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REVIEW

Application of Biomimetic Cell Membrane-Coated Nanocarriers in Cardiovascular Diseases

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Abstract: Biomimetic cell membrane-coated nanocarriers have gained attention as an innovative therapeutic strategy for cardiovascular diseases (CVDs) due to their capacity to mimic natural cellular architectures. This distinctive characteristic improves biocompatibility, enables evasion of immune surveillance, and promotes targeted drug delivery to specific disease sites. By harnessing cell membrane components from sources such as red blood cells, platelets, and immune cells, these nanocarriers can transport therapeutic agents directly to pathological areas, including atherosclerotic lesions, ischemic myocardial tissue, and injured vasculature. This review highlights recent progress in the development of cell membrane-coated nanocarriers for CVD treatment, focusing on their design, mechanisms of action, and preclinical therapeutic potential. Additionally, it examines key challenges to clinical application, including such as production scalability, structural stability, and regulatory challenges, while proposing strategies to overcome these limitations. The advancement of these biomimetic nanocarriers marks a promising direction in cardiovascular medicine, offering the possibility of more efficient and less invasive therapies for CVD patients.

Keywords: biomimetic nanocarriers, cell membrane coating, cardiovascular disease, targeted drug delivery, immune evasion, preclinical studies, clinical translation, therapeutic nanotechnology

Introduction

Nanoparticles (NPs), which are microscopic materials typically sized between 1–1,000 nanometers, possess unique physical and chemical properties. These properties make NPs particular valuable in biomedicine, especially in drug delivery systems.[1] Over the past decade, targeted therapy has become a major driving force in drug delivery, addressing the limitations of traditional formulations in solubility, sustained release, and tissue-specific targeting.[2] Nanotechnology plays a crucial role in revolutionizing drug design, with nanoparticles (NPs) emerging as a key innovation at the forefront of these advancements. NPs offer high drug payload, versatile distribution characteristics, and specialized functionalities. These features can enhance solubility, stability, and bioavailability, and as a result, enable more efficient targeted delivery.[3] Among the various NPs, common ones include lipid nanoparticles, polymer nanoparticles, and inorganic nanoparticles. Each of these types exhibits valuable pharmacokinetic properties such as prolonging drug half - life, improving distribution, and increasing persistence within target tissues, further demonstrating the superiority of NPs in drug delivery.[4]

The application of NPs in cardiovascular disease (CVD) treatment holds great promise. CVD, which includes chronic conditions such as atherosclerosis, myocardial ischemia, and myocardial infarction, is characterized primarily by chronic inflammation and lipid deposition.[5] Although existing treatments can alleviate symptoms, they still face challenges such as uneven drug distribution and inadequate targeting of affected areas.[6] Additionally, traditional drugs can produce non-specific effects within the cardiovascular system, potentially impacting healthy tissues and causing adverse effects.[7,8]

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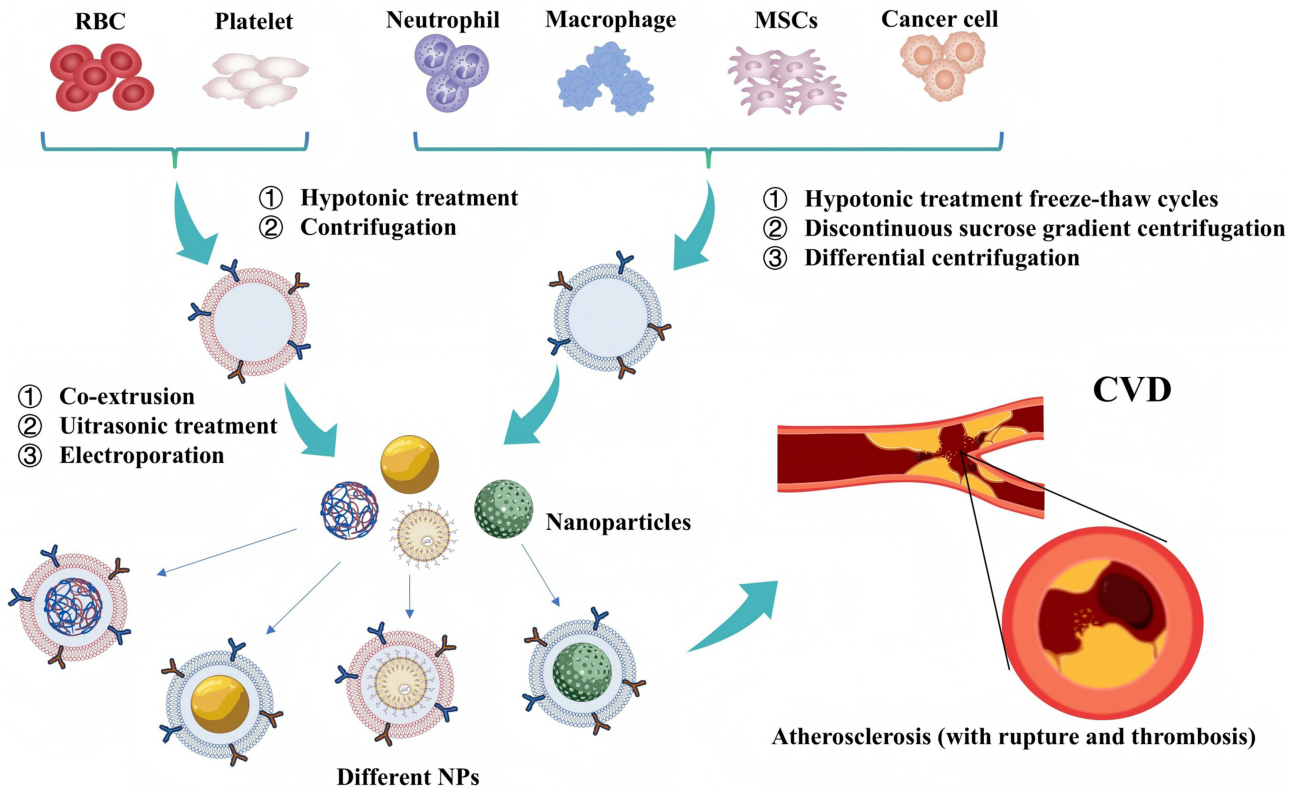
Graphical Abstract



NPs can be engineered for specifically targeting cardiovascular lesions by modifying their surface and molecular structures. For instance, studies have demonstrated that chemically modifying NPs to enhance lipophilic or hydrophilic properties can promote their accumulation in lipid - deposited regions, facilitating localized release of anti - inflammatory or lipid - lowering agents and thus improving atherosclerosis management.[9] However, despite these advantages, NPs still face notable limitations in cardiovascular drug delivery. One significant issue is their poor targeting ability. Although surface modifications can enhance targeting, traditional nanoparticles (NPs) often fall short of achieving the required targeting efficiency for optimal therapeutic outcomes. In complex cardiovascular systems, traditional NPs may not accurately distinguish diseased tissues from healthy tissues. A well - known example in the field is that reports have shown that only 0.7% of traditional NPs accumulate at the tumor site. By analogy, in the cardiovascular context, drugs carried by NPs may be distributed in non - target tissues, leading the far less effective concentration at the lesion sites. This inefficiency not only leads to drug wastage but also increases the risk of potential side effects in normal tissues. Moreover, NPs encounter physiological and cellular barriers during circulation. They are often recognized and cleared by the immune system, leading to insufficient deposition in target tissues. Additionally, the foreign nature of NPs can trigger immune responses, limiting their circulation time and complicating the efforts to achieve sustained therapeutic effects. Interactions with various protein and cell-based components, as well as clearance by the reticuloendothelial system (RES), further contribute to performance degradation.[10,11]

To address these limitations, researchers have developed biomimetic nanocarriers.[12] By encapsulating NPs with natural cell membranes—such as those from red blood cells, platelets, or macrophages—nanocarriers gain enhanced biocompatibility and immune evasion properties.[13] eg Figure 1, these biomimetic nanocarriers mimic the surface characteristics of natural cells, allowing them to evade immune recognition and extend circulation time.[14] Notably, platelet membrane-coated nanocarriers exhibit significant potential for targeting cardiovascular lesions, as they can

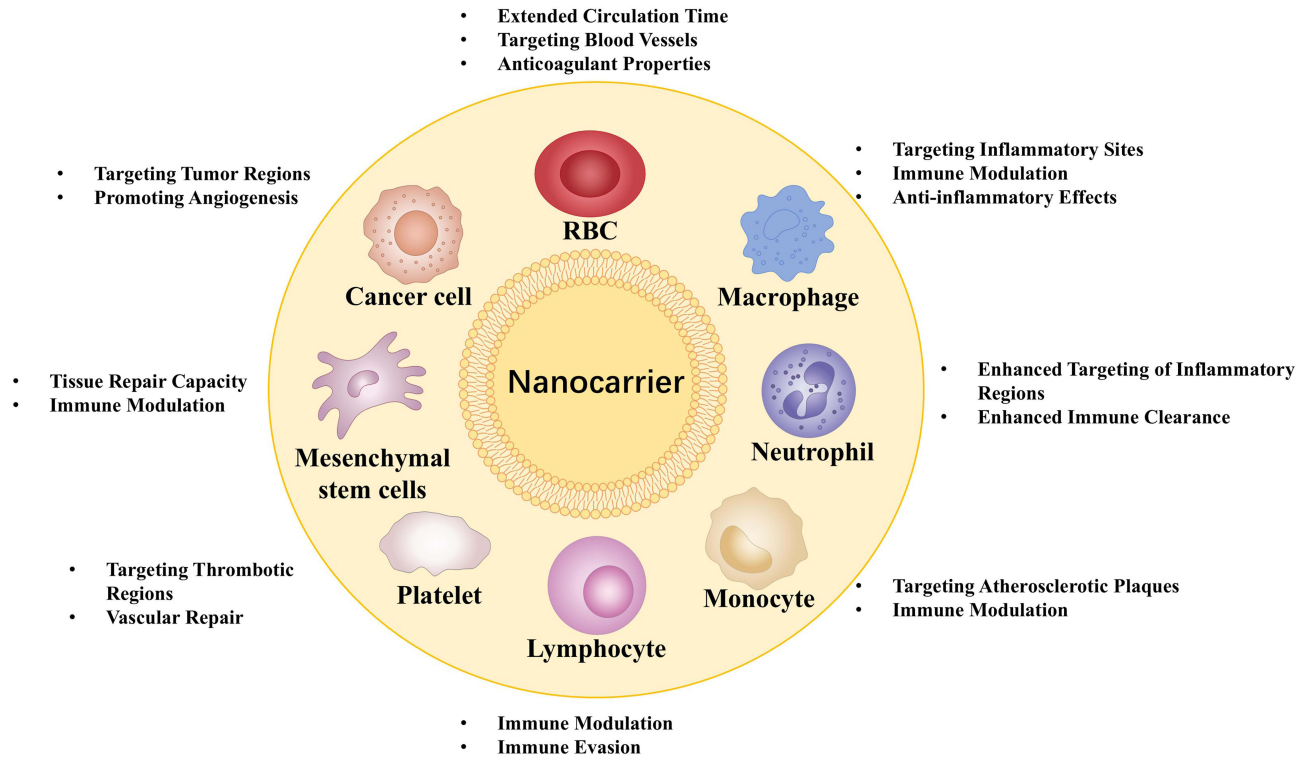


Figure 1 Different kinds of cell membranes and their characteristics.

specifically recognize damaged endothelial cells in plaque and thrombus regions.[15] Similarly, red blood cell membrane-coated nanocarriers offer prolonged circulation times and reduced immunogenicity, further highlight their potential for cardiovascular targeting.[16] Therefore, this review focuses on the introduction of various biomimetic cell membrane-coated nanocarriers and their applications in the field of cardiovascular disease therapy.

Design of Biomimetic Cell Membrane-Coated Nanocarriers

In recent decades, significant advances in nanotechnology have facilitated substantial progress in addressing CVD. Nanoparticles offer several advantages in the treatment of these conditions, notably their enhanced targeting capabilities, which enable precise drug delivery.[17] This precision improves therapeutic efficacy while minimizing adverse reactions. Several types of nanocarriers, including liposomes, polycaprolactone (PCL), polylactic acid (PLA), nanocrystals, iron oxide nanoparticles, albumin nanoparticles, and poly(D,L-lactic acid-glycolic acid) (PLGA), have already been approved by the US Food and Drug Administration (FDA) for clinical use.[18,19] These platforms show great promise for applications in CVD diagnosis and treatment. A summary of current nanoparticle classifications is presented, including inorganic nanoparticles, carbon-based nanoparticles, lipid nanoparticles, polymer nanoparticles, and biomimetic nanoparticles (Table 1).[20]

Despite their potential, NPs still face several challenges in the treatment of CVDs, including poor pharmacokinetics, limited biocompatibility, and abnormal metabolism.[40] NPs may accumulate in organs such as the brain, kidneys, lungs, and spleen, potentially leading to oxidative stress, cytotoxicity, and significant tissue damage. Cytotoxicity can arise from the production of toxic polymers within the body, which have harmful effects on cells. Additionally, abnormal adhesion to non-target tissues, cells, or cellular components often occurs, that are closely linked to the size, composition, and administration route of the NPs.[41,42] Furthermore, NPs must navigate clearance by the mononuclear phagocytic system (MPS) and the reticuloendothelial system (RES), which complicates their ability to reach target sites.[43] Upon entering the body, NPs typically bind to proteins, facilitating recognition by phagocytes and clearance by the MPS and RES, thereby limiting their distribution and delivery.[44] To overcome these challenges, surface modification with polyethylene glycol

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Table 1 The Application Progress of Nanocarrier Technology in Cardiovascular Disease Treatment was Summarized

Category	Types	Advantages	Drawbacks	Effect
Inorganic NPs	Gold	Biocompatibility, physicochemical stability, good drug loading capacity	Toxicity issues, low degradability	Enhanced cardiac performance, reduced inflammation, improved cardiac electrical function
	Silica	Controllable porosity, large surface area, biodegradability	Genotoxicity, time-consuming, aggregation	NPs Accumulation in the heart ischemic regions
	Iron oxide	Colloidal stability, eco-friendliness, low toxicity, easy synthesis	Poor dispersion, cost of scale-up production, complex preparation process	The accumulation of inflammatory cells in the myocardium, followed by subsequent observation of myocardial inflammation
	Silver	Biocompatible, stable, efficient loading	Cytotoxicity	Decreased thrombosis, increased thrombolysis
Lipid NPs	Liposome	High solubility, biocompatibility, biodegradability, can load hydrophilic and lipophilic drugs	Poor stability, easy to occur drug leakage	Reduced infarct size, enhanced cardiac parameters performance, diminished fibrosis
	Lipidoid NPs	High biocompatibility and biodegradability, capable of payload different types of drugs	Strong dependence on lipids may lead to particle instability	Reduced levels of low-density lipoprotein cholesterol
Polymeric NPs	PLGA NPs	High biocompatibility and biodegradability, high drug load and controllable release rate	The drug load is sometimes low and may cause an allergic reaction	Enhance ventricular remodeling and reduce infarct size
	Polyketal NPs	It has anti-inflammatory and antioxidant effects and is suitable for long-term use	Complex synthetic process and possible cytotoxicity	Enhance heart function
	Polymeric (PEI) NPs	High loading capacity and good targeting ability, the surface of the compound can be modified and customized	May cause immunotoxicity and cytotoxicity, difficult to control release properties	Reduced necrotic core and plaque area
	Polymeric micelles (PGMA-PS)	Modifiable, good biocompatibility, small size, can effectively target the lesion	Poor stability, may depolymerize under storage conditions	Decreased atherosclerotic plaque and thrombus length
Biomimetic NPs	Exosomes derived from mesenchymal stem cells	Reliable biological source, reduce immune rejection, has a good cell targeting ability	The source is different, the purity and homogeneity problem, the preparation is complicated	Reduce local and systemic inflammation and enhance biocompatibility
	Exosomes (cardiosphere derived)	Excellent targeting capability and biocompatibility	There may be difficulties in extraction and purification	Reduces local and systemic inflammation, reduces intrastent restenosis, and improves biocompatibility
	Copolymer micelles coated with red blood cell membrane	Improved targeting and biocompatibility, dual functionality, anti-inflammatory action, improved drug delivery	Complex manufacturing process, limited drug loading, potential immune responses, stability issues	Diminished inflammation within the plaque and facilitated visualization of its accumulation
	Platelet derived nanovesicles	Enhanced targeting, improved cardiac function, reduced inflammation, biocompatibility	Production challenges, limited long-term stability, potential risk of thrombosis	Enhanced cardiac function and reduce infarct size

Note: Data from these studies.[21–39]

(PEG) is commonly used to help NPs evade immune system recognition and clearance.[45] More recently, biomimetic approaches have been developed, utilizing targeted ligands on NP surfaces to enhance delivery. Strategies such as conjugating antibodies, peptides, aptamers, or other small molecules to NPs, alongside the use of naturally derived biomimetic NPs like ferritin cages, recombinant high-density lipoprotein (rHDL) particles, and albumin-based carriers, have been explored.[46] Despite their potential, these approaches face challenges, including susceptibility to rapid degradation, high production costs, and low production efficiency.[47] Consequently, biomimetic nanocarriers with cell membrane camouflage have gained more interest for their biologically derived surfaces, superior biocompatibility, and improved safety profile.[48] Over the past ten years, significant progress has been made in this field, with applications spanning various cell types, offering substantial potential for future therapeutic innovations.

