proteins, and ligands, which promote either adhesion or targeting.[156] Besides, exosomes rely on matrix stress and aquaporin-1 to achieve free diffusion and rapid transport in confined environments.[157] Exosome membranes camouflaged nanoparticles (EMCNPs) have been extensively studied and emerged as a type of excellent drug carriers. Compared with other types of cell membranes camouflaged nanoparticles, EMCNPs show improved biocompatibility, low immunogenicity, and prolonged circulation time. EMCNPs demonstrate homologous targeting ability depending on source cells and enhanced cellular uptake through receptor-mediated endocytosis, pinocytosis, or membrane fusion. Furthermore, exosomes are

Table 3 Hybrid Membranes Camouflaged Nanoparticles Applied for Nucleic Acid Delivery

Cell Membranes Sources	Nanoparticles	Mice Model	Effects	References
SW1990 cells and RAW 264.7	β-CD based nanoparticles	SW1990 pancreatic tumor, patient-derived xenograft tumor	Immune escape, homotypic targeting	[147]
MC38 cells and M1 macrophages	Nano-ZnO	Murine colon adenocarcinoma MC38 tumor	Immune escape, homotypic targeting	[148]
Platelets and RAW 264.7	Polypeptides	Ischemia reperfusion injury	Inflammation homing, microthrombus targeting	[149]
PCa cells and MSCs	Lipoic acid micelles	Bone metastatic castration-resistant prostate cancer	Bone targeting, homotypic targeting	[150]
ID8 cells and bone marrow dendritic cells	PLGA	OC subcutaneous tumor, patient-derived xenograft tumor	Immunogenicity, antigen presenting	[151]
J774.A.1 and U87 glioblastoma cells	ZIF-8	Glioblastoma tumor	Blood brain barrier penetration, homologous targeting	[152]
HEK 293T cells, HeLa cells, and HepG2 cells	PEI	-	Lower cytotoxicity, homologous targeting	[153]

convenient to be engineered as expected through the advanced genetic engineering and molecular biology technology, which endows the exosomes with improved surface functions or enhanced specificity. These approaches are reasonable to be considered as the alternatives to deliver nucleic acids.

EMCNPs not only improve the biocompatibility of nanoparticles, but also enlarge the utility of exosomes, showing great potential for nucleic acid delivery. Although exosomes can encapsulate nucleic acid, the low loading efficiency limits the applications. Roerig et al mixed extracellular vesicles with siRNA loaded calcium phosphate nanoparticles to improve both siRNA encapsulation efficiency and loading efficiency.[158] Zhupanyn et al used extracellular vesicles to modify the PEI/siRNA complexes prior to incubation and ultrasound bath at room temperature.[159] Extracellular vesicles from different cell lines increased the transfection efficiency of modified PEI/siRNA complexes. Interestingly, their cross-over experiments found a more general improvement of complex properties upon modification with certain ECVs rather than cell line specificity targeted delivery. Inspired by this, we developed a type of EMCNPs called internally and externally engineered exosomes (I3E), which was consisted of Poly-β amino ester (PBAE) nanoparticles and camouflaged with HEK 293T exosome membranes engineered to display TAM-specific peptides on their surface (Figure 9A).[160] I3E was able to load clustered regularly interspaced short palindromic repeats interference (CRISPRi)-encoded plasmid, selectively home to tumor tissues (Figure 9B), and target M2 tumor-associated macrophages by retinoid X receptor β (Figure 9C).[161] This type of engineered exosomes resulted in significant repression of PI3Kγ expression and induced the TAMs polarizing to M1 phenotype both in vitro and in vivo (Figure 9D). Our work developed a type of engineered exosomes based on the CRISPR/Cas9 knock-in technology, which produced the exosomes modified with targeting ligands as expected, and enhanced the specificity and surface functions beneficial for nucleic acid delivery.

EMCNPs also have been used to co-deliver nucleic acid and chemical drugs. Han et al designed a type of cascade EMCNPs (S+G@ELP) by fusing M1 macrophage exosomes with photothermal-sensitive liposomes to efficiently co-deliver inhibitor and siRNA.[162] The S+G@ELP nanoparticles are multifunctional membranes camouflaged nanoparticles. They not only retained the advantages of M1 exosomes such as tumor-specific targeting, macrophage polarization, and immune evasion, but also provide cascade targeting to tumors combined with photothermal therapy through stimulating the expression of VCAM-1 in tumor tissue.