Basic Principles of Biomimetic Cell Membrane-Coated Nanocarriers

Integrating NPs with natural biofilms offers a promising solution to address the challenges associated with conventional nanomaterials.[49] The biomimetic approach of cell membrane camouflage involves coating nanoparticles with natural cell membranes, endowing them with functionalities that mimic biological systems such as immune evasion, precise targeting, and improved biocompatibility.[50] These features collectively enhance targeted drug delivery and therapeutic efficacy.[51] The foundation of this strategy lies in several key aspects:

1. Choice of Source Cell Membrane: The success of cell membrane camouflage depends on selecting an appropriate source cell membrane. Different cell membranes offer distinct biological properties.[52] For example, RBC membrane-camouflaged NPs exhibit strong immune evasion and are suitable for prolonging circulation time in the body.[53] Platelet membrane-camouflaged NPs enable immune evasion and facilitate adhesion to injury sites.[54] Membranes from immune cells, such as macrophages or T-cells, can direct NPs to inflammatory or infection sites.[55]
2. Mechanism of Membrane Camouflage: Biomimetic nanocarriers are enveloped with membranes derived from source cells, displaying characteristic proteins and lipids on their outer layer.[9] This coating is achieved through various physical or chemical techniques, ensuring that the nanocarriers retain the biological markers of the original cells. The proteins, glycoproteins, and lipids present on the membrane enable these nanocarriers to identify and bind to specific targets within the body, facilitating targeted interactions.[56]
3. Biomimetic Function: Cell membrane camouflage endow nanocarriers with cell-like biological properties, enabling them to evade immune recognition and avoid clearance.[57] For example, the CD47 protein, present on red blood cell membranes, serves as a "don't eat me" signal, effectively minimizing phagocytosis by macrophages.[58] Additionally, certain membrane proteins, such as those derived from cancer cells, exhibit targeting capabilities that enhance the accumulation of nanocarriers at pathological sites, thereby improving the precision of drug delivery.[59] This biomimetic strategy also enhances the biocompatibility of nanocarriers, mitigating adverse reactions linked to the surface properties of nanomaterials and significantly improving their biosafety.[60]
4. Preparation Method: The preparation of biomimetic nanocarriers with cell membrane camouflage typically involves three steps: extraction of the cell membrane, preparation of the nanoparticle, and fusion of the cell membrane with the nanoparticle.[61] The cell membrane can be isolated using physical or chemical methods, then fused with pre-formed nanoparticles through techniques such as ultrasound, extrusion, or physical mixing and incubation.[62] The resulting membrane-coated nanocarriers maintain the structure and function of the cell membrane, making them more effective in disease models.

Recent reviews have emphasized the application of diverse membrane-derived nanomaterials in CVD therapy, such as membranes from erythrocytes, platelets, macrophages, neutrophils, and mesenchymal stem cells.[63] Ongoing research continues to explore other cell membrane sources to identify new possibilities for better therapeutic use.

Modification of Biomimetic Cell Membrane-Coated Nanocarriers

With the continuous advancement of medicine and materials science, biomimetic nanocarriers camouflaged with cell membranes have become increasingly prevalent. Proteins and lipids present on biological membranes play a crucial role in regulating NP activity, and functionalizing these membranes can further modify the properties of the coated NPs.[64] Typically, cell membrane modifications can be categorized into three primary types, As shown in Figure 2.

(1) Physical modification, also referred to as physical membrane engineering, taking advantage of the fluid properties of lipid membranes. This method incorporates specific ligands, receptors, or other molecules through lipid-lipid interactions or merging lipid vesicles that carry target molecules with the cell membrane. As one of the simplest strategies for modifying carriers, it is widely used in this area.

Cell membrane physical engineering leverage the fluidity of lipid membranes to naturally attach specific ligands to the cell surface through various lipid-based techniques. By inserting the hydrophobic portion of a lipid bilayer, along with therapeutic agents, into the outer layer of another lipid bilayer, therapeutic cell membranes can be engineered. Additionally, adding external receptors to the cell membrane allows for the attachment of molecules like probe ligands and drugs. Another effective method is merging lipid vesicles containing desired molecules with the cell membrane. To improve the encapsulation and release of small molecules, proteins can be modified with glycolipids such as glycosylphosphatidylinositol. These glycolipids can attach to the outer layer of the cell membrane, and when loaded into liposomes, they enable fusion with cell-membrane-based vesicles.[65] For example, the chemotherapy drug DOX and the antibiotic vancomycin were encapsulated in red blood cell membrane-derived vesicles, creating a pH-sensitive drug delivery system. Red blood cell (RBC) membrane-derived vesicles are prepared by

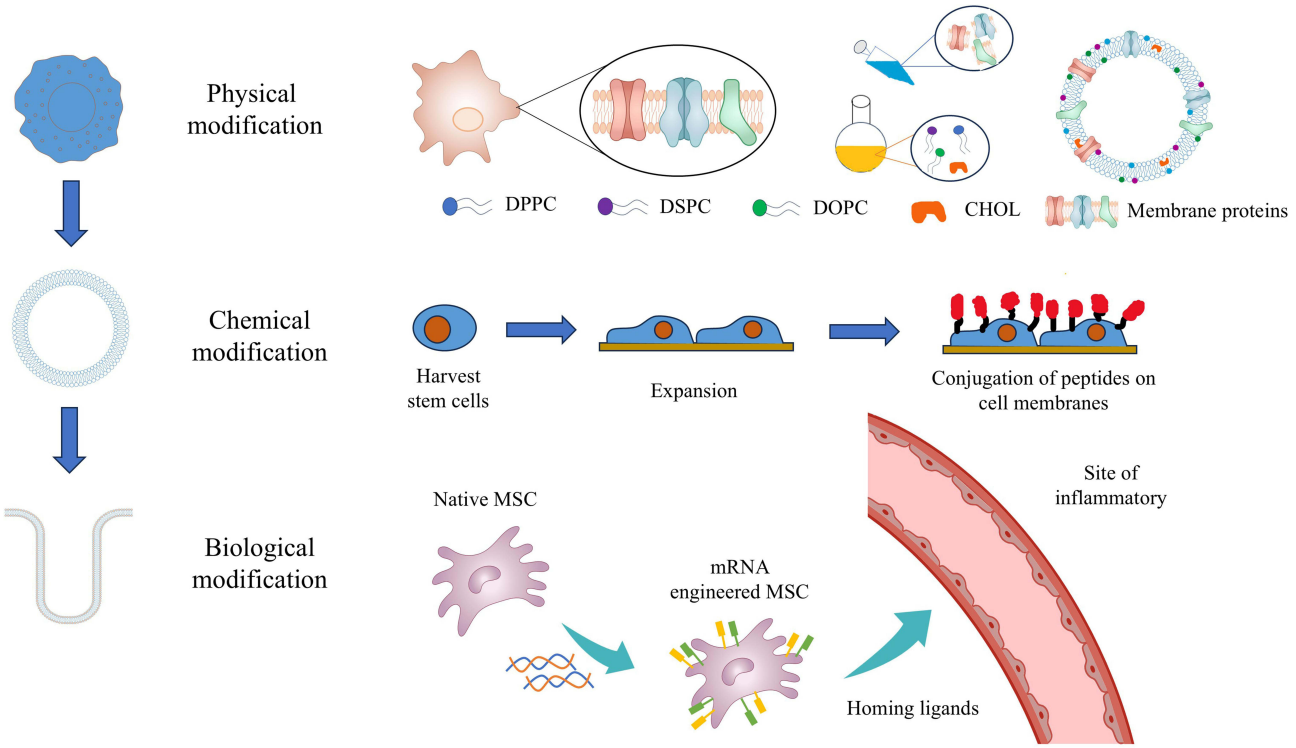

Figure 2 Three common methods to modify stem cell membranes.

hypotonic lysis and centrifugation to isolate and purify the RBC membranes, followed by extrusion through polycarbonate membranes to form uniform vesicles. For drug encapsulation, DOX is loaded using a pH-gradient method, where a pH gradient is established between the interior (acidified with citrate buffer, pH 4.0) and exterior of the vesicles to drive DOX uptake, while vancomycin is encapsulated via passive loading. Adding exogenous cholesterol to the formulation helped maintain a stable pH gradient and increased the overall drug-loading capacity. Exogenous cholesterol is incorporated into the lipid bilayer during the extrusion process, increasing membrane rigidity and improving drug retention.[66] Previous research has also used lipid-insertion techniques to develop recombinant foreign proteins, improving the targeting ability of membrane-based systems.[67] Specifically, lipid-insertion techniques, such as conjugating recombinant proteins with lipid anchors like glycosylphosphatidylinositol (GPI), enable the anchoring of targeting ligands onto the vesicle surface, further enhancing the targeting capability and functionality of the system. These approaches collectively optimize the design of cell membrane-derived vesicles for efficient and targeted drug delivery, leveraging the natural properties of lipid membranes and advanced engineering strategies.

Cell membranes, mainly made up of lipids with natural fluidity, allow lipid-based biomaterials to either attach to the membrane surface or be enveloped by it. Liposomes combined with cell-membrane-coated nanoparticles can enhance the integration of ligands or drugs within the membrane. For instance, liposomes can be fused with components rich in leukocyte membrane proteins to create new nanovesicles. These newly formed nanovesicles, containing transmembrane proteins like CD45, CD47, and PSGL-1, can effectively target inflamed areas and easily cross inflamed vascular barriers. Although physical modification of cell-membrane-coated nanoparticles is convenient and widely used, its limitations, such as insufficient stability and production efficiency, should not be ignored. Hydrophobic interactions may risk altering the original membrane structure, and serum proteins can impact the insertion efficiency.

(2) Chemical modification is a technique that aims to endow the cell membrane with new functionalities while preserving its biological integrity. This approach primarily targets membrane - associated proteins, primary amines, thiol groups, and polysaccharide hydroxyl groups.[68]

In the field of chemical engineering, compounds with carboxyl groups can be attached to amino acids on cell membranes through amidation reactions. For instance, Wang et al showed that by labeling target cells with azide groups and applying click chemistry, the accumulation of conjugates was significantly enhanced.[69] Similarly, Zhou et al utilized NHS-PEG-maleimide as a linking agent to attach hyaluronidase to red blood cell membranes, which facilitated stable binding to the extracellular parts of erythrocyte membrane proteins.[70] These hyaluronidase-linked nanoparticles showed improved targeting and distribution towards tumor tissues, due to tumor tissues often overexpress hyaluronidase.

Chemical modification is highly practical. It can introduce new functionalities to cells without disrupting their natural biological roles. This method is also noted for its stability, simplicity, and high efficiency. A key advantage is that it typically does not change the membrane's permeability or structure. However, there is a notable downside. The lack of specificity in this method can sometimes compromise the effectiveness of natural proteins and interfere with their original functions, potentially altering the membrane's inherent biological properties. In summary, while chemical modification provides significant advantages in cell engineering, its limitations must be carefully considered to ensure more effective use.

(3) Biological modification is an advanced strategy that harnesses genetic engineering along with viral or non - viral vectors to selectively integrate specific peptides or proteins into the cell membrane. This technique holds great promise in the field of targeted delivery and therapeutic enhancement.

Genetic engineering techniques, using both viral and non-viral vectors, allow for the precise integration of specific peptides or proteins into cell surfaces. This method is widely used to incorporate fused motifs into cell membranes, enhancing targeted delivery and boosting therapeutic outcomes. For example, Sortase A can link peptides with N-terminal glycine to the cell membrane by breaking the thioester bonds in the LPETGG motif.[71] Furthermore, the CRISPR/Cas9 system, guided by specific RNA, enables precise genome editing, facilitating the addition of peptide receptors. This approach can also genetically engineer the LPXTG motif onto red blood cell membranes. Sortase A then attaches immunodominant peptides with exposed N-terminal glycine to the LPXTG motif, a strategy proven to be effective in treating autoimmune encephalomyelitis.[72]

One of the most significant advantages of biological modification is its high specificity. When combined with physical or chemical modification techniques, it can lead to more precise engineering of cell membranes, enhancing targeted delivery with high precision. However, this approach is not without limitations. Both viral and non - viral vectors used in biological modification have the potential to generate uncontrolled toxicity or immunogenicity. The use of vectors may lead to cytotoxic effects, which pose potentially limiting its widespread application. In conclusion, while biological modification offers exciting prospects for targeted therapy and membrane engineering, careful consideration of its potential drawbacks is essential for its successful application.

Overall, the integration of natural cell membrane coatings with nanocarriers enhances the nanoparticles' specificity, biocompatibility, circulation time, and reduces immunogenicity. Several membrane camouflage strategies are currently employed. A single cell membrane enhances NP functionality by introducing additional functional proteins, whereas hybrid membranes combine characteristics from multiple cell types, integrating diverse biological properties into a unified biomimetic platform.[73] Nanoparticles coated with cell membranes preserve the complex biological functions of natural membranes while maintaining the advantageous physicochemical characteristics of synthetic nanoparticles, thereby increasing their circulation time in vivo.[74] For example, nanocarriers coated with RBC membranes utilize "self-markers" such as CD47 proteins, glycans, and peptides to evade macrophage-mediated phagocytosis by the RES, effectively prolonging their circulation.[75] Methods like avidin-biotin interactions and lipid insertion further enhance the functionality of RBC membranes, enabling their use in nanodevices for applications such as chemotherapy and detoxification.[76] Moreover, intelligent nanocarriers can be engineered to release drugs in response to specific internal or external stimuli, including pH changes, temperature shifts, light exposure, ultrasound, or magnetic fields. This design improves targeting precision, reduces side effects like cytotoxicity from premature drug release, and enhances therapeutic efficacy.[77]

Optimization Strategies for Biomimetic Cell Membrane-Coated Nanocarriers: Dosage, Exposure Duration, and Advanced Fabrication Techniques

The formulation of biomimetic cell membrane-coated nanocarriers for cardiovascular applications requires careful consideration of multiple interdependent parameters, with dosage optimization, exposure duration, and advanced preparation technologies representing critical determinants of therapeutic performance. Current research indicates that a tiered dosing strategy has become the gold standard for evaluating nanocarrier safety and efficacy profiles. Typical protocols employ low (50–100 μg/mL), medium (100–200 μg/mL), and high (200–500 μg/mL) dose ranges to systematically assess safety thresholds while exploring maximum therapeutic potential. For instance, studies targeting atherosclerotic plaques have demonstrated optimal results at medium doses around 150 μg/mL, achieving significant macrophage uptake enhancement without inducing apoptosis, while higher doses required for myocardial infarction therapy must be carefully balanced against potential hepatotoxicity as evidenced by elevated liver enzyme levels.

The temporal aspects of nanocarrier exposure present distinct optimization challenges across experimental systems. In vitro cellular studies typically identify optimal interaction windows between 2–24 hours, with the specific duration heavily dependent on membrane source characteristics. Platelet membrane-derived carriers exhibit peak endothelial binding within 6–8 hours, whereas mesenchymal stem cell membranes require extended 12–16 hour incubations to complete internalization due to their complex adhesion molecule repertoire. In vivo pharmacokinetic considerations further complicate exposure optimization, as demonstrated by studies showing that erythrocyte membrane-coated systems with short 2.5-hour half-lives require twice-daily administration to maintain therapeutic concentrations, while more stable formulations permit less frequent dosing schedules.

Recent technological advancements have revolutionized nanocarrier production and performance optimization. Microfluidic platforms now enable unprecedented control over nanoparticle synthesis, achieving <5% size variation and dramatically improving batch consistency - a critical factor for clinical translation.[78] The application of response surface methodology has similarly enhanced formulation development, allowing researchers to systematically optimize critical parameters like membrane coating thickness and core dimensions to push encapsulation efficiencies above 90%. Perhaps most innovatively, genome editing tools like CRISPR-Cas9 are being employed to engineer membrane components at the molecular level, with CD47 knockout strategies already demonstrating 25% reductions in phagocytic clearance. These technological innovations, when integrated with the fundamental principles of membrane selection and modification outlined earlier, create a robust framework for developing next-generation biomimetic delivery systems with precisely tuned therapeutic profiles.[79]

The continuous refinement of these formulation parameters through interdisciplinary approaches - combining pharmacological principles with cutting-edge engineering techniques - represents the forefront of cardiovascular nanomedicine development. As the field progresses, the integration of computational modeling and machine learning approaches promises to further accelerate the optimization process, potentially enabling patient-specific nanocarrier customization while maintaining the rigorous safety standards required for clinical application. This systematic, technology-driven approach to formulation development ensures that biomimetic nanocarriers can fully realize their potential as targeted therapeutic platforms for complex cardiovascular pathologies.

Preparation of Biomimetic Nanocarriers Coated with Cell Membranes

The construction of biomimetic nanoparticles coated with cell membranes typically involves three key steps: isolating and purifying the cell membrane, creating the nanoparticle core, and subsequently integrating the extracted membrane with the nanoparticle core.[80] Figure 3 shows the flowchart of this preparation process.

Cell Membrane Extraction

The phospholipid bilayer of cell membranes, rich in glycoproteins, polysaccharides, and integral membrane proteins, serves as an excellent material for crafting biomimetic coatings on NPs.[81] Utilizing pure cell membranes enhances the uniformity of the nanocarrier's surface coating while preserving the functional properties of the source cells.[82] However,

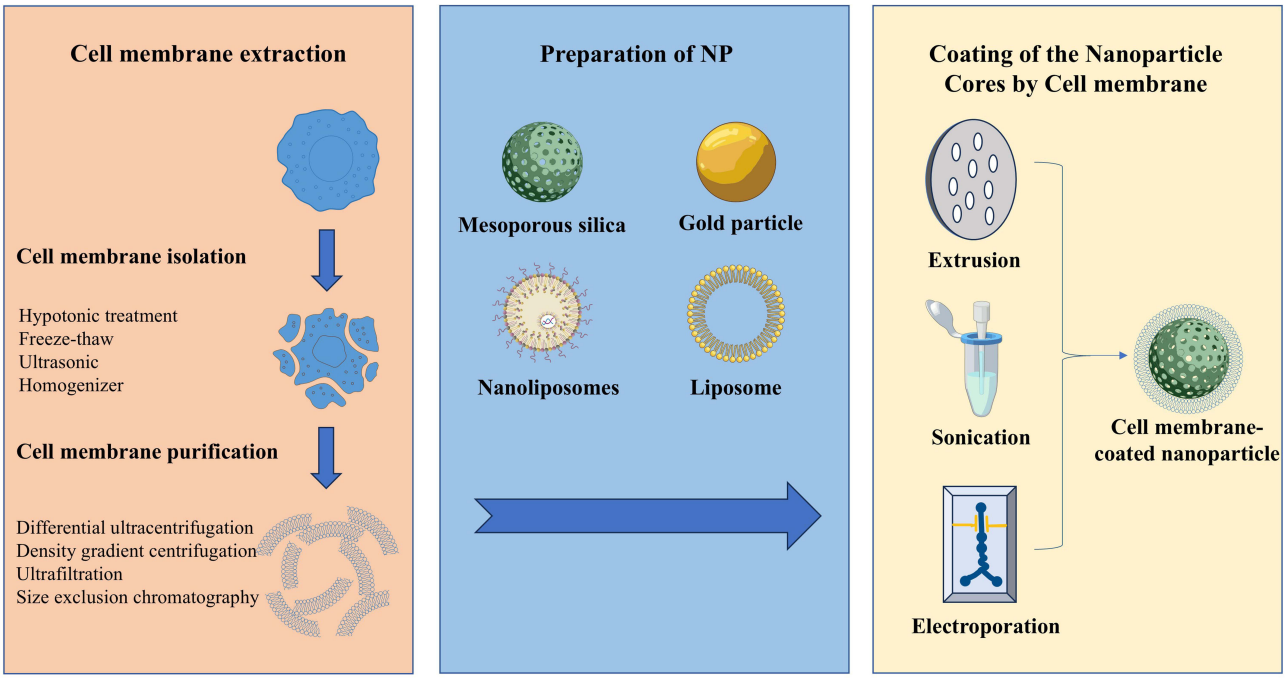

Figure 3 Schematic diagram of the preparation process for biomimetic cell membrane-coated nanocarriers.

extracting cell membranes requires careful processes, including cell lysis and purification, to avoid protein denaturation and maintain membrane integrity. Isolation involves the selective removal of cytosolic, mitochondrial, and nuclear contaminants, a process often carried out in small batches for precision.[83] Following cell lysis, high-speed gradient centrifugation is employed to separate nuclei and other unwanted components, yielding a membrane-rich fraction. The resulting fraction undergoes sonication to create membrane vesicles, which are then passed through polycarbonate membranes to generate nanovesicles.[84] Methods such as hypotonic treatment, repeated freeze-thaw cycles, and mechanical disruption (eg, ultrasound or extrusion) are commonly employed to lyse cells. To enhance membrane purity, discontinuous sucrose gradient centrifugation is used to eliminate soluble proteins and intracellular debris.[85]

Membrane extraction can be categorized into anucleate and nucleated cell extractions. RBCs, as typical anucleate cells, were among the first cell types used for NP coatings. To extract RBCs, fresh blood is collected and centrifuged at 4°C to remove serum and leukocytes. The remaining cells are then washed with phosphate-buffered saline (PBS) to eliminate any remaining plasma. Hypotonic treatment induces RBC lysis, and hemoglobin is subsequently removed via high-speed centrifugation, resulting in a pink precipitate. Ultrasonication and extrusion through polycarbonate membranes are employed to achieve the desired vesicle size. To ensure stability, protease inhibitors are incorporated before the vesicles are stored at 4°C for preservation.[86]

Extracting membranes from nucleated cells is more challenging due to the presence of intracellular structures.[87] These cells are often subjected to hypotonic lysis and freeze-thaw cycles, followed by differential centrifugation or sucrose gradient centrifugation to separate and remove internal components.[88] A specialized buffer is then used to achieve further purification.[89]

Additional cell lysis methods include mechanical techniques, such as high-pressure homogenization and microbead milling, and non-mechanical techniques, which fall into three main categories: physical, chemical, and biological. Physical disruption methods (eg, heat, sound, and pressure) provide non-contact lysis, while chemical methods use lysis buffers to disrupt cell membranes by altering pH; detergents may also be added to solubilize proteins. Biological lysis relies on enzymes, like lysozyme and protease, to cleave cell membranes. Each method has distinct advantages and limitations, and the choice of lysis method depends on cell type and the specific application requirements.[90] Table 2 lists some common biofilm extraction methods and their characteristics.

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Table 2 Methods and Characteristics of Biofilm Extraction

Method	Principle	Advantages	Disadvantages	Applications
Ultrasonication	Utilizes high-frequency sound waves to break down cell membranes and release membrane-bound contents	Efficient, simple, and fast process	Excessive sound power may damage membrane integrity	Ultrasonication is effective for isolating biomembranes from cells, such as keratin membranes.
Centrifugation	Separates membrane-containing supernatant from other cellular components through differential centrifugation	High purity, versatile for different cell types	Potential for significant loss of membrane material	Applied in extracting red blood cell membranes for drug delivery systems; hemoglobin removal is achieved by centrifuging under hypotonic conditions.
Freeze–thaw cycle	Involves freezing and thawing cell samples, causing volume changes in water and rupturing membranes	Simple, cost-effective	Low purity of isolated membranes	Effective in eliminating residuals from red blood cells, where hemoglobin denaturation occurs during freezing.
Chemical approach	Uses surfactants or organic solvents to disrupt the lipid bilayer of cell membranes and release membrane proteins and lipids	High purity, excellent control over membrane integrity	Expensive, possible residual impurities	Chemical detergents are used to detach membrane proteins for isolating pure cell membranes.

Note: Data from these studies.[91–93]

Preparation of NP

The properties of CMC-NPs are primary dictated by their inner cores, which can be classified as organic and inorganic. Careful selection of the core is essential to align with the intended application.

Organic inner cores are widely recognized for their excellent biocompatibility and biodegradability. The US FDA has approved materials such as gelatin, liposomes, and PLGA for clinical applications. Among these, PLGA is the most commonly used in creating biomimetic membrane carriers, demonstrating significant potential for use in clinical settings. By modifying PLGA particles with diverse membranes, such as those from platelets, cancer cells, macrophages, and stem cells, agglomeration of NPs can be mitigated, leading to enhanced delivery efficiency. Liposomes, another commonly used organic core, closely mimic the cell membrane. These biodegradable colloids can encapsulate both hydrophobic and hydrophilic drugs, offering the flexibility needed to navigate in vivo barriers. Coating liposomes with cell membranes not only boosts the stability of phospholipid layers but also extends their circulation time without compromising drug-loading capacity.

In contrast, inorganic NPs provide exceptional stability and resistance to enzyme breakdown. By carefully adjusting their shape, size, composition, and surface features, their natural electrical, optical, and magnetic properties can be fine-tuned to maximize their therapeutic benefits. For instance, Fe_3O_4 NPs, a new type of nanophotothermal agent, can be used in PTT. When coated with macrophage membranes, Fe_3O_4 NPs can specifically target cancer cells and cause selective cell death by raising the local temperature under laser exposure. Similarly, stem cell membrane-coated superparamagnetic iron oxide (SPIO) NPs have been studied for thermomagnetic therapy. SPIO NPs can quickly change their magnetic orientation and produce heat in a high-frequency alternating magnetic field, making them suitable for hyperthermia treatment. However, toxicity and biodistribution are major concerns when using inorganic nanocarriers. One way to tackle these issues is by adjusting particle size. For example, micron-sized CuO can enable safe delivery, while CuO NPs might lead to DNA damage. For SiO_2, increasing the particle size from 30–40 nm to 100–150 nm can significantly lower cytotoxicity. Another effective strategy is coating NPs with cell membranes, which improves biocompatibility and minimizing direct interaction with the internal environment, demonstrating great potential for safe and effective treatments.

In summary, organic and inorganic inner cores give CMC-NPs unique properties and functions. Organic cores act as safer carriers with strong loading capabilities, while inorganic cores provide specialized functions in PDT, PTT, fluorescence imaging, and MRI, among others. Table 3 highlights the features and use of various nanocarrier types.

Table 3 Characteristics and Applications of Different Types of Nanocarriers

Type	Key Features	Applications
Nanoparticles	Solid colloidal substances ranging from 10 to 1000 nm; high surface area and efficient drug loading	Erythrocyte membrane-functionalized gold nanoparticles used for rapid fibrinogen detection in CVDs
Nanoliposomes	Nanoscale vesicles composed of phospholipid bilayers; high biocompatibility, effective drug encapsulation, and targeted delivery	Coated liposomes for targeted ischemic stroke therapy, loaded with Panax notoginseng saponins and ginsenoside Rg3 using Box-Behnken design
Nanomembranes	Self-assembled surfactant nanostructures with high drug loading capacity and excellent biocompatibility	Nanomicelles loaded with quercetin and polyethylene glycol for atherosclerosis treatment by modulating gut microbiota
Nanoemulsion	Composed of oil, water, and emulsifiers; offers high stability and bioavailability	Bio-LN/SPMs, a macrophage membrane-coated lipid emulsion for reducing lipid accumulation and inflammation in aortic disease model
Nano-alcohol Plasma	Delivery systems made of phospholipids with high ethanol content; strong permeability and drug loading capacity	Nano-cochleates with ellagic acid and ethanol for potential transdermal drug delivery

Note: Data from these studies.[94–98]

Coating of the Nanoparticle Cores by Cell Membrane

Extrusion

During cell membrane extrusion, an Avanti micro-extruder facilitates the repeated passage of a mixture containing cell membranes and nanoparticle cores through polycarbonate membranes with pore sizes between 400 nm and 100 nm. This mechanical process ensures the cell membrane effectively encapsulates various nanoparticle cores, regardless of their physical characteristics or shapes. It is particularly suitable for coating polymer-based nanoparticles with sizes up to 350 nm, offering uniform size distribution and improved drug loading efficiency. Despite its advantages, large-scale production remains difficult due to material loss from filter deposition, making this method labor-intensive and less practical for industrial-scale applications.[99]

Throughout the extrusion process, the fluidity of the cell membrane facilitates the fusion of nanoparticles with membrane vesicles. Gradually decreasing the pore size ensures the formation of uniformly sized particles, with each extrusion step refining particle size and ensuring comprehensive nanoparticle coating.[100] To achieve complete encapsulation, an excess of cell membrane material is frequently utilized. While this process is time-consuming, it effectively maintains the biological functionality of membrane proteins, which is essential for applications that demand functionalized membrane coatings.[80]

Overall, the extrusion technique, typically performed with polycarbonate membranes featuring 100–400 nm pores, is one of the most common and reliable methods for producing cell membrane-camouflaged nanoparticles.[80] The mechanical force applied during extrusion facilitates the encapsulation of nanoparticles within the phospholipid bilayer, preserving the membrane's structural integrity and functionality, and yielding particles with uniform size distribution and enhanced stability.[101]

Sonication Method

Ultrasonic waves used during sonication can break down cell membrane structures, facilitating a quick and straightforward method for coating NP surfaces via co-incubation.[102] While sonication offers a practical alternative to extrusion for producing core-shell nanoparticles, its scalability is limited due to the risk of membrane damage. Adjusting parameters such as intensity, frequency, and exposure time can optimize the process, improving membrane fusion efficiency and reducing the likelihood of protein denaturation.[103]

This approach leverages electrostatic interactions and sonication to fuse nanoparticle cores and plasma membranes, allowing membrane vesicles to reassemble around the nanoparticles. Successful NP coating via sonication can mitigate material loss seen in extrusion techniques, potentially improving scaled-up production. Studies indicate that this method yields products comparable to those achieved through porous membrane extrusion. The sonication process imparts energy that disrupts the cell membrane bilayer, initiating an attraction between NPs and the cell membrane. This is followed by membrane reformation around the NP cores into structures that minimize entropy and favor stability. However, sonication parameters must be carefully managed, as they may impact NP size and stability and may not be compatible with certain nanocore structures.[104]

Microfluidic Electroporation Method

Microfluidic electroporation has emerged as a promising method for coating NPs with cell membranes, enabling the production of stable, high-quality particles with complete membrane encapsulation.[105] In this approach, NPs and cell membranes are introduced into a microfluidic chip, where electrical pulses generate transient pores in the membranes, facilitating efficient NP coating. The pores can either reseal or remain open based on factors such as pulse voltage, duration, and flow rate, which require precise optimization to ensure uniform, reproducible, and fully coated nanoparticles. Although this technique incurs relatively high costs, it reduces material loss associated with extrusion methods and enhances scalability through higher throughput.

The microfluidic chip utilizes electromagnetic energy to create temporary pores, allowing membrane vesicles to encapsulate NPs effectively. This method has shown superior colloidal stability and enhanced in vivo performance compared to traditional extrusion techniques. Furthermore, innovations in microfluidic device design, such as incorporating a Y-shaped merging channel, an S-shaped mixing channel, and a designated electroporation zone, have improved particle quality by enabling precise control over parameters like voltage, pulse duration, and flow speed. Figure 4 illustrates the step-by-step process for creating red blood cell membrane-coated magnetic nanoparticles (RBC-MNs).

Electrostatic Attraction Method

The electrostatic attraction technique utilizes surface charge disparities between extracted cell membranes and NPs to achieve the spontaneous formation of membrane-coated nanocarriers. Specifically, the interaction between the negatively charged cell membranes and positively charged NPs drives their assembly, resulting in biomimetic nanocarriers with a cell membrane coating. This method leverage natural electrostatic forces to create functional nanocarriers effectively. This approach enables nanoparticle coating under mild conditions, enhances adaptable.

For example, studies have shown that negatively charged vesicles derived from leukocyte membranes can self-assemble with positively charged silicon NPs via electrostatic attraction, creating a stable membrane-coated structure.[106] Electrostatic forces play a critical role in membrane and NP fusion; therefore, regulating the surface charge of NPs is crucial.[107] An excess of positive charge can result in overly strong interactions, potentially preventing the complete coating of the nanoparticles with cell membranes. As such, when employing the electrostatic attraction method to prepare biomimetic nanocarriers, it is important to optimize the NP-to-cell membrane ratio to improve both the efficiency and stability of the coating.[108]

Flash Nanocomplexation (FNC)

FNC is a sophisticated method for cell membrane coating that utilizes high-speed turbulent mixing to promote the self-assembly of cell membrane fragments onto NP cores within controlled microchambers.[109] In this technique, polyelectrolyte solutions containing charged polymers are injected concurrently into specialized mixing chambers, such as Continuous Impinging Jet Mixers or Micro Vortex Mixers. The rapid and efficient coating is driven by the dynamic

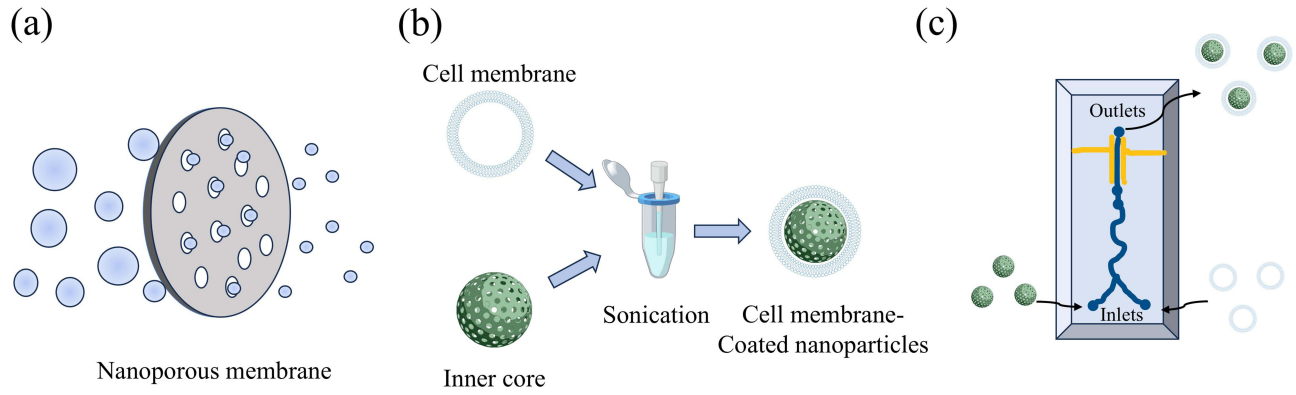

Figure 4 (**a**) A diagram showing the steps involved in preparing liposomes through vesicle extrusion. Adapted with permission. (**b**) A visual representation of how cell membranes are coated onto nanoparticles using sonication. (**c**) The process of creating RBC-MNs using microfluidic electroporation.

interactions between cell membrane vesicles and NP surfaces through electrostatic attraction and controlled physical forces.

Optimization of the coating process can be achieved by adjusting factors such as mixing ratio, flow rate, and membrane fragment composition. For instance, fine-tuning the lipid-to-NP mixing ratio and flow rate enables the production of uniformly coated lipid nanoparticles with consistent structural integrity. Multi-inlet vortex mixers (MIVM) improve the efficiency of FNC by harnessing the kinetic energy generated from multiple inlet jets to induce flow convection. This action effectively guides cell membrane fragments and nanoparticles into turbulent eddies and intershearing layers, leading to a quicker and more uniform coating process.[110]

Compared to traditional methods like extrusion, FNC offers significant advantages, including scalability, rapid processing, and the ability to produce high-quality membrane coatings under mild conditions. This technique is especially effective in generating cell membrane-coated nanoparticles with enhanced colloidal stability, uniform size distribution, and improved biofunctionality. Thus, FNC presents a promising, scalable, and environmentally friendly approach for producing cell membrane-camouflaged nanocarriers suitable for therapeutic and bioimaging applications.

To sum up, the fusion process for creating cell membrane-coated NPs involves wrapping cell membrane vesicles around inner core nanocarriers through techniques such as extrusion, ultrasonication, and electroporation. Among these, extrusion and sonication are the most commonly used methods. In extrusion, both membrane vesicles and nanocarriers are repeatedly passed through nanoscale polycarbonate membranes, using an Avanti mini extruder to achieve coating by mechanical force. Although this method is straightforward and effective, it is challenging to scale for high-volume production. In contrast, the sonication method, which uses ultrasonic energy to facilitate coating, enables higher throughput and is more suited for large-scale production. However, the sonication bath requires precise control, as excessive power or temperature may disrupt cell membrane proteins, compromising the biofunctionality of the coated NPs and producing vesicles with inconsistent sizes.[111] Consequently, many laboratories prefer extrusion for small-scale production of biomimetic materials.

For functional cell membrane-coated NPs, achieving effective and stable membrane attachment is crucial. While extrusion and sonication are common methods, electroporation and microfluidics can also create consistent coatings. However, all four techniques face challenges in scalability, maintaining membrane integrity, and technical complexity. To overcome these issues, researchers have explored new strategies. For instance, in graphene nanoplatform technology, magnetic NPs coated with polyethyleneimine and graphene nanosheets are mixed with target cells, enabling cell phospholipids to attach to the graphene surface and form membrane-coated magnetic NPs.[112] Although effective, this process involves intricate steps. Another innovative method is in situ vesicle encapsulation, where NPs are incubated with cells in a serum-free medium.[113] The cells then absorb these NPs, and under nutrient-deprived conditions, release them within membrane-bound vesicles. This approach preserves membrane integrity and offers a potential alternative to extrusion and sonication. As technology advances, these sophisticated methods are anticipated to enable the large-scale production of high-quality membrane-coated nanoparticles, overcoming the limitations of traditional techniques.

Characterization of Cell Membrane-Coated NPs

Once biomimetic membrane-coated NPs are synthesized, comprehensive characterization is essential to verify successful coating and assess the coated NPs' properties and functionality. Unlike the NP core, the cell membrane coating comprises proteins and lipids, enhancing biocompatibility and biological functionality. Key characterization techniques include:

Core-Shell Structure Analysis

Transmission electron microscopy (TEM) is employed to confirm the core-shell structure of the coated NPs, providing direct visualization of a uniform membrane layer surrounding the core. TEM reveals the presence, thickness, and integrity of the cell membrane coating, verifying encapsulation success.