The bioinspired nanoparticles constructed with exosome membranes shows great potential in carrying nucleic acids, which opens a new avenue for the design of nucleic acid carriers for the complex environments.

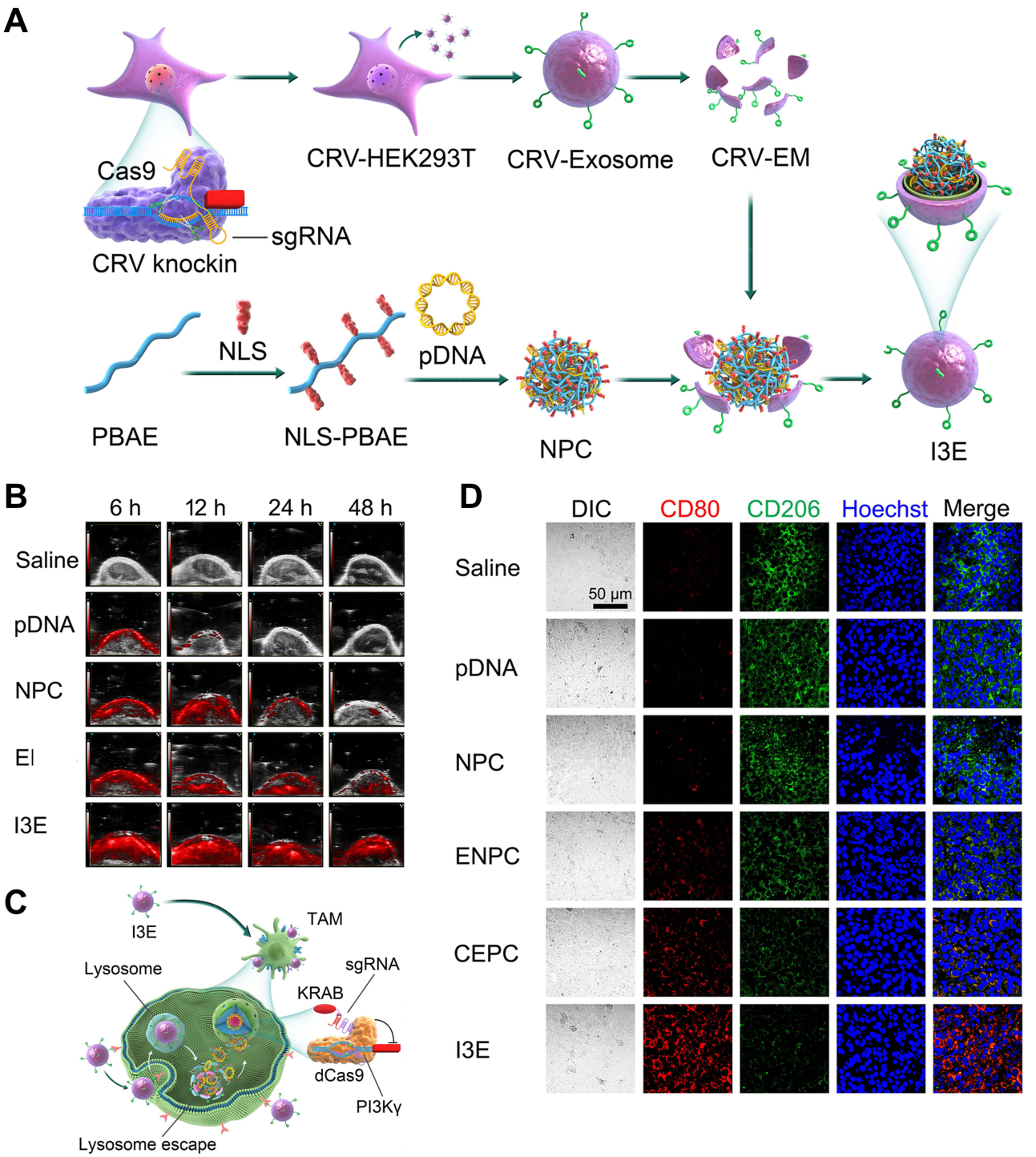


Figure 9 Design and biological effects of I3E in vivo. (**A**) Scheme of I3E preparation. (**B**) PA image of I3E in tumor. (**C**) Scheme of tumor associated macrophages reprogramming by I3E in situ. (**D**) Tumor associated macrophages reprogramming effect of I3E in vivo. Reprinted with permission from Zhang L, Lin Y, Li S, Guan X, Jiang X. In situ reprogramming of tumor-associated macrophages with internally and externally engineered exosomes. *Angew Chem Int Ed*. 2023;62(11): e202217089.[160] Copyright 2023 John Wiley & Sons, Inc.