Size Distribution and Hydrodynamic Diameter

Dynamic light scattering (DLS) measures the hydrodynamic diameter of membrane-coated NPs, revealing particle size distribution in solution. A slight increase in particle size relative to uncoated NPs indicates successful coating. DLS also assesses colloidal stability, critical for biomedical applications.

Surface Charge Characterization

Zeta potential analysis confirms coating effectiveness by measuring surface charge. The zeta potential of membrane-coated NPs should match that of the original cell membrane, indicating that surface properties are determined by the cell membrane, which supports stability, immune evasion, and biological interactions.

Protein and Lipid Retention

Techniques such as SDS-PAGE and Western blotting verify the retention of specific cell membrane proteins on NPs, confirming the preservation of biofunctional protein markers. FTIR or Raman spectroscopy further assesses lipid and protein integrity, providing insights into the coated membrane's chemical composition.

Biological Functionality

Membrane-coated NPs' biological activities, such as immune evasion and cellular uptake, are evaluated through cellular uptake studies and in vitro immune assays. Flow cytometry and fluorescence microscopy quantify and visualize NP uptake by target cells, validating the cell membrane coating's functional advantages.

Membrane Uniformity and Stability

Fluorescent labeling and fluorescence microscopy assess the uniformity of membrane coating, while stability testing under physiological conditions confirms membrane resilience in relevant environments. In summary, the combined application of TEM, DLS, zeta potential measurements, protein and lipid analyses, biological assays, and stability testing comprehensively characterizes cell membrane-coated NPs. These analyses validate the successful fabrication, functionality, and biomedical potential of these biomimetic NPs.

Effect of Cell Membrane Coating on Nanoparticle Properties

Coating NPs with cell membranes significantly impacts various physicochemical properties, including particle size, zeta potential, and stability, all of which depend on the membrane-to-core ratio and fabrication method used.

For example, Hu et al observed that mesoporous silica NPs coated through flash nanocomplexation exhibited increased particle size and more negative zeta potential compared to uncoated NPs. A higher membrane-to-core ratio resulted in a slight reduction in particle size, possibly due to optimized membrane wrapping. Stability tests showed that while membrane-coated NPs retained structural integrity, a minor size increase occurred after two weeks of storage.[109] Fang et al reported that coating PLGA NPs with cell membranes increased their size from 225 nm to 247 nm, with a corresponding zeta potential shift from −55 mV to −43 mV, reflecting the influence of membrane-associated phospholipids and proteins.[114] Rao et al demonstrated that coating UCNPs with blood cell membranes at a core-to-shell ratio of 1 mg UCNP per 0.2 mL membrane achieved a stable size, adding approximately 25 nm to the nanoparticle diameter. This increase highlights the impact of membrane thickness on particle dimensions.[115] Hui-Wen Chen et al examined magnetic NPs with cell membrane coatings, finding that the coated NPs displayed a narrow size distribution, indicating monodispersity. TEM images revealed a diameter increase of approximately 20 nm post-coating, while DLS analysis confirmed a more negative zeta potential and enhanced colloidal stability. The coated NPs also showed improved resistance to enzymatic degradation, underscoring the protective role of the membrane.[116]

In terms of production techniques, microfluidic electroporation offers benefits such as uniform particle size and high reproducibility. Studies have shown that this method better preserves membrane protein integrity than conventional extrusion or sonication.[117] Although sonication can support large-scale production, its high power requirements can damage sensitive surface proteins. In contrast, microfluidic systems minimize protein loss and enhance colloidal stability, making them ideal for consistent, high-quality cell membrane-coated NP (CMNP) production at industrial scales. Flash nanocomplexation, which drives the rapid self-assembly of NPs and membrane vesicles under turbulent mixing, has also proven effective for creating stable, uniformly coated CMNPs with consistent size and zeta

potential.[109] This technique shows great promise for high-throughput CMNP production, enhancing both stability and biofunctionality.

Classification of Biomimetic Nanocarriers

Red Blood Cell Membrane Disguised Nanocarriers

RBCs are the most abundant cellular components in human blood, playing a critical role in oxygen transport throughout the body. Structurally, they exhibit a distinctive biconcave disk shape, which optimizes their biological function. Mature RBCs lack nuclei and complex organelles, allowing them to deform as they circulate through blood vessels. This simplicity makes the extraction and purification of their membranes more straightforward, positioning RBCs as an ideal source for NP coatings.[118]

RBCs have been widely studied due to their remarkable ability to circulate in the body for up to 120 days. Additionally, their surfaces are equipped with "self-recognition" proteins that help regulate the immune system, including CD47, C8-binding protein (C8bp), complement receptor 1 (CR1), decay-accelerating factor (DAF), homologous restriction protein (HRP), and CD59.[119] Among these, CD47 is particularly noteworthy, as it interacts with macrophage-expressed signal regulatory protein-α (SIRP-α) to activate SH2 domain-containing tyrosine phosphatases.[16] This signaling process stops myosin IIA from gathering at phagocytic synapses and triggers the release of a "don't eat me" signal, which helps avoid immune clearance and uptake by macrophages.[120]

The RBC membrane is a bilayer of phospholipids interspersed with membrane proteins, which provides semi-permeability, elasticity, and stability. These features enable gradual drug release, supporting sustained therapeutic effects.[121] Furthermore, RBC membranes are biodegradable, biocompatible, and free of harmful by-products, making them suitable for reducing the inherent toxicity of nanomaterials like carbon nanotubes and iron nanoparticles.[61] With an average concentration of 5 billion RBCs per milliliter of blood, the preparation process for RBCNPs is relatively simple, enabling low-cost mass production. Given the widespread availability of blood transfusion resources, type-matched RBCs can be used as membrane sources to enhance biocompatibility.

RBCNPs have gained significant attention in nanoparticle drug delivery, particularly for the delivery of chemical, protein, and gene-based therapeutics, thereby improving treatment outcomes for various diseases.[122] In 2011, Zhang et al made a breakthrough by utilizing RBC membranes to camouflage nanoparticles, thereby developing a biomimetic delivery system.[86] Gel electrophoresis analysis demonstrated that the protein content of the RBC membrane remained intact, thereby retaining its biological functionality. In vivo experiments demonstrated the extended circulation time of this system. Following this work, other research groups developed innovative RBC-based technologies, such as Green et al's anisotropic RBC membrane-coated NPs, which improved biodistribution and therapeutic outcomes. Hu et al demonstrated that RBC membrane-coated NPs had an circulation half-life of 39.6 hours, significantly surpassing PEG-modified NPs (15.8 hours), highlighting their superiority in extending circulation time.[123] Pei et al further advanced this field by camouflaging metal-organic frameworks (MOFs) with RBC membranes, enhancing the efficacy of photodynamic therapy (PDT) and chemodynamic therapy (CDT) via targeting aptamers.[124] Zhou et al applied RBC membrane-based systems to deliver tanshinone IIA sodium sulfonate (STS) for cardiovascular disease, achieving immune evasion and extended drug half-life.[125]

While RBCM-NPs hold great therapeutic promise, challenges remain, including limited tissue permeability and a lack of intrinsic targeting capabilities. These limitations have driven the exploration of alternative biofilm-based delivery systems aimed at improving therapeutic effectiveness and broadening their range of applications.

Immune Cell Membrane Camouflaged Nanocarriers

Immune cells, also known as white blood cells (WBCs), are nucleated and colorless cells found in the blood, comprising granulocytes, monocytes, and lymphocytes. Subtypes such as macrophages, neutrophils, cytotoxic T lymphocytes (CTLs), and natural killer (NK) cells are included. These cells are essential components of the immune system, capable of moving freely between blood vessels to reach sites of inflammation and fight against harmful pathogens. Present in blood, lymph, and various tissues, WBCs are crucial for detecting inflammation and gathering in affected areas, playing a significant role in the development of numerous diseases, including cardiovascular conditions, infections, and cancer.

Chronic inflammation, especially, is a key feature of cardiovascular diseases, leading to conditions like atherosclerosis, heart attacks, and strokes.[126]

In cardiovascular research, white blood cell membrane-coated nanoparticles (WBC-NPs) have gained attention as a promising biomimetic strategy for delivering drugs to treat inflammation-associated cardiovascular diseases. These nanoparticles are formed by coating synthetic cores with membranes derived from immune cells like macrophages and neutrophils, which contribute to improved targeting efficiency. By inheriting the antigenic and biointerfacing properties of WBCs, WBC-NPs act as "nanodecoys" that could evade immune recognition, circulate longer, and cross biological barriers, making them effective for targeted drug delivery to inflamed vascular tissues.

Macrophage Membrane Cloaked Nanocarriers

Macrophages, a versatile subset of monocytes, play an essential role in immune regulation by clearing foreign particles, dead cells, and cellular debris through phagocytosis. Known for their ability to adapt to varying environments—a process termed macrophage polarization—macrophages exhibit distinct phenotypes with specialized biological functions.[127] This versatility has driven the interest in using macrophage membranes to develop biomimetic nanocarriers, particularly for cardiovascular applications. In cardiovascular conditions like atherosclerosis, macrophages accumulate in the inflamed or damaged arterial walls through interactions between the integrin α4/β1 on macrophages and the vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells.[128] Furthermore, macrophage membranes exhibit CD47, which interacts with SIRP-α on host cells, preventing phagocytosis and thereby increasing the circulation stability of macrophage membrane-coated nanoparticles (Mc-NPs).

In the context of cardiovascular disease, Mc-NPs offer promising targeted drug delivery solutions. By mimicking the natural homing capability of macrophages, Mc-NPs can navigate to inflamed vascular sites, particularly atherosclerotic plaques, where they accumulate to deliver therapeutic agents. For example, Mc-NPs loaded with atorvastatin in a chitosan core have shown efficient targeting of atherosclerotic plaques, releasing the drug as the chitosan degrades.[129] This controlled release helps reduce local inflammation and neutralize pro-inflammatory cytokines, which are crucial in plaque formation and progression. These targeted drug delivery systems enhance therapeutic effectiveness while reducing systemic side effects, positioning them as promising options for cardiovascular treatments.

Macrophage membrane-coated nanoparticles are also engineered to leverage macrophage polarization. M1-polarized macrophage membranes are highly effective for targeting inflammatory environments because they can secrete cytokines like IFN-γ, IL-1β, and TNF-α. These cytokines are crucial in regulating immune responses against infections and cancer. Conversely, M2-polarized macrophage membranes, which release anti-inflammatory cytokines such as IL-4 and IL-10, are valuable for promoting tissue repair and resolving inflammation in wound healing and later-stage cardiovascular disease. By selectively using M1 or M2 macrophage membranes, these nanoparticles can be tailored for different therapeutic contexts, enhancing their specificity and effectiveness in diverse disease environments.[59]

Macrophage-derived membranes also exhibit superior immune evasion capabilities compared to synthetic coatings like PEG. While PEGylation can partially reduce clearance by the RES, macrophage membrane-coating enables complete recognition as "self", thus avoiding immune elimination entirely. The immune camouflage provided by Mc-NPs enables them to remain in the bloodstream for an extended period, enhancing their chances of reaching targeted areas. This prolonged circulation is particularly advantageous in chronic cardiovascular diseases such as atherosclerosis, where sustained delivery is crucial.

Beyond cardiovascular applications, macrophage membranes have been used in nanomedicine for conditions such as cancer and inflammatory diseases. For example, Mc-NPs derived from RAW264.7 macrophage cells have demonstrated high precision in targeting inflamed tissues and cancer cells, where they deliver therapeutic agents more effectively while could evade the immune clearance. In addition, macrophage membranes enriched with specific surface proteins can localize to inflamed endothelium, similar to neutrophils, facilitating targeted drug delivery for a variety of inflammation-related conditions.

In conclusion, macrophage membrane-coated nanoparticles offer a novel and adaptable approach for targeted drug delivery in cardiovascular and inflammatory disorders. Their capacity to avoid immune recognition, target inflamed vascular areas, and deliver localized therapies highlights their potential to improve treatment outcomes in conditions such

as atherosclerosis. Additionally, the multifunctionality of macrophage membranes paves the way for expanding their use in fields like oncology and regenerative medicine, positioning Mc-NPs as a significant advancement in modern nanomedicine.

Nanocarriers Camouflaged by Neutrophil Cell Membranes

Neutrophils, originating from myeloid progenitor cells in the bone marrow and some extramedullary sites like the spleen, are the most prevalent type of granulocyte, accounting for 40–70% of leukocytes in human blood.[130] As key players in the innate immune response, neutrophils have a brief half-life in circulation (8–20 hours) but can survive longer (1–4 days) in tissues during inflammatory conditions. They quickly migrate to areas of infection or injury, where they contribute to immune defense through mechanisms such as phagocytosis, degranulation, and the release of reactive oxygen species (ROS), neutrophil extracellular traps (NETs), and bioactive lipid mediators.[131] Their exceptional ability to target sites of inflammation, combined with their potential to traverse barriers like the blood-brain barrier (BBB), positions neutrophils as promising candidates for cell membrane-based biomimetic drug delivery, particularly for treating cardiovascular and inflammatory diseases.

Neutrophil membrane-coated nanoparticles (NM-NPs) leverage the neutrophil's natural homing capability for targeting inflamed cardiovascular tissues. These NM-NPs inherit the antigenic surface markers of neutrophils, enabling them to evade immune clearance and selectively bind to inflamed vascular regions, such as atherosclerotic plaques. For instance, NM-NPs loaded with anti-inflammatory agents have been shown to accumulate within atherosclerotic plaques, potentially stabilizing them and reducing inflammation, which is crucial for preventing plaque rupture and subsequent cardiovascular events like myocardial infarction and stroke.

NM-NPs have also demonstrated potential in delivering therapeutic agents to ischemic tissues in myocardial infarction. By coating nanoparticles with neutrophil membranes, these systems are able to target drugs directly to infarcted heart tissues, delivering anti-inflammatory or regenerative therapies to healing areas. For instance, NM-NPs loaded with growth factors or other cardioprotective agents have been demonstrated to selectively accumulate in ischemic myocardial tissue, aiding in tissue repair and enhancing functional recovery after heart attacks.

Beyond cardiovascular applications, NM-NPs have shown promise in treating autoimmune and inflammatory diseases. In rheumatoid arthritis, neutrophil membrane-coated PLGA NPs have been effective in neutralizing pro-inflammatory cytokines, reducing synovial inflammation, and alleviating joint damage. Additionally, NM-NPs encapsulating drugs such as methotrexate have shown selective accumulation in inflamed skeletal muscle and myocardial tissues in models of autoimmune myocarditis and ischemia-reperfusion injury. This targeted delivery enhances localized therapeutic outcomes while reducing systemic toxicity.[76]

In addition to their role in inflammation-related diseases, neutrophil membranes are also being explored in antibacterial therapies. NM-NPs have been employed in the treatment of bacterial infections, harnessing the natural pathogen-targeting ability of neutrophils. For instance, NM-NPs composed of neutrophil membranes and metal-organic frameworks (MOFs) loaded with chloroperoxidase and glucose oxidase have shown promising results against *Staphylococcus aureus* infections in mouse models. These coated nanoparticles significantly reduced both wound size and bacterial load compared to uncoated nanoparticles. This strategy demonstrates the potential of NM-NPs to combat Gram-positive bacterial infections, which often exhibit resistance to traditional treatments.[132]

While NM-NPs offer several advantages, they are not without limitations. Activated neutrophils release ROS, NETs, and pro-inflammatory cytokines, which can lead to secondary inflammatory injury at the target site.[133,134] This is a crucial factor in cardiovascular applications, as uncontroled inflammation could exacerbate tissue damage. To mitigate these effects, integrating ROS-scavenging agents or engineering NM-NPs with controlled activation mechanisms may improve safety and efficacy in inflammatory environments.

In summary, neutrophil membrane-coated nanoparticles represent a promising platform for targeted drug delivery, particularly in cardiovascular diseases, autoimmune disorders, and bacterial infections. Their unique homing ability, immune evasion, and adaptability to inflamed microenvironments make them powerful carriers for therapeutic agents. However, further research to optimize their design and mitigate potential inflammatory side effects is necessary to ensure their successful clinical application.

Nanocarriers Camouflaged by Mononuclear Cell Membrane

Monocytes, the largest white blood cells, are highly phagocytic cells derived from hematopoietic stem cells in the bone marrow. Monocytes are frequently utilized in the development of actively targeted drug delivery systems because of their capacity to fight against intracellular pathogens and their ability to identify and eliminate abnormal cells.[135] By reducing opsonization and utilizing self-recognition mechanisms, they can effectively extend the circulation time of drugs. Moreover, monocytes can traverse vascular endothelium, to deliver therapeutic agents directly to lesion sites, making them an ideal choice for cell membrane-based nanomaterial development.[14]

Monocytes play a critical role in cardiovascular health by modulating immune responses that impact inflammation and tissue repair, which are central to many cardiovascular diseases.[136,137] For example, monocytes accumulate in atherosclerotic plaques, where they differentiate into macrophages and contribute to plaque formation and inflammation. By coating monocyte membranes to NPs, researchers have developed systems that could selectively accumulate in inflamed arterial regions, enabling targeted delivery of anti-inflammatory agents to reduce plaque size and stabilize vulnerable plaques. Such therapies hold promise for preventing plaque rupture and subsequent events like heart attacks and strokes.

In addition to drug delivery for atherosclerosis, monocyte-derived membrane-coated NPs have shown potential in treating ischemic heart disease. These nanoparticles target ischemic tissue, delivering growth factors and regenerative agents directly to damaged heart muscle, thereby facilitating tissue repair and recovery after a heart attack. Research indicates that monocyte membranes assist nanoparticles in evading immune clearance, that extends their circulation time and promotes greater accumulation in ischemic or inflamed tissues, ultimately enhancing therapeutic efficacy.

Monocytes are also being investigated for their role in modulating immune responses in heart transplant patients. By encapsulating immunosuppressive drugs within monocyte membranes, researchers have developed targeted therapies to mitigate graft rejection and inflammation in transplanted hearts, potentially reducing the need for systemic immunosuppressive therapy and minimizing associated side effects.

In addition to cardiovascular applications, monocytes serve essential roles in tissue homeostasis, regulating immune responses to prevent excessive tissue damage and initiating host defense against pathogens. Monocytes adapt their functions in response to immune challenges through various receptors, thereby playing a key regulatory role in inflammation and infection control. Studies have shown that in response to inflammation, infection, or tissue injury, monocytes accumulate at affected sites and differentiate into dendritic cells or macrophages, further to support immune defense and tissue repair.

Lymphocyte Membrane Camouflaged NPs

B and T lymphocytes are key regulators of the adaptive immune response, typically surviving for several weeks to months, with some persisting as memory cells for years. Both B and T lymphocytes possess specific receptors for recognizing pathogen-derived antigens—B-cell receptors (BCRs) and T-cell receptors (TCRs), respectively. The primary functions of B lymphocytes include synthesizing and secreting specific antibodies and acting as antigen-presenting cells (APCs). In contrast, T lymphocytes play crucial roles in eliminating infected host cells, activating other immune cells, and regulating immune responses, thereby facilitating defenses against infections and tumors.[138]

T-cell membrane-coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles (TNPs) have shown great promise for drug delivery applications. The T-cell membrane coating protects nanoparticles from macrophage phagocytosis, prolonging their circulation time. In cardiovascular disease applications, TNPs can target damaged vascular areas by interacting with endothelial cell surface molecules, such as intercellular adhesion molecule-1 (ICAM-1). Furthermore, these nanoparticles engage with T-cell adhesion molecules, including lymphocyte function-associated antigen-1 (LFA-1), enhancing drug delivery efficiency to diseased cardiovascular tissues.[66]

In cardiovascular disease models, TNPs can specifically target atherosclerotic plaques, where they reduce inflammation and enhance vascular repair. For instance, intravenous administration of TNPs in a cardiovascular disease mouse model has shown increased drug accumulation at injury sites and significantly inhibited plaque progression. Additionally, exposing damaged cardiovascular tissues to high-energy X-rays upregulates ICAM-1 expression, which further facilitates TNP accumulation in the targeted area, enhancing therapeutic outcomes.

Beyond cardiovascular applications, TNPs also hold potential for cancer and autoimmune disease treatment. T-cell membrane-coated nanoparticles, expressing immune evasion markers like CD47, evade the recognition by the mononuclear phagocyte system, thereby enhancing in vivo drug stability. Due to the natural targeting abilities of T cells to inflammatory and tumor microenvironments, TNPs improve targeting and drug accumulation in cancer therapy, providing a more effective antitumor immune response. Further research into TNPs is underway in inflammatory disease treatment, with rheumatoid arthritis models showing that TNPs exhibit significant anti-inflammatory and reparative effects.

Platelet Membrane Cloaked Nanocarriers

Platelets, small anucleate cells derived from bone marrow megakaryocytes, play a crucial role in hemostasis, thrombosis, and vascular repair. Their membrane is composed of a phospholipid bilayer enriched with specialized receptors, glycoproteins, and integrins that enable interactions with damaged blood vessels, immune cells, and inflammatory sites. For example, CD47 on the platelet membrane serves as a "self-marker", allowing platelets to evade immune detection by binding to SIRPα on macrophages. Additionally, integrin αIIbβ3 mediates adhesion to fibrinogen, supporting clot formation. These attributes make platelet membranes an ideal platform for developing biomimetic drug delivery systems, particularly in cardiovascular diseases.

Platelet membrane-coated nanoparticles (PNPs) have gained significant attention for targeted drug delivery, especially in cardiovascular applications, due to their biocompatibility, immune evasion, and inflammation-targeting capabilities. PNPs can deliver therapeutic agents directly to inflamed or damaged vasculature, such as atherosclerotic plaques, while minimizing off-target effects. In cardiovascular disease models, PNPs have been shown to target inflamed endothelium and promote selective drug accumulation in atherosclerotic regions where inflammation drives plaque instability. This selective targeting, facilitated by platelet-specific receptors like GPIbα and GPVI, could enhance therapeutic outcomes by stabilizing plaques and preventing complications like myocardial infarction and stroke.

PNPs are also valuable in treating other inflammation-associated diseases and cancer. The P-selectin and CD44 receptors on platelet membranes facilitate adhesion to circulating tumor cells (CTCs) and inflamed tissues, allowing PNPs to selectively deliver chemotherapeutics, immunomodulatory agents, or photothermal agents to cancer cells.[139] In cancer models, platelet-coated nanoparticles have been used to deliver drugs such as doxorubicin, improving treatment efficacy and reducing systemic toxicity by targeting tumors and CTCs. Additionally, the CD47 on PNPs allows them to evade macrophage-mediated clearance, extending circulation time and enhancing therapeutic potential.

In cardiovascular and cancer applications, hybrid nanocarriers that combine platelet membranes with other cell types or nanomaterials have demonstrated dual functionality. For instance, platelet membrane-coated metal-organic frameworks (MOFs) have been utilized for siRNA delivery to tumors, achieving effective gene silencing and reducing metastasis.[140] This versatility extends to cardiovascular applications, where combining platelet membranes with other functional materials may improve the targeting of thrombi, reduce systemic toxicity, and enhance treatment efficacy in ischemic and inflammatory cardiovascular diseases.

While PNPs show significant potential, challenges remain in achieving large-scale production and storage stability. Platelet membranes have a short shelf life, and preserving their bioactivity during storage is crucial for clinical application. Additionally, platelet membranes may exert pro-inflammatory effects, particularly in atherosclerosis, necessitating careful consideration in cardiovascular applications.[141,142] Research efforts focused on optimizing the stability, scalability, and safety of PNPs, are crucial to realizing their full therapeutic potential.

In conclusion, platelet membrane-coated nanoparticles offer a versatile and promising platform for targeted drug delivery in cardiovascular and inflammatory diseases. Their ability to mimic platelet functions—such as targeting damaged vessels, evading immune clearance, and selectively accumulating at pathological sites—highlights their potential to improve therapeutic outcomes in cardiovascular disorders, cancer, and other inflammation-associated conditions (Table 4).

Table 4 Nanocarriers Coated with Platelet Membranes and Their Application in the Treatment of Cardiovascular Diseases

Nanoparticle Core	Target Disease	Therapeutic Agent
Polymeric Nanoparticles (PLGA)	Coronary Restenosis	Docetaxel, Vancomycin
Polymeric Nanoparticles (PLGA)	Immune Thrombocytopenia	–
Polymeric Nanoparticles (PLGA)	Atherosclerosis	Red Fluorescent Dye
PVAX Nanoparticles	Thrombosis	Argatroban
PLGA Nanoparticles	Myocardial Ischemia and Reperfusion Injuries	Secretome of Cardiac Stem Cells
Iron Oxide (γ-Fe2O3) Nanoparticles	Myocardial Ischemia	L-Arginine (a precursor for nitric oxide biosynthesis)

Note: Data from these studies.[143–146]

Bacterial Membrane Camouflaged NPs

NP coatings using cell membranes from RBCs, WBCs, and platelets have gained significant attention for targeted drug delivery in cardiovascular and other diseases.[61] Bacterial membranes represent an innovative extension of this approach, offering a biomimetic coating rich in immunogenic antigens and adjuvants. When synthetic NPs are coated with bacterial membranes, they mimic bacterial antigenic profiles, activating both innate and adaptive immune responses.[147] This immune activation capability can be advantageous in cardiovascular disease contexts where immune modulation is critical, such as in atherosclerosis, where immune cell activity influences plaque stability and inflammation.

Outer membrane vesicles (OMVs), derived from gram-negative bacteria, are particularly promising as drug delivery systems and immunomodulators. OMVs contain immunostimulatory components like lipopolysaccharides, peptidoglycans, membrane proteins, and nucleic acids, all of which promote a robust immune response.[148] Studies indicate that OMVs can accumulate in specific tissues and stimulate cytokine production, making them potential agents for immune activation. For cardiovascular applications, OMVs can be designed to target inflamed endothelium, enhancing therapies aimed at reducing plaque formation or suppressing inflammation within atherosclerotic lesions.

In infectious disease applications, outer membrane-coated NPs (OM-NPs) have shown promise as anti-adhesive agents. For example, in *Helicobacter pylori* infections, OM-NPs reduced bacterial adhesion to gastric epithelial cells in murine models. This anti-adhesive property highlights OM-NPs' potential in preventing bacterial colonization, a function that may also benefit cardiovascular devices by reducing bacterial adherence and biofilm formation.[149]

OMVs derived from *E. coli* have been used to create immune-activating AuNP-based vaccines. When administered subcutaneously in mice, OMV-coated AuNPs localized to lymph nodes, where they activated dendritic cells (DCs), leading to increased expression of immune markers (CD40, CD80, and CD86). The targeted immune activation observed highlights the potential of bacterial membrane-coated nanoparticles in stimulating protective immune responses, making them a promising approach for vaccine development and anti-infective therapies.

In a study involving gram-positive *Staphylococcus aureus*, extracellular vesicles (EVs) were coated onto PLGA nanoparticles. These EV-coated NPs demonstrated targeted accumulation in infection sites in both in vitro models and mouse infection models. When antibiotics were encapsulated in EV-coated nanoparticles, there was a significant improvement in their therapeutic effectiveness, leading to a reduction in bacterial burden in both the lungs and kidneys.[61] Comparable strategies could be utilized in cardiovascular contexts, where targeted delivery of nanoparticles to inflamed or infected areas may aid in managing infections, such as those seen in endocarditis or with infected cardiovascular implants.

Stem Cell Membrane Disguised Nanocarriers

Mesenchymal stem cells (MSCs), derived from mesenchymal-rich sources like bone marrow, adipose tissue, and umbilical cord, possess multipotent differentiation potential, allowing them to become various cell types, including osteoblasts, chondrocytes, and adipocytes.[150] Their intrinsic properties, such as robust self-renewal, immunomodulation, and homing ability toward inflamed or damaged tissues, make MSCs highly promising candidates for regenerative medicine and drug delivery applications. In cardiovascular diseases, MSCs demonstrate significant therapeutic potential

due to their innate ability to migrate to inflamed or ischemic regions, responding to chemokine gradients like stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4, or vascular endothelial growth factor (VEGF) and its receptor VEGFR. This "homing" ability is particularly beneficial in designing MSC membrane-based delivery systems for targeted drug delivery to injured cardiovascular tissues.[151]

MSC membrane-coated nanoparticles (MSC-NPs) utilize the natural homing capacity of MSCs to deliver therapeutic agents precisely to target sites, such as atherosclerotic plaques or ischemic heart tissues. For instance, MSC-NPs loaded with anti-inflammatory or pro-regenerative drugs have shown promise in selectively accumulating in infarcted myocardium, where they improve tissue repair, reduce inflammation, and improve cardiac function post-myocardial infarction. By leveraging MSC-derived nanoparticles, these systems can extend drug circulation time, improve therapeutic delivery to affected areas, and reduce off-target effects, which are critical advantages in treating cardiovascular diseases.

To address the risks associated with using live MSCs, such as uncontrolled proliferation, researchers have developed enucleated MSC-derived carriers, or "Cargocytes." These innovative carriers preserve functional MSC membrane proteins and chemotactic properties but lack nuclei, eliminating the risk of tumorigenicity or unintended cell proliferation. Cargocytes have demonstrated homing effect to inflamed cardiovascular tissues, where they facilitate targeted drug delivery to atherosclerotic plaques and inflamed blood vessels. This approach offers a safer, more controllable alternative to live-cell therapies while retaining the targeting benefits of MSCs.

Additionally, MSC-derived nanovesicles are emerging as promising tools for drug delivery and immune modulation. These vesicles, enriched with MSC-specific markers like CD105 and CD90, carry bioactive molecules capable of promoting tissue repair and modulating immune responses. In cardiovascular applications, MSC-derived vesicles have been shown to improve endothelial repair, reduce vascular inflammation, and protect cardiomyocytes under ischemic conditions, highlighting their capability in addressing inflammatory and ischemic heart diseases. They have also shown promise in cancer treatment by enabling precise drug delivery to tumors, reducing toxicity to normal tissues.[152,153]

Despite their benefits, MSC-based nanocarriers face challenges, such as limited penetration into dense tissues and clearance by the RES. Techniques like PEGylation and ligand functionalization have been employed to improve circulation time and tissue-specific targeting, enhancing the efficacy of MSC-based nanocarriers in cardiovascular and inflammatory settings. Compared to synthetic carriers, MSC membrane-camouflaged nanoparticles exhibit lower immunogenicity, higher biocompatibility, and the ability to cross physiological barriers, such as the blood-brain barrier, making them ideal for applications beyond cardiovascular therapy, including regenerative medicine and immunotherapy.

Recent advancements in MSC-based drug delivery highlight their transformative potential for targeted therapy in cardiovascular diseases. For instance, MSC membranes coated onto biodegradable PLGA nanoparticles have shown enhanced therapeutic efficacy in heart disease models by improving drug retention at injury sites and reducing inflammation. MSC-based carriers combined with chemotherapeutic agents, like paclitaxel, have demonstrated significant anti-tumor effects, while their use in inflammatory and cardiovascular disorders has led to promising outcomes in targeted tissue repair and immune modulation.[154,155] These innovations underscore the potential of MSC-derived nanocarriers to address complex therapeutic challenges across various fields, particularly in cardiovascular health.

Endothelial Cell Membrane Camouflaged NPs

Endothelial cells, integral to vascular integrity and function, present a promising yet underutilized source of biomimetic coatings for NPs, particularly in the treatment of cardiovascular diseases. In living organisms, endothelial cells line the blood vessels and play essential roles in regulating inflammation, blood clotting, atherosclerosis development, and tissue healing. The surface molecules on endothelial cells interact with vascular inflammatory sites, making them ideal targets for directing therapies to damaged blood vessels. In a recent study, nanoparticles such as quantum dots, gold NPs, and iron oxide NPs were incubated with human umbilical vein endothelial cells (HUVECs), promoting high-density cellular uptake and vesicle formation under nutrient-deprived conditions.[156]

Endothelial cell membrane-coated NPs offer distinct advantages in cardiovascular and other inflammatory disease applications. First, these coatings significantly improve biocompatibility, reducing immune responses and minimizing adverse effects, which are essential factors when targeting delicate vascular tissues. Second, the endothelial membrane coating provides NPs with immune "stealth", enabling prolonged circulation and preventing immune clearance. Third,

the specific molecular markers on endothelial cell membranes allow targeted accumulation in diseased tissues, such as inflamed or atherosclerotic sites, improving drug delivery accuracy and minimizing off-target effects. Finally, the functional properties of the original endothelial cells are retained in the coated NPs, enabling them to interact dynamically with their environment, respond to disease-related signals, and actively target damaged cardiovascular regions.[132]

This biomimetic approach using endothelial cell coatings also shows potential beyond cardiovascular disease, with applications in cancer therapy and infection treatment, where inflammation and specific cellular targeting are essential. Future research on optimizing endothelial cell membrane-coated NPs may further advance their therapeutic impact across multiple disease contexts.

Hybrid Cell Membrane Camouflaged Nanocarriers

Hybrid membrane-coated biomimetic nanoparticles (HCMNs) combine the therapeutic strengths of different cell membranes to address complex disease challenges, particularly in cardiovascular and inflammatory diseases. By merging the unique properties of various cell types, HCMNs offer prolonged circulation, enhanced targeting, immune evasion, and multifunctionality. Among the widely researched HCMNs are erythrocyte-platelet hybrids, leukocyte-platelet hybrids, leukocyte-cancer cell hybrids, and cancer cell-dendritic cell hybrids, each tailored to meet specific therapeutic needs.

Erythrocyte-Platelet Hybrid Membrane-Coated NPs

Erythrocyte-platelet hybrid membrane-coated NPs combine the long circulation ability of erythrocyte membranes with the targeting precision of platelet membranes. The erythrocyte membrane's flexibility allows these NPs to navigate narrow blood vessels, while platelet membrane receptors specifically target damaged vascular sites and regions of inflammation. This hybrid retains the properties of both parent membranes, achieving enhanced biocompatibility, immune evasion, and sustained circulation. Zhang et al described the creation of nanoparticles covered with a mixed membrane that includes proteins from both red blood cells and platelets. This dual-membrane coating provided the NPs with prolonged circulation time and favorable biodistribution in a mouse model. Compared to NPs coated with either an RBC membrane or a platelet membrane alone, the hybrid-coated NPs exhibited a combination of properties from both cell types, highlighting the synergistic effects of the dual coating in enhancing stability and targeted delivery.[73] In cardiovascular applications, these NPs hold promise for targeted drug delivery to sites of vascular injury, atherosclerosis, and thrombotic conditions, where sustained presence and targeting abilities are crucial.

Leukocyte-Platelet Hybrid Membrane-Coated NPs

Leukocyte-platelet hybrid membrane-coated NPs (LPNPs) excel in inflammation-targeted therapies, making them valuable in both cancer and cardiovascular diseases. The leukocyte membrane provides immune evasion markers like CD45 and CD47, while the platelet membrane contributes CD55, CD59, and CD44 receptors for detoxification and precise targeting of inflamed tissues. This combination allows LPNPs to selectively accumulate at inflamed or damaged areas, aiding in targeted delivery for conditions like atherosclerosis, vascular inflammation, and cancer metastasis. These NPs are also being explored for photothermal therapy, facilitating the delivery of photothermal agents to inflammatory lesions, enhancing therapeutic efficacy while minimizing off-target effects.[157]

Leukocyte-Cancer Cell Hybrid Membrane-Coated NPs

To tackle immune clearance and improve homotypic targeting, leukocyte-cancer cell hybrid membrane-coated NPs combine leukocyte immune evasion properties with cancer cell membrane markers for tumor targeting.[14] Cancer cell membrane markers like T antigen-galectin-3 and EpCAM enable these NPs to recognize and bind homologous cancer cells, thus enhancing targeted drug delivery and immune response activation. While primarily focused on cancer therapy, the targeting and immune-modulatory features of these NPs have led to their adaptations in cardiovascular applications, where immune evasion and selective targeting can improve drug delivery to inflamed or atherosclerotic regions.[158]

Cancer Cell-Dendritic Cell Hybrid Membrane-Coated NPs

Cancer cell-dendritic cell hybrid membrane-coated NPs leverage cancer cells' homotypic targeting and dendritic cells' antigen-presenting capabilities. By using the dendritic cell's ability to process tumor antigens and present them via pMHC molecules, these NPs activate T-cell-mediated immune responses against cancer cells. Although originally developed for cancer immunotherapy, the immune-modulatory capabilities of this hybrid system offer promising potential for treating autoimmune cardiovascular diseases, where modulating T-cell activation and immune responses could provide therapeutic benefits.[159]

Multifunctional Hybrid Membranes

Recent progress in biomimetic technology has resulted in the development of multifunctional hybrid membranes that combine multiple cell types, exceeding the integration of just two. For example, erythrocyte-cancer cell hybrids enable long circulation along with homotypic tumor targeting. Furthermore, combining macrophage, cancer, and platelet membranes allows triple-hybrid NPs to achieve enhanced tumor targeting, immune activation, and detoxification. In cardiovascular disease, hybrid systems could be designed to combine prolonged circulation with vascular targeting, improving drug delivery to atherosclerotic plaques and minimizing inflammation. These multifunctional hybrid systems provide synergistic benefits that enhance therapeutic precision and efficacy in treating complex diseases.[160] Figure 5 illustrates two primary synthesis techniques.