Challenges and Prospects for Nucleic Acid Delivery by Cell Membrane-Camouflaged Nanoparticles

Overall, the approaches for nucleic acid delivery by cell membrane-camouflaged are diverse and versatile and can be tailored for specific therapeutic purposes. This technology holds great promise in the field of gene therapy, and ongoing

research is expected to lead to significant advancements in the development of safer and more effective gene therapies. Meanwhile, several challenges need to be addressed to fully harness the potential of cell membrane camouflaged nanoparticles for nucleic acid delivery.

One of these challenges is the variability of the cell membrane source, which can impact the properties of the nanoparticles. The choice of cell type affects the targeting ability, biocompatibility, and immunogenicity of the CMCNPs. Moreover, the variability in membrane protein composition influences the stability and activity of the encapsulated nucleic acids. Thus, methods of membrane extraction should be carefully considered to ensure compatibility with diverse cell types while preserving the activity of membrane proteins. The current technology is primarily suitable for preclinical research, and scaling up for industrial production is still challenging.

Secondly, the present work usually ignored the evaluations on the coating quality and the effects on the nucleic acid induced by the production procedure. The procedures are associated the exact dosage and the integrality of nucleic acids within the nanoparticles, which was critically important for the future applications. The comprehensive analysis of the coating quality and the effects on the nucleic acid will improve the technology on nucleic acid delivery greatly.

Another challenge is the potential immunogenicity of the delivery system. Although all cell membranes consist of lipids and proteins, the exact composition can vary among different cell types. This variation may trigger immune responses and lead to the formation of anti-nanoparticle antibodies, which limit the effectiveness of CMCNPs in subsequent treatments. Additionally, the immune response can cause inflammation and tissue damage, which is detrimental to overall health.

Furthermore, it is crucial to thoroughly evaluate the long-term safety and effects of CMCNPs. Minimizing potential toxicity and off-target effects is essential to mitigate harm to patients. Rigorous evaluation and optimization of CMCNPs are necessary to ensure their safety and effectiveness in any clinical applications in the future.

Despite these challenges, the field of cell membranes camouflaged nanoparticles for nucleic acid delivery is exciting and rapidly evolving which holds great promise for gene therapy. Ongoing research and technological developments are expected to lead to significant breakthroughs in the development of efficient and safe nucleic acid delivery systems. With continued efforts, it is anticipated that these innovative approaches will revolutionize gene therapy and provide effective treatments for various diseases.

Conclusion

The delivery of nucleic acids with non-viral vehicles currently encountered many challenges. Bioinspired technology has emerged as a promising solution to address issues related to circulation lifetime, specificity, and safety. In this review, we summarized the development and applications of cell membrane-camouflaged nanoparticles in the field of nucleic acid delivery and outlooked their potential developments. Natural cell-derived membranes, including those from erythrocytes, platelets, macrophages, mesenchymal stem cells, cancer cells, and exosomes, have been utilized to camouflage the nucleic acid-loaded structures. These cell membranes derived from different cell types offer diverse capabilities, which may be useful for clinical applications.

Abbreviations

siRNA, small interfering RNA; CMCNPs, Cell membranes camouflaged nanoparticles; EMCNPs, Erythrocytes membranes camouflaged nanoparticles; PMCNPs, Platelet membranes camouflaged nanoparticles; MMCNPs, Macrophages membranes camouflaged nanoparticles; MSCs, Mesenchymal stem cells; MSCMCNPs, Mesenchymal stem cells membranes camouflaged nanoparticles; CCMCNPs, Cancer cell membranes camouflaged nanoparticles; HMCNPs, Hybrid cell membranes camouflaged nanoparticles; EMCNPs, Exosome membranes camouflaged nanoparticles.

Acknowledgments

We appreciated the National Natural Science Foundation of China (82070406, 82072047, and 82170008), Research Foundation of Education Bureau of Guangdong Province (2021ZDZX2004), Guangdong Province Postgraduate Education Innovation Plan Project (2022SFKC054), and The Open research funds from The Sixth Affiliated Hospital of Guangzhou Medical University (Qingyuan People's Hospital, 202201-303). We thank for the help from BioRender.com for drawing illustration.

Disclosure

The authors declare that there are no competing interests.

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