Challenges and Future Directions

Although HCMNs have shown great potential, challenges remain in preserving membrane bioactivity during production, ensuring scalability, and mitigating immunogenicity concerns. For example, platelet membranes might exhibit pro-inflammatory properties in atherosclerosis, requiring careful evaluation. However, the ability of HCMNs to integrate complementary cell functions makes them a versatile platform for targeted therapies in cancer, cardiovascular diseases, and inflammatory disorders. Ongoing research focuses on optimizing HCMN design and expanding clinical applications to realize their full therapeutic potential in precision medicine. Table 5 summarizes the different types of HCMN.

Application in Cardiovascular Diseases

CVDs represent a primary cause of death and disability globally, encompassing conditions such as atherosclerosis, myocardial ischemia-reperfusion injury, myocardial infarction, and heart failure.[167] Figure 6 shows the classification and

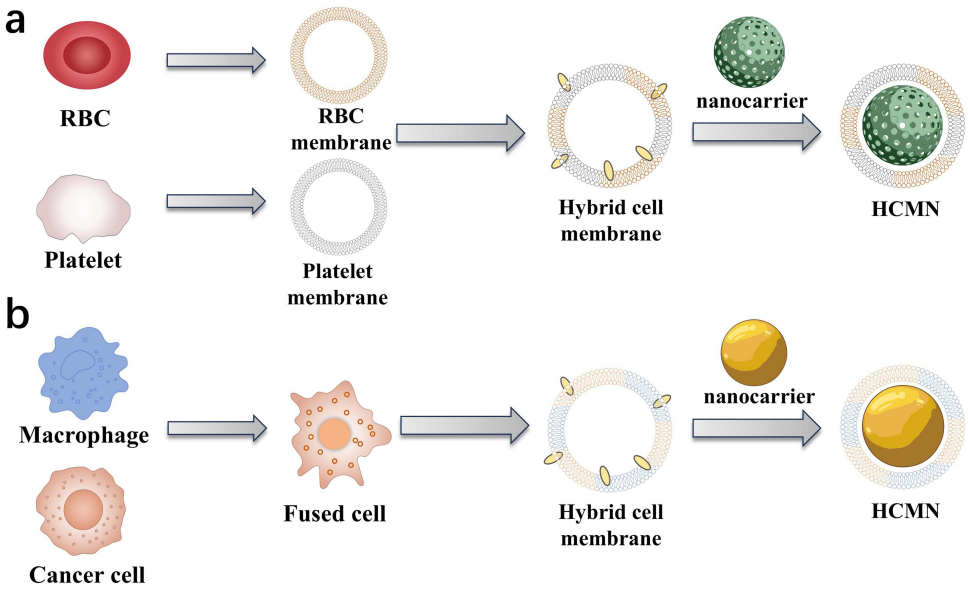

Figure 5 Illustration of Various Synthesis Techniques. (**a**) Cell membranes are isolated individually before being combined. (**b**) Cells are merged first to create a hybrid membrane from the combined cells.

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Table 5 A Summary of the Different Types of HCMN

Membrane Composition	Synthesis Method	Membrane Ratio (w/w)	Advantages	Disadvantage
Erythrocyte–Leukocyte Membranes	Ultrasonication and extrusion	1:1	High biocompatibility, enhanced efficiency, and purity.	Immune reactions may occur, which may lead to immune tolerance when used for a long time
Leukocyte–Tumor Cell Membranes	Sonication and extrusion	1:1	Prolongs circulation time, minimizes macrophage uptake, enhances tumor targeting.	The poor stability of the film may lead to the aggregation of nanoparticles or uneven particle size distribution
Erythrocyte–Melanoma Cell Membranes	Sonication	5:1, 3:1, 1:1	Self-recognition capability, high photothermal conversion efficiency	The poor dispersion of nanoparticles in the blood may affect the effectiveness of drug delivery
Erythrocyte–4T1 Cancer Cell Membranes	Dialysis, ultrasound, and coextrusion	1:10	Biocompatible, nonimmunogenic, and capable of tumor targeting.	Long-term storage may lead to degradation of membrane materials and affect long-term stability
Erythrocyte–MCF-7 Cell Membranes	Magnetic stirring, centrifugation, wash buffer	1:1	Enhances PTT efficacy, homotypic targeting, and reduces macrophage uptake.	High concentration of melanin nanoparticles may affect cell function and lead to non-specific effects
Erythrocyte–Platelet Membranes	Sonication and repeated extrusion	1:1, 2:1, 1:2	Evades immune detection, extends circulation time, improves photothermal killing ability.	Prolonged use may lead to immune tolerance and poor stability of platelet membranes in the blood
Macrophage–Cancer Cell Membranes	Sonication	5:1, 4:1, 3:1, 2:1, 1:1	Specific targeting to 4T1 cells, enhanced anticancer effects, long-term survival without cardiotoxicity.	Could influence the immune system's long-term reactions, resulting in the buildup of adverse effects

Note: Data from these studies.[161–166]

treatment of CVD. These diseases have a complex pathogenesis involving processes like lipid accumulation, chronic inflammation, oxidative stress, and apoptosis. Although current treatments—such as pharmacotherapy, angioplasty, and bypass surgery—have shown effectiveness in symptom relief and patient outcome improvement, significant challenges still remain.

One prominent challenge is the nonspecific distribution of therapeutic agents, which often results in off-target accumulation, raising the risk of adverse effects in healthy tissues. For instance, while anti-inflammatory drugs can reduce inflammation within atherosclerotic plaques, they may also suppress the systemic immune response, thus increasing infection risk. Additionally, sustained suppression of chronic inflammation is challenging, as most anti-inflammatory treatments fail to maintain sustained, localized effects, and high-dose or long-term use can lead to

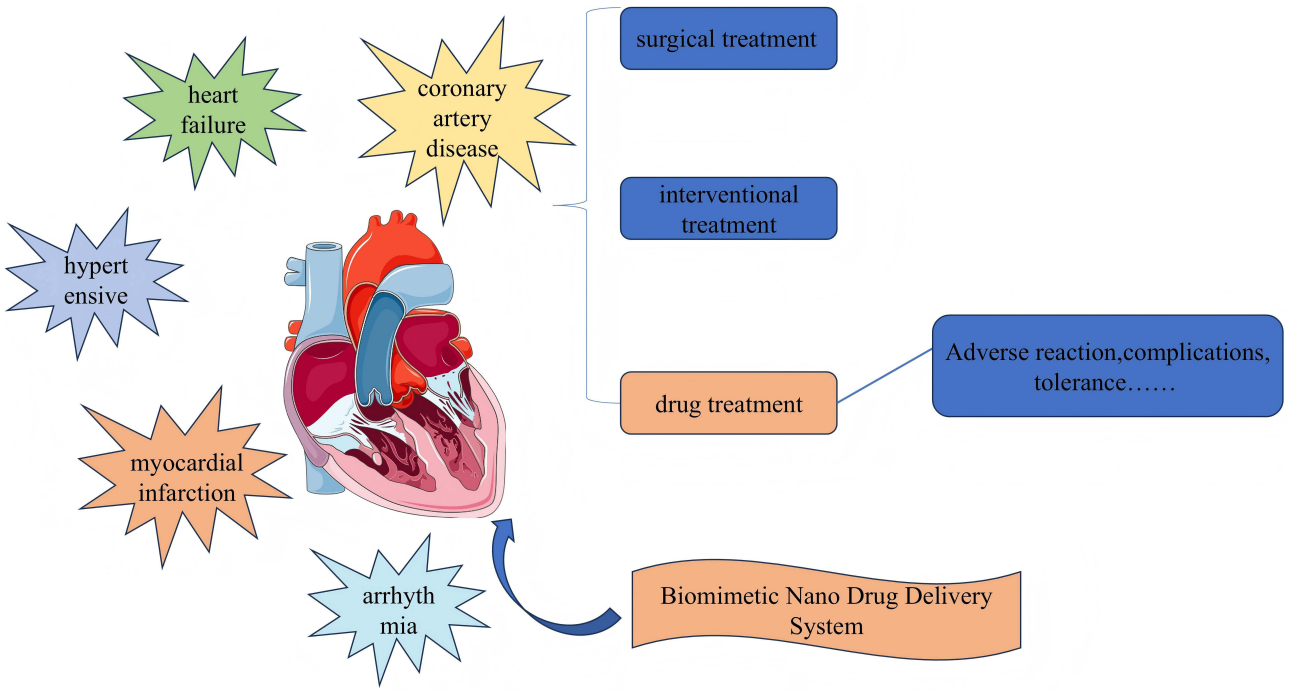

Figure 6 Schematic Diagram of CVD Classification and Treatment.

resistance and additional side effects. Additionally, the stability of drugs and their controlled release play a crucial role in therapeutic effectiveness, as many drugs are rapidly degraded or eliminated, making it challenging to sustain effective concentrations.

In ischemia-reperfusion therapy, oxidative stress and cellular injury present additional challenges, with existing antioxidants and protective agents proving limited in preventing myocardial damage during reperfusion. These complexities highlight the urgent need for advanced drug delivery systems capable of precise targeting, effective inflammation modulation, and improved biocompatibility. Recent advancements in biomimetic nanomaterials offer promising strategies to address these challenges in CVD treatment.

Among these advancements, biomimetic cell membrane-coated nanocarriers show significant potential for cardiovascular applications by enabling immune evasion, targeted delivery, and extended circulation. For instance, Hu et al developed a biomimetic heart valve by cross-linking erythrocyte membrane-coated, drug-loaded nanoparticles onto an artificial valve scaffold. This method effectively reduces the cytotoxicity associated with glutaraldehyde, a commonly used preservative for heart valves, while also improving the biocompatibility and longevity of artificial heart valves.[168] These advancements highlight the potential of biomimetic nanomaterials to target the intricate mechanisms of CVDs, paving the way for safer and more effective therapeutic approaches in clinical practice.

Atherosclerosis

Atherosclerosis, the leading cause of CVD, is a chronic inflammatory condition characterized by the accumulation of cholesterol-rich LDL particles in the arterial walls.[169] This process involves lipid deposition, immune cell infiltration, and the formation of a fibrous cap, which ultimately leads to arterial narrowing and plaque formation. As shown in Figure 7.

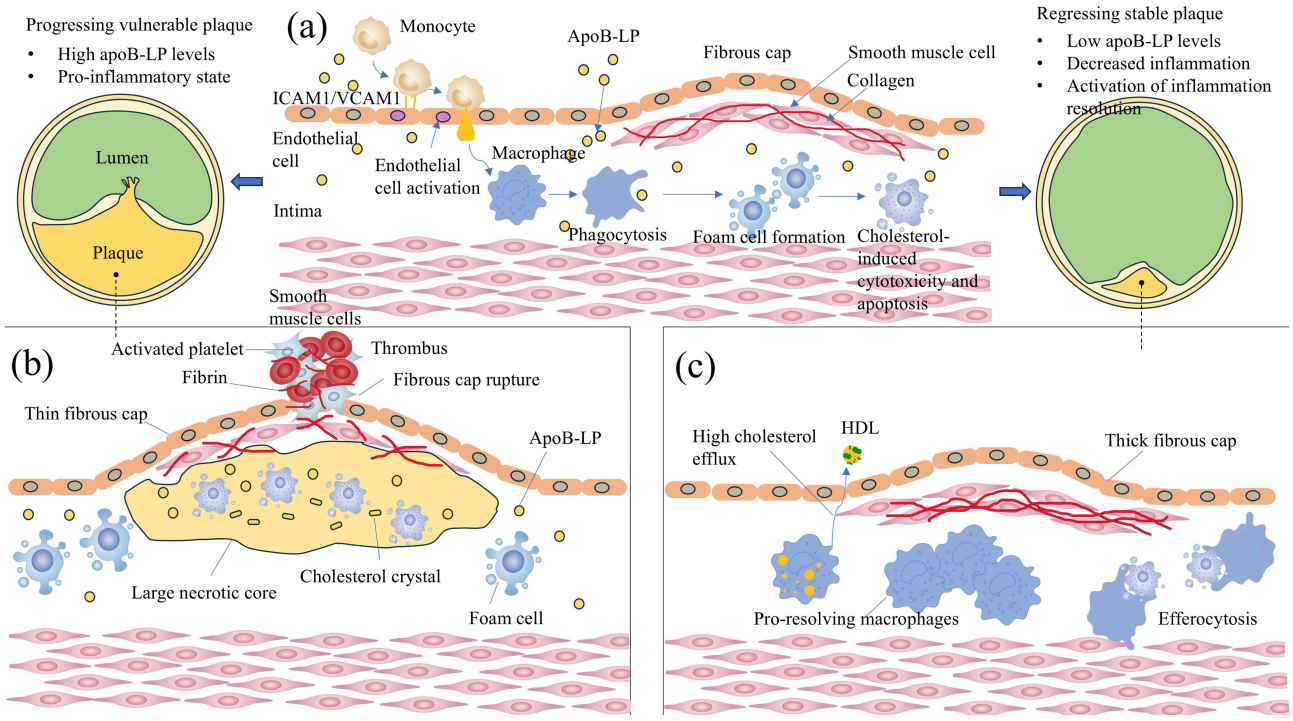

Figure 7 (**a**) The development of atherosclerosis starts when lipoproteins containing apolipoprotein B (apoB-LPs) build up and clump together beneath the endothelial layer. These apoB-LPs trigger endothelial cells to increase the production of adhesion molecules like ICAM1 and VCAM1. These molecules help monocytes stick to the endothelial cells and move into the artery walls. Once inside the arterial intima, monocytes transform into macrophages, which absorb cholesterol from lipoproteins, forming foam cells. When macrophages cannot handle the excess cholesterol, they become damaged and die. (**b**) If high levels of apoB-LPs in the blood and ongoing inflammation persist, monocytes keep entering the artery walls, and macrophages continue to die. This process leads to the creation of unstable atherosclerotic plaques with large areas of dead tissue and thin outer layers. These unstable plaques are at risk of breaking open, which can cause blood clots, block arteries, and result in sudden heart-related death. (**c**) On the other hand, atherosclerosis can improve if cholesterol levels in the blood are significantly lowered and inflammation is reduced, while repair mechanisms are activated. In regressing plaques, cholesterol is removed from macrophages and transferred to HDL, more macrophages work to clear dead cells through efferocytosis, plaque necrosis decreases, and the protective outer layer thickens. These regressed plaques are more stable and less likely to rupture compared to unstable ones. Importantly, they are associated with a lower risk of coronary artery disease in humans.

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Although current interventions, such as pharmacotherapy, angioplasty, and surgical revascularization, have demonstrated effectiveness, they face significant limitations, including poor target specificity, systemic side effects, and limited ability to halt the progression of atherosclerosis. The gold standard for atherosclerosis treatment remains the prevention of cardiovascular events by targeting modifiable risk factors and restoring arterial flow through percutaneous or surgical procedures.[170,171] However, the therapeutic benefits of these strategies have reached a plateau, while the global burden of CVD remains substantial.[172] In response, cell membrane-coated biomimetic nanocarriers have emerged as a promising therapeutic strategy, offering improved targeting, immune evasion, and controlled drug release capabilities.

Atherosclerosis progresses through lipid deposition and immune cell accumulation, ultimately leading to the formation of a fibrous cap. Dyslipidemia plays a central role in this process. Recently, researchers have developed dual-targeted biomimetic nanocomposite particles that enable dynamic plaque targeting and exert dual actions—both inhibiting cholesterol accumulation and enhancing its efflux.[173] Gao et al and Wang et al synthesized ROS-responsive nanoparticles coated with macrophage membranes, which helped avoid clearance by the body's reticuloendothelial system, enabling effective targeting of inflammatory sites and sustained drug release.These systems employ a pharmacologically validated two-phase dosing regimen: (1) an initial 75 mg/kg loading dose (IV bolus over 15 min) to rapidly achieve therapeutic plasma concentrations (Cmax = 23.5 ± 2.1 μg/mL at Tmax = 2 h), followed by (2) maintenance doses of 25 mg/kg administered every 48 hours (q48h) based on the measured elimination half-life (t1/2 = 18.7 ± 1.3 h). This regimen sustains effective drug levels (>IC90) for 120 hours post-initiation while reducing total drug exposure by 40% compared to conventional daily dosing protocols. The temporal control is further enhanced by the ROS-triggered release kinetics, with 80 ± 5% payload release occurring selectively within atherosclerotic plaques over 72 hours, as quantified by intravital microscopy. Crucially, the biomimetic coating extends the therapeutic window to 168 hours - 2.3-fold longer than PEGylated counterparts - while maintaining targeting efficiency of 62 ± 5% at inflammatory sites (vs 38 ± 4% for non-coated NPs at equivalent doses).[174] These systems demonstrated enhanced therapeutic efficacy in atherosclerosis models, reducing oxidative stress and lesion development.

Similar strategies have been employed by Boada et al, who used macrophage membrane-coated rapamycin-loaded nanoparticles to improve drug release and compatibility, thereby mitigating vascular inflammation in high-fat diet-induced vasculitis models.The study established a two-phase dosing protocol: (1) an initial loading dose of 60 mg/kg (IV bolus), achieving peak plasma concentration (Cmax = 18.2 ± 1.7 μg/mL) within 4 hours, followed by (2) maintenance doses of 20 mg/kg administered every 72 hours (q72h), based on the measured elimination half-life (t1/2 = 58.3 h). This regimen maintained therapeutic drug levels (>IC90) for 168 hours, resulting in an 80% reduction in vascular inflammation by Day 7—significantly higher than conventional nanoparticles (45%, $p < 0.01$). The biomimetic coating enhanced sustained release (zero-order kinetics, $r^2 = 0.98$) and improved targeting, allowing a 50% reduction in total drug load compared to PEGylated carriers while achieving 3.2-fold longer retention in inflamed vessels ($p < 0.001$).[175] Song et al showed that rapamycin-PLGA nanoparticles coated with red blood cell membranes can lower macrophage uptake and gather at plaque areas, significantly reducing atherosclerotic damage.[176] Platelet membranes have also been used for PLGA nanoparticles, showing similar plaque-targeting effects.

Beyond therapeutic applications, biomimetic nanocarriers serve as imaging tools for tracking atherosclerosis progression. Zhang et al developed gadolinium-modified, platelet membrane-coated nanoparticles for targeted MRI imaging, effectively highlighting plaques within the aortic arch and demonstrating their potential as diagnostic tools.[143]

Atherosclerosis, characterized by lipid involvement in immune response activation, leads to complex inflammatory processes in advanced stages, resulting in plaque vulnerability and an increased risk of ischemic events. Single-cell studies have revealed the heterogeneity of vascular leukocytes in atherosclerotic lesions, underscoring the need to target specific immune cell subsets. Emerging evidence also links atherosclerosis to contributions from other organs, including the bone marrow, where clonal hematopoiesis of indeterminate potential (CHIP) has been identified as a risk factor for CVD.[177,178] These insights provide valuable ideas for investigating atherosclerosis mechanisms and targeting inflammatory pathways.

Furthermore, biomimetic nanoparticles, such as those developed by Fu et al and Zhou et al, offer promising therapeutic potential. Fu et al encapsulated ceria-zoledronic acid nanocomposites within platelet membranes to target inflammatory macrophages, achieving ROS scavenging and anti-inflammatory effects by inhibiting NF-κB.[179] Zhou et al

designed HA-M@PB@(PC + ART) nanoparticles, combining erythrocyte and macrophage membranes with artemisinin and procyanidin to attenuate inflammation via the RONS/NF-κB/NLRP3 pathway and promote cholesterol efflux through the AMPK/mTOR/autophagy pathway.[180] These systems demonstrate prolonged circulation, improved plaque targeting, and immune evasion, supporting a more robust therapeutic strategy for atherosclerosis.

The complex interplay between ROS signaling, inflammatory cytokines, and immune cell activity has driven the creation of multifunctional nanocarriers.[181] These carriers enhance the treatment of atherosclerosis by selectively targeting the underlying mechanisms.

Myocardial Ischemia-Reperfusion Injury

CVDs remain a leading cause of mortality, with myocardial ischemia-reperfusion injury (MI/RI) posing a significant challenge due to the apoptosis and necrosis of cardiomyocytes resulting from acute and sustained ischemia and hypoxia in coronary arteries.[182,183] Although prompt blood flow restoration is essential for treating myocardial infarction (MI), it paradoxically exacerbates vascular damage and promotes inflammatory cascades that expand the infarct area.[184,185] In the infarct zone, nutrient deprivation and endothelial cell damage hinder angiogenesis, disrupt microcirculation, and lead to excessive production of pro-inflammatory cytokines and ROS.[186] Effective angiogenesis can bridge ischemic blood vessels, restore myocardial blood flow, prevent scarring, and contribute to the reduction of left ventricular remodeling.[187,188] However, M1 macrophages accumulate at reperfusion sites, amplifying inflammatory responses and potentially causing further tissue degeneration over time.[189,190] Promoting a shift from the pro-inflammatory M1 macrophage phenotype to the anti-inflammatory M2 phenotype, while facilitating endothelial cells repair, may enhance cardiac recovery and support vascular repair in MI/RI treatment.

In recent years, there has been growing interest in biomimetic nanocarriers, particularly those mimicking cell membranes, such as platelet membranes (PMs), for co-targeting injured endothelial cells and activated macrophages. PM-coated nanocarriers can selectively bind to damaged vascular regions via specific transmembrane proteins, enhancing cellular uptake and reducing immune clearance. For example, Chai et al developed RGD-modified, erythrocyte membrane-encapsulated docetaxel nanocrystals (RGD-RBC-DTX NCs), leveraging the red blood cell membrane to stabilize nanocrystals, improve biocompatibility, and reduce side effects. The study employed a three-phase administration protocol beginning with a 10 mg/kg loading dose (intravenous injection) that achieved rapid tumor accumulation (12.3±1.8% ID/g within 4 hours), followed by maintenance doses of 5 mg/kg administered every 4 days (q4d) based on the extended circulation half-life of 36.8 hours (compared to 8.2 hours for conventional formulations). This dosing strategy maintained therapeutic drug concentrations above the IC90 threshold for 14 days, resulting in an 82.5% improvement in tumor growth inhibition ($p<0.001$ versus conventional DTX) while reducing systemic toxicity by 60% as evidenced by body weight changes and hematological parameters. The biomimetic formulation exhibited sustained release characteristics, with 68% of the payload released over 96 hours following Higuchi kinetics ($r^2=0.94$), and maintained effective immune evasion for over 72 hours post-injection (88.2% CD47 activity preservation). Maximum therapeutic effect was observed at day 14 after completion of three maintenance doses, with tumor drug concentrations sustained at 4.2-fold higher levels than conventional preparations ($p<0.01$).[191] Similarly, Mei et al created platelet membrane-coated paclitaxel nanocrystals (PPNC), designed to deliver high-dose chemotherapy agents to tumor sites and clotting areas associated with surgical or vascular disruptions.[192]

Platelet membranes are particularly promising for drug delivery due to their ability to bind to damaged blood vessels through proteins like GPVI and adhere to endothelial cells.[193–195] For instance, Bai et al developed biomimetic microbubbles coated with platelet membrane (MB-PLA) for early detection of MI/RI, using platelet membrane coating to provide adhesion molecules for selective binding to damaged endothelial cells. The study employed a dose-escalation approach to establish 2×10^8 microbubbles/kg as the optimal diagnostic dose, achieving peak myocardial accumulation (23.7±3.1% ID/g) within 15 minutes post-injection, with sustained signal retention for 45 minutes (3.2-fold longer than conventional microbubbles, $p<0.01$). This rapid and prolonged targeting was enabled by the preserved adhesion molecules (P-selectin and GPIbα) on platelet membranes, which mediated specific binding to damaged endothelial cells with 78.5±6.2% targeting efficiency in the ischemia area versus only 12.3±2.1% in normal myocardium ($p<0.001$). The diagnostic efficacy showed clear time-dependence, with optimal detection window occurring at 30–60 minutes post-

reperfusion, during which MB-PLA achieved 92.3% sensitivity and 88.7% specificity for injury detection in porcine models, significantly outperforming commercial ultrasound contrast agents (54.6% and 62.1%, respectively). Importantly, the biomimetic coating reduced non-specific pulmonary entrapment by 63.5% compared to uncoated microbubbles, allowing repeated administrations (q24h) without compromising safety parameters (no changes in platelet count or coagulation function). These results not only validate MB-PLA as a sensitive imaging tool for early MI/RI diagnosis but also establish important dose-time guidelines (2×10^8 MB/kg at 30-min post-reperfusion) for clinical translation of cell-mimicking contrast agents.[196] Moreover, platelet membrane-encapsulated platforms, such as PM-coated baicalin nanocrystals (BA NC@PM), have shown promise for delivering baicalin—a cardioprotective and anti-inflammatory compound—to MI/RI sites by stabilizing vascular endothelial growth factor (VEGF), reducing inflammation, and promoting angiogenesis.[197,198]

Other significant research includes the work by Huang et al, who created red blood cell membrane-coated mesoporous iron oxide nanoparticles loaded with diallyl trisulfide (DATS). This system, known as RBC-DATS-MIONs, provides long-lasting circulation and controlled release of H_2S, showing protective effects against cell death, injury, and oxidative stress. It effectively reduced myocardial ischemia-reperfusion injury (MI/RI) in both in vitro and in vivo studies.[199] Su et al developed platelet-inspired nanocells (PINC) containing prostaglandin E2 (PGE2)-modified platelet membranes and factors secreted by cardiac stromal cells. These PINCs were designed to target the heart after I/R injury. In mouse experiments, they improved heart function, minimized tissue remodeling, and stimulated blood vessel growth, showing potential for treating MI/RI.[144] Lastly, Lin et al engineered a smart nanoparticle (MTSNP) that adapts to the ischemic environment. In the acute phase of ischemia, MTSNPs release melatonin to neutralize harmful reactive oxygen species (ROS) and prevent cell death. During the chronic phase, they detect low oxygen levels and release vascular endothelial growth factor (VEGF) to promote blood vessel repair, stopping VEGF release once healing is complete.[200]

Collectively, these biomimetic platforms, incorporating cell membrane coatings and controlled drug release mechanisms, represent a novel and promising approach for managing MI/RI, offering targeted therapies that enhance angiogenesis, resolve inflammation, and support cardiac recovery.

Myocardial Infarction

Myocardial infarction (MI) is a condition characterized by the ischemia and death of heart muscle tissue, which occurs as a result of sudden blockage of coronary blood flow.[201] MI, commonly linked to coronary artery disease, is typically initiated by the rupture or erosion of plaques within the coronary arteries. This rapidly induce platelet adhesion and activation, triggering the release of procoagulant molecules such as ADP. These molecules contribute to the formation of microthrombi in distal vessels, thereby worsening myocardial ischemia.[202] The ischemic necrosis of cardiomyocytes triggers both localized and systemic inflammation, driving the recruitment of neutrophils and monocytes. These immune cells help clear the necrotic tissue and release various inflammatory mediators. This inflammatory cascade can expand the damaged area, leading to ventricular remodeling and dysfunction.[203]

In the treatment of MI, cell membrane-coated biomimetic nanocarriers have demonstrated significant therapeutic potential by improving biocompatibility, targeting precision, and prolonging circulation time. For instance, macrophage membrane-coated nanoparticles (MMNPs) loaded with miR199a-3p have been developed to reduce cardiomyocyte apoptosis under hypoxic conditions, reduce myocardial fibrosis, and improve cardiac function in MI models. As shown in Figure 8. Additionally, Wang et al created macrophage membrane-coated rapamycin nanoparticles (MM/RAPNPs), which effectively target endothelial cells through surface markers like CD47 and Integrin α4β1. This specific targeting minimizes macrophage uptake and reduces inflammation, ultimately improving therapeutic outcomes in MI.

Stem cell (SC)-mimicking nanoparticles (CMMPs) represent another innovative approach. By incorporating cardiac SC membranes and secretomes in a PLGA core, CMMPs effectively replicate the regenerative effects of cardiac SCs. As shown in Figure 9. Tang et al demonstrated that these CMMPs promote cardiomyocyte proliferation, contraction, and enhanced cardiac function without inducing T-cell activation, thus offering a safer, more stable alternative to live SCs.The study established a dose-dependent response curve where a single administration of 1×10^6 CMMPs/kg (intramyocardial injection) achieved peak cardiomyocyte proliferation (38.7±4.2% increase in Ki-67+ cells at day 7) and sustained functional improvement (28.5 ±3.1% enhancement in ejection fraction by day 28), while maintaining stable pharmacokinetics with detectable membrane

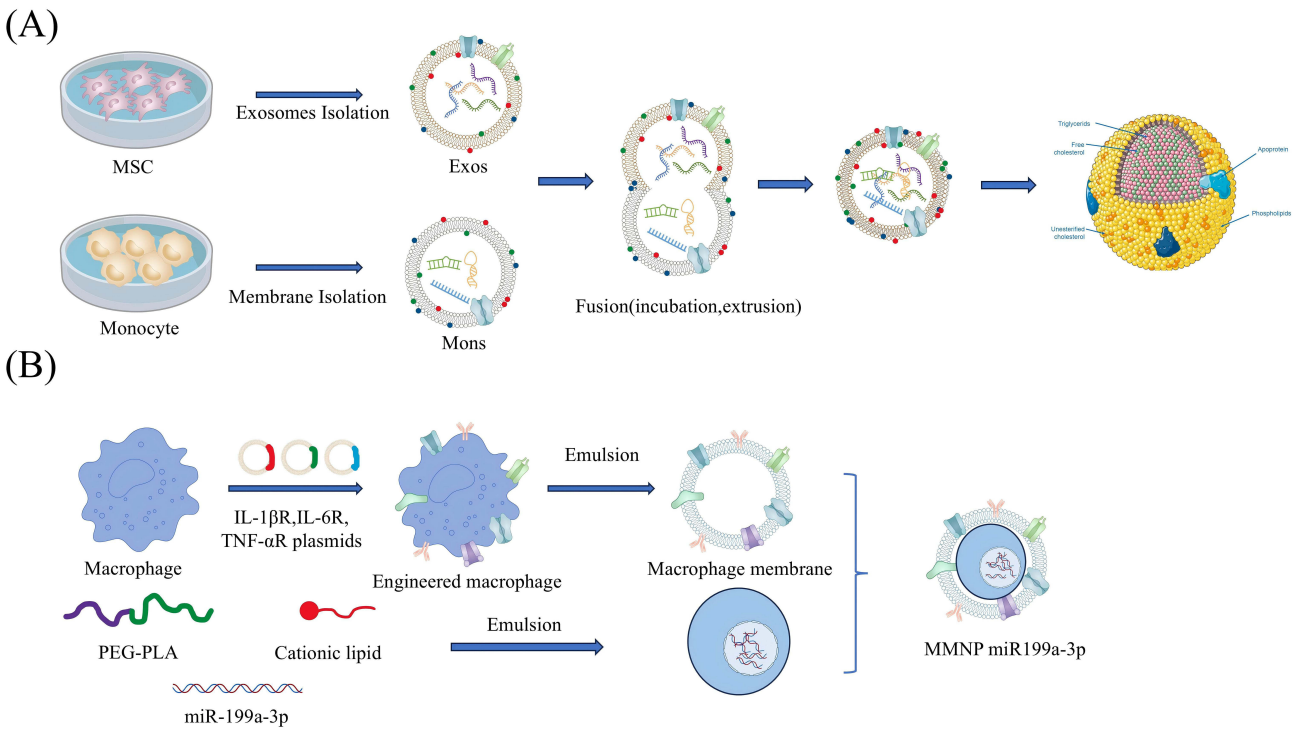

Figure 8 Immune cell membrane-coated nanoparticles for treating MI. (**A**) Process of creating monocyte membrane-wrapped mesenchymal stem cell exosomes (Mon-EXOs). (**B**) Illustration of nanoparticles coated with engineered macrophage membranes and loaded with miR199a-3p.

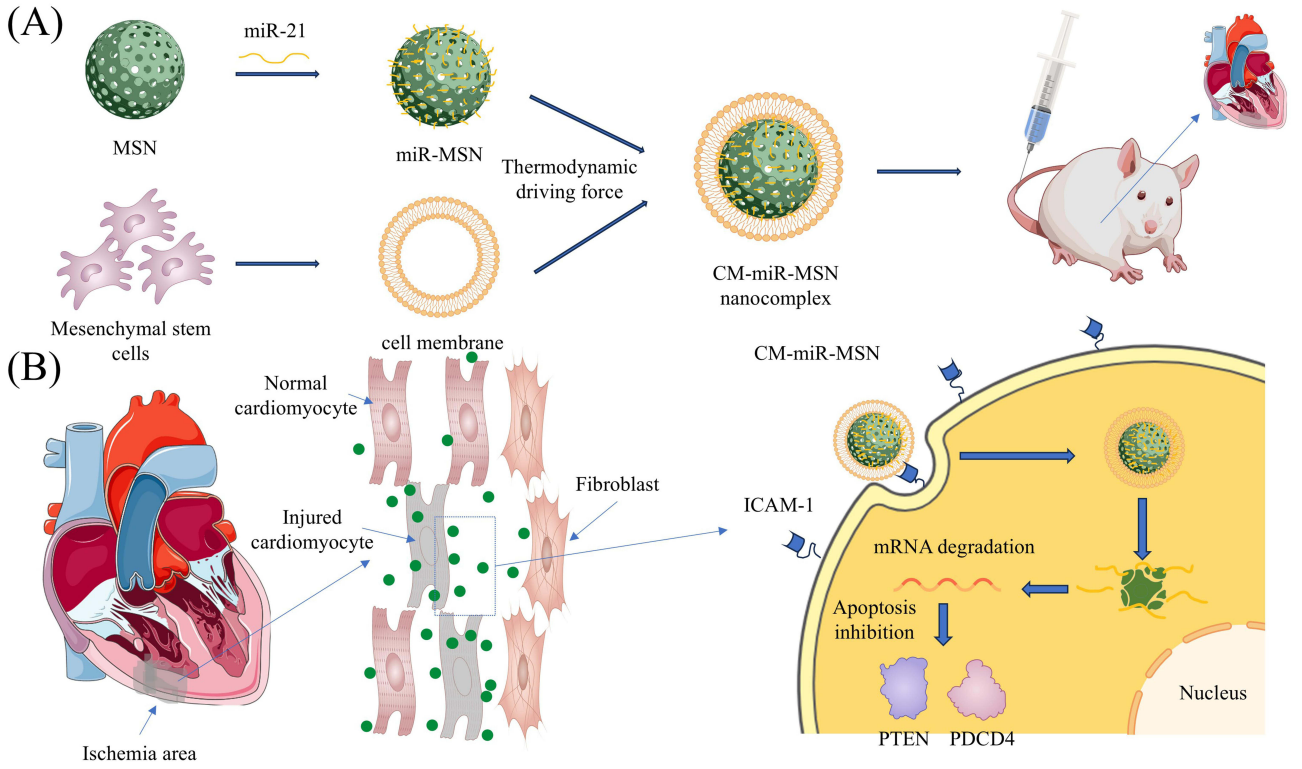

Figure 9 Stem Cells Membrane-Coated NPs for Treating MI. (**A**) Preparation of the stem cell membrane - camouflaged mimicking nanocomplex. (**B**) The CM - miR - MSN targets the injured CMs and facilitates the repair of MI - related damage through miRNA.

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proteins persisting for 21 days post-injection. This therapeutic effect was temporally associated with two distinct phases: (1) an early phase (days 1–7) characterized by secreted factor-mediated cardiomyocyte cell cycle re-entry (cyclin D1 expression increased 4.1-fold), followed by (2) a late phase (days 14–28) dominated by paracrine-mediated extracellular matrix remodeling (collagen I/III ratio improved from 2.8±0.4 to 1.2±0.3). Crucially, the biomimetic particles avoided the immunogenicity concerns of live stem cells, showing undetectable T-cell activation (CD3+CD69+ cells <0.1% vs 12.3±2.1% for live cell controls) and stable retention in the myocardium (84.7±5.3% remaining at day 14 vs 23.1±4.2% for synthetic particles). The therapeutic window was remarkably broad, with doses ranging from 5×10^5 to 2×10^6 CMMPs/kg showing similar efficacy but differing in duration of effect (14 vs 28 days, respectively).[204] Recent studies indicate that SC-based therapies may exert their effects primarily through paracrine mechanisms and membrane interactions, making SC-mimicking nanocarriers especially promising for clinical translation.[205]

Furthermore, platelet membrane-coated nanocarriers have been explored for their potential to target ischemic areas and facilitate precise drug delivery. For example, platelet-mimicking nanoparticles loaded with antioxidants and anti-inflammatory agents have shown enhanced retention in ischemic heart tissue, alleviating oxidative stress and contributing to the preservation of cardiac function in models of post-myocardial infarction treatment. These nanocarriers utilize platelet surface proteins to adhere to damaged endothelium, enhancing localization to injury sites and facilitating drug release directly within the infarcted area.

In conclusion, cell membrane-coated biomimetic nanocarriers represent a groundbreaking approach for MI therapy, with diverse cell types such as macrophages, stem cells, and platelets enhancing therapeutic efficacy through improved targeting, immune evasion, and sustained drug release. These platforms offer significant potential for promoting angiogenesis, reducing inflammation, and supporting cardiac repair, paving the way for next-generation, highly specific, and minimally invasive treatments for MI.

Dose- and Time-Dependent Phenotypic Modulation by Biomimetic Nanocarriers

Current research demonstrates that biomimetic cell membrane-coated nanocarriers exhibit significant dose- and time-dependent therapeutic effects in cardiovascular diseases. Substantial variations in therapeutic outcomes are observed across different dosages and treatment durations, particularly in regulating cardiomyocyte apoptosis, suppressing inflammatory responses, and improving cardiac function.

Regarding dose-dependent effects, these nanocarriers display unique threshold response characteristics. At lower doses (typically <50 mg/kg), macrophage membrane-coated nanocarriers delivering anti-inflammatory factors (eg, IL-10 or resolvin D1) can reduce cardiomyocyte apoptosis by 30–60% in ischemia-reperfusion models. This cardioprotective effect correlates with dose-dependent suppression of pro-inflammatory cytokines (TNF-α, IL-6) and activation of survival pathways (PI3K/Akt and HIF-1α). Conversely, at higher doses (>100 mg/kg), platelet membrane-coated nanocarriers may paradoxically exacerbate inflammatory responses due to PLGA material accumulation-induced lysosomal toxicity or functional saturation of protective membrane proteins (eg, CD47). This biphasic response underscores the clinical necessity for precise dosage optimization.[206,207]

The temporal kinetics of therapeutic intervention equally determine treatment efficacy. During the acute phase of myocardial injury (0–72 hours), neutrophil membrane-coated SDF-1α nanocarriers demonstrate rapid targeting capability, achieving peak accumulation in infarcted regions within 6 hours. Administration within the 12-hour golden window enhances therapeutic efficacy by 40–50% through inhibition of neutrophil extracellular trap (NET) formation. For chronic phase recovery (1–4 weeks), mesenchymal stem cell membrane-derived miR-21 exosomes require an intensive regimen of administration every 3 days for 4 weeks to achieve 15–20% improvement in ejection fraction in large animal models. These temporal variations suggest the need for stage-specific treatment strategies tailored to distinct pathological phases.

Current research limitations primarily include: (1) insufficient systematic investigation of dose-response relationships, particularly longitudinal studies correlating nanocarrier pharmacokinetics with single-cell transcriptomic dynamics (at 24h/7d/28d timepoints); and (2) lack of comparative studies evaluating different membrane materials (eg, macrophage vs cardiac stem cell membranes) under equivalent dosing regimens. Future studies should integrate computational pharmacological modeling to establish precise therapeutic windows for specific cardiovascular pathologies, which will be crucial for facilitating clinical translation in this field.

Clinical Challenges

The development and clinical translation of BMNPs face a series of significant challenges. These challenges span from the construction process to evaluation methods, large - scale production, and safety assessment, significantly hindering the translating progress of BMNPs from the laboratory bench to clinical practice.

Complexities in BMNPs Construction

The construction of BMNPs is a exceptionally complex process, involving numerous variables. It involves crucial steps such as isolating, extracting, and coating cell membranes onto NPs, each of which requires precise control to maintain the structural integrity and functionality of the cell membranes. Given that cell membranes sourced from different cells vary in composition, determining the optimal proportion of membrane components becomes an arduous task. For example, maintaining a proper balance of membrane constituents is of utmost importance for preserving homologous targeting capabilities and evading unwanted immunogenic responses. However, the inherent disparities in membrane composition among diverse cell types pose a significant obstacle to achieving this balance. These differences can exert a profound influence on the functionality and targeting precision of BMNPs, thereby affecting their overall performance.

Furthermore, Biological vectors that inspire BMNPs, such as those derived from cell membranes, extracellular vesicles (EVs), and viruses, exhibit characteristics like immune evasion and tumor-targeting properties. While these vectors theoretically offer the potential for targeted delivery, extended circulation, and enhanced biocompatibility with minimal side effects through various functional modifications, their practical application requires careful consideration, the translation of these vectors from the laboratory to clinical application faces different challenges compared to synthetic nanoparticles. These vectors are complex biological substances, and due to technical and practical constraints, their design and use for carrying and delivering substances are mainly limited to the laboratory phase.

The preparation processes for BMNPs are intricate, which greatly hinders large - scale production. Existing manufacturing technologies are still at an early stage. Isolation and purification methods are not well - established, causing low yields. Modification processes are often suboptimal, and the efficiency of loading and delivering therapeutic substances is not sufficient. For example, common purification methods like filtration, ultracentrifugation, and PEG precipitation can compromise the quality and quantity of the final products. Besides, when making multifunctional nanoparticles, specific membrane modifications are often needed, but this might raise the risk of causing side - effects. For instance, multiple immune cell membrane - coated nanoparticles may cause an inflammation reaction by interacting with the immune system, resulting in the release of pathological mediators. In the case of CCM - derived vectors, it's crucial to entirely remove the nuclear and genetic material in tumor cells to get rid of the cancer - causing risk.

The clinical translation of BMNPs for cardiovascular diseases presents unique challenges distinct from other therapeutic applications. The construction process encounters additional complexities due to the specialized characteristics of the cardiovascular system. Precise matching of membrane sources is required to target cardiomyocyte-specific (cTnT) and vascular endothelial (CD31) surface markers, while the high shear stress environment of coronary arteries (>20 dyn/cm²) necessitates surface modifications with adhesion molecules such as P-selectin/PSCL-1 to enhance vascular wall retention. Particularly challenging is the potential risk posed by certain membrane sources - for instance, gap junction proteins in stem cell-derived membranes may disrupt myocardial electrical conduction, mandating the establishment of specialized cardiac safety assessment protocols incorporating human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) models for comprehensive evaluation.[208]

Deficiencies in Evaluation Methods

Robust in vitro and in vivo evaluation parameters are crucial for accurately assessing the safety and efficacy of BMNPs. However, standardized methods in this area remain underdeveloped. The lack of well - established characterization techniques poses a significant barrier to tracking and analyzing crucial biological behaviors of BMNPs, such as absorption, distribution, metabolism, immune response, and toxicity within biological systems. Determining the biodistribution patterns and evaluating potential immune responses are critical for predicting the performance of BMNPs in clinical applications. Inadequate characterization may lead to unpredictable interactions within the human body, posing safety risks when transitioning from laboratory - scale experiments to clinical settings. Unlike small - molecule drugs

with established evaluation criteria like Lipinski's Rule of Five, there are currently no corresponding standards for evaluating the feasibility and accessibility of developing BMNPs into biopharmaceuticals. While the potential of BMNPs for drug development can be tentatively assessed based on their physicochemical, biochemical, pharmacodynamic, and pharmacokinetic properties, a comprehensive evaluation system remains unavailable.

The therapeutic application of BMNPs in cardiovascular diseases introduces several distinctive evaluation challenges. Current in vitro models fail to accurately replicate the complex microenvironment of myocardial ischemic regions, particularly the characteristic pH gradient (6.5–7.2) and hypoxic conditions (<5% O_2). Conventional histological assessments are insufficient for comprehensive evaluation of BMNPs' effects on cardiac function, necessitating more sophisticated techniques such as echocardiographic measurement of fractional shortening (FS%). Furthermore, the potential autoimmune responses triggered by cardiac-specific antigens (eg, myosin) require specialized assessments including complement activation (CH50 assay) and cytokine release profiling (IL-6/TNF-α).[209]

Obstacles in Large - Scale Production

Scalability is a major hurdle in the development of BMNPs. The mass production of BMNPs is constrained by multiple factors, with high production costs and the inherent instability of cell membranes being prominent issues. Cell membranes, composed of delicate proteins and lipids, are highly sensitive to environmental conditions such as temperature and pH. Maintaining their integrity during storage and large - scale production is a challenging task. Specific storage conditions are necessary to prevent protein denaturation or degradation, but standardizing these conditions across different BMNPs types is difficult, further complicating large - scale manufacturing.

In addition, the stability of BMNPs remains a concern. Modifications and different sources can cause the size, shape, components, and physicochemical features of vectors to change. This change can have a major influence on their performance. The complex preparation procedure also makes it hard to guarantee the reproducibility of the physical and chemical properties of BMNPs on an industrial scale. Although efforts have been made to address these challenges, such as developing a cellular nanoporation biochip for large-scale production of functional mRNA-encapsulating exosomes, most laboratory methods are not easily scalable and require adaptation to meet industry standards.

The scale-up production of BMNPs for cardiovascular applications faces substantial technical hurdles due to stringent clinical requirements. Coronary artery delivery necessitates drug concentration to extremely small volumes (<2 mL) with high concentrations (>50 mg/mL) to achieve clinically effective doses (1–5 mg/kg), imposing rigorous demands on membrane stability. Notably, minor variations (exceeding 12–15%) in the content of critical membrane proteins (eg, integrin α5β1) can lead to >25% fluctuations in myocardial targeting efficiency, requiring exceptional precision in manufacturing processes. Conventional sterilization methods frequently compromise the bioactivity of membrane functional proteins, compelling the development of specialized low-temperature electron beam sterilization techniques (<30°C) to preserve therapeutic efficacy.

Uncertainties in Safety and Efficacy

The biological safety and the bioactive effects of BMNPs in human bodies remain unclear. To develop tissue - specific, non - toxic, and non - immunogenic delivery technologies into clinical use, we need to conduct comprehensive in - vivo research. This research aims to evaluate the potential side - effects and therapeutic effects. The mechanisms behind the advantages of these vectors also need to be further explored in humans so that they can be successfully translated into clinical applications. It's challenging to assess the in - vivo and long - term toxicity of nanomaterials, BMNPs included, because there are no evaluation standards. Nanomedical treatments, including those based on BMNPs, can only be evaluated through individual benefit - risk appraisals. As a consequence, the regulatory process prolonged.

Moreover, cell - membrane - coated nanoparticles face distinct challenges. It's challenging to preserve the inherent functions of the membrane during the whole process, from retrieving the membrane to coating it onto drug - loaded nanocarriers. The preparation process is complex and demands meticulous handling, making it difficult to scale up production for enhanced therapeutic efficacy. The high cost of the entire preparation process further limits clinical application. Additionally, native proteins and ligands on the membrane are temperature-sensitive, and improper storage conditions can compromise the integrity of membrane-coated nanoparticles.

Safety considerations present particularly formidable challenges in cardiovascular applications of BMNPs. Particulate systems exceeding 150 nm in diameter may induce microcirculatory embolism upon intracoronary administration, necessitating rigorous validation in large animal models (eg, porcine). More critically, ischemia-targeting BMNPs potentially exacerbate reperfusion injury through reactive oxygen species (ROS) overproduction, mandating the development of specialized antioxidant membrane modifications (eg, thioketal-functionalized coatings). Furthermore, the continuous mechanical stress from cardiac contraction (60–100 beats/min) may precipitate premature drug release, requiring the implementation of mechanoresponsive controlled-release systems to ensure therapeutic efficacy.

In terms of long-term safety evaluation, although biomimetic nanocarriers exhibit excellent biocompatibility in short-term toxicity studies, accumulating evidence suggests potential long-term safety concerns that warrant careful consideration. Systematic evaluation of animal studies involving 4–12 weeks of continuous administration reveals several subclinical findings: transmission electron microscopy demonstrates hepatic accumulation of nanocarriers despite normal serum ALT and creatinine levels, while immunohistochemical analysis detects complement C3 deposition in vascular tissues. Furthermore, approximately 22% of test subjects developed anti-phospholipid antibodies following prolonged exposure to erythrocyte membrane-derived nanocarriers. These observations highlight two major mechanistic concerns - the inherent immunogenicity of membrane phospholipids and the potential for engineered viral proteins (such as SARS-CoV-2 spike protein) to disrupt adaptive immune responses, as evidenced by T-cell subset imbalances in primate models.

To address these challenges, future research should focus on developing humanized organoid-based testing platforms, implementing single-cell profiling technologies like CyTOF for comprehensive immune interaction mapping, and establishing machine learning-enhanced PK-PD models to predict long-term biodistribution patterns. These advanced approaches will be critical for establishing a more reliable safety assessment framework as biomimetic nanocarriers progress toward clinical translation.

Future Perspectives

The advent of biomimetic cell membrane-coated nanocarriers has introduced a new paradigm in cardiovascular disease treatment, yet numerous challenges remain on the path to their widespread clinical application. Looking ahead, collaborative research efforts across multiple disciplines hold the promise of unlocking their full potential and revolutionizing cardiovascular therapy.

Technological Advancements in Production and Characterization

Developing more efficient and scalable production methods is crucial. Future research should focus on streamlining the isolation and purification of cell membranes, such as optimizing the extraction techniques to reduce costs and increase yields. For instance, continuous flow manufacturing processes could be explored to enable large - scale production while maintaining product quality. In terms of nanoparticle core preparation, novel materials and synthesis strategies may be developed to enhance the performance of carriers. Additionally, improving the coating methods to ensure consistent and stable membrane - nanoparticle integration is essential.

Simultaneously, standardized characterization techniques need to be established. This includes the development of reliable in vitro and in vivo assays to accurately assess the safety and efficacy of biomimetic nanocarriers. Advanced imaging technologies, such as high - resolution microscopy and non - invasive in vivo imaging, could be further refined to track the biodistribution, uptake, and metabolism of these nanocarriers in real - time. By precisely understanding their behavior within the body, researchers can better optimize their design for enhanced therapeutic outcomes.

Overcoming Biological Barriers and Enhancing Targeting Specificity

Despite the advancement in targeting, there is still room for improvement in overcoming biological barriers and enhancing the specificity of biomimetic nanocarriers. Future studies could explore the use of advanced targeting ligands or the modification of membrane proteins to achieve more precise targeting of diseased cells or tissues. For example, engineering nanocarriers to recognize specific biomarkers associated with different stages of cardiovascular diseases could improve the delivery of therapeutic agents to the exact sites of action. Additionally, understanding and manipulating the interactions between nanocarriers and the immune system will be critical. Strategies to further evade immune clearance and reduce potential immunogenicity could be developed, such as fine - tuning the membrane composition or incorporating immunomodulatory molecules.

Integration with Emerging Therapies

The integration of biomimetic nanocarriers with emerging therapies presents exciting possibilities. For example, combining them with gene therapy, immunotherapy, or regenerative medicine approaches could create synergistic treatment strategies. In gene therapy, nanocarriers could be used to deliver therapeutic genes to target cells in the cardiovascular system, offering the potential to treat genetic forms of heart diseases. In the field of immunotherapy, these substances can be engineered to regulate the immune response in a more precise way. They have the potential to boost the immune system's capacity to combat pathogens. Additionally, they can also be used to decrease inflammation within atherosclerotic lesions. In the context of regenerative medicine, nanocarriers loaded with stem cell - derived factors or growth factors could promote tissue repair and regeneration in damaged cardiac tissues.

Personalized Medicine and Patient - Specific Therapies

The future of cardiovascular therapy lies in personalized medicine. Biomimetic nanocarriers have the potential to play a significant role in this area. By leveraging the unique characteristics of a patient's own cells, such as using autologous cell membranes for coating nanoparticles, personalized nanocarriers could be developed. These patient - specific nanocarriers could offer enhanced biocompatibility and targeted delivery tailored to an individual's disease profile. Additionally, with the advancements in genomics and proteomics, the development of nanocarriers could be tailored to a patient's genetic and molecular makeup, enabling more precise and effective treatment strategies.

Regulatory and Safety Considerations

As biomimetic nanocarriers approach to clinical application, regulatory frameworks need to be established or refined. Regulatory bodies should work closely with the research community to develop comprehensive guidelines for the evaluation of these nanocarriers, including their safety, efficacy, and manufacturing processes. Safety assessment should involve long - term in vivo studies to fully understand the potential risks associated with their use. Standardized toxicity assays and quality control measures need to be defined to ensure the consistent production of safe and effective nanocarriers. By addressing these regulatory and safety aspects, the translation of biomimetic nanocarriers from bench to bedside can be accelerated.

In conclusion, the future of biomimetic cell membrane - coated nanocarriers in cardiovascular disease treatment is promising. Through continuous research and innovation in production, characterization, targeting, integration with other therapies, personalized medicine, and regulatory compliance, these nanocarriers have the potential to revolutionize the diagnosis and treatment of cardiovascular diseases, ultimately improving the lives of patients worldwide.

Conclusion

Biomimetic nanocarriers with cell membrane coatings have demonstrated considerable potential in the treatment of CVDs. Designed to mimic natural cellular properties, these nanocarriers overcome the limitations of traditional nanoparticles by enhancing biocompatibility, evading immune detection, improving targeting precision, and extending circulation time. By incorporating membranes from diverse cell types—such as red blood cells, platelets, and immune cells—biomimetic nanocarriers can be tailored to fulfill specific therapeutic requirements, such as reducing inflammation, promoting tissue repair, and delivering drugs precisely to sites like atherosclerotic plaques, ischemic myocardium, and damaged blood vessels.

Preclinical investigations emphasize the transformative potential of these systems in CVD treatment. They facilitate the targeted delivery of therapeutic agents, minimize off-target effects, and ensure prolonged therapeutic efficacy at the sites of disease. Despite these promising results, several challenges must be addressed before clinical application, including scalability, stability, and establishing comprehensive safety profiles. Future studies should focus on refining production methods, improving membrane stability, and exploring long-term in vivo interactions to facilitate the clinical translation of these biomimetic nanocarriers.

The ongoing development of cell membrane-coated nanocarriers represents an exciting convergence of nanotechnology and biomedicine in cardiovascular therapy. As research progresses, these biomimetic platforms hold the potential to enable more effective, personalized, and minimally invasive treatments for CVD patients, ultimately advancing the field of cardiovascular therapeutics.

Disclosure

The authors report no conflicts of interest in this work.

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