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Biomimetic and Cell Membrane-Coated Nanocarriers for Targeted Drug Delivery: Design, Immune Evasion, and Therapeutic Applications

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Abstract:

Background: Synthetic nanocarrier drug delivery systems face a fundamental biological challenge: the immune system recognizes them as foreign materials, triggering rapid opsonization, complement activation, and phagocytic clearance by the mononuclear phagocyte system that removes the majority of intravenously injected nanoparticles from circulation within minutes to hours, limiting their accumulation at intended therapeutic targets. Biomimetic nanocarriers — nanoparticles coated with natural cell membranes or functionalized with biological molecules derived from cells — address this challenge by disguising synthetic nanoparticle cores within biological cloaks that inherit the immune-evasive surface properties, cell-type-specific homing molecules, and functional proteins of the source cells, enabling nanocarriers to circulate in blood, penetrate biological barriers, and target specific tissues with a degree of biological specificity inaccessible to conventional PEGylated synthetic nanoparticles.

Objective: This review comprehensively examines the biological rationale, preparation technologies, characterization methods, mechanisms of immune evasion and cellular targeting, and therapeutic applications of biomimetic cell membrane-coated nanocarriers derived from red blood cells, white blood cells, platelets, cancer cells, stem cells, and hybrid membranes, with emphasis on research advances through 2024.

Results and Discussion: Cell membrane-coated nanocarriers from diverse source cells demonstrate superior circulation half-lives (two- to fivefold longer than equivalent PEGylated nanoparticles), organ- and cell-type-specific biodistribution patterns determined by the source cell's natural homing behavior, and preservation of functional surface proteins including CD47 (don't-eat-me signaling), integrin complexes (cell adhesion), and receptor ligands (homotypic targeting) that collectively provide biological targeting specificity unobtainable by synthetic surface functionalization. Hybrid membrane systems combining membrane components from two or more cell types create designer biomimetic surfaces with combined biological functions exceeding what any single cell membrane can provide.

Conclusion: Biomimetic cell membrane-coated nanocarriers represent one of the most biologically sophisticated drug delivery platforms to emerge in the past decade, offering immune evasion, biological targeting, and functional protein retention that collectively address the most fundamental limitations of synthetic

nanocarrier systems. Scale-up of cell membrane extraction and coating processes, quality control of biological membrane preparations, and clarification of the regulatory pathway for this novel hybrid bio-synthetic product class are the principal translation barriers requiring resolution.

Keywords: *Biomimetic nanocarriers; cell membrane coating; red blood cell membrane; cancer cell membrane; platelet membrane; immune evasion; CD47; homotypic targeting; white blood cell membrane; hybrid membrane nanoparticles*

1. Introduction

The development of nanoparticle-based drug delivery systems over the past three decades has been driven by the promise of targeted drug delivery — concentrating therapeutic agents at disease sites while minimizing exposure of healthy tissues to drug toxicity. The enhanced permeability and retention (EPR) effect, passive accumulation of nanoparticles in tumor tissue through the leaky vasculature and impaired lymphatic drainage characteristic of solid tumors, provided the theoretical foundation for tumor-targeted nanocarrier drug delivery and motivated the development of dozens of liposomal, polymeric, and inorganic nanocarrier drug products [1,2].

However, the translation of nanoparticle drug delivery from laboratory promise to clinical benefit has been substantially limited by the biological barriers encountered by nanoparticles in the bloodstream and body. Immediately upon intravenous injection, nanoparticles are recognized by the immune system through a process of opsonization — adsorption of serum proteins including immunoglobulins, complement components, and fibronectin onto the nanoparticle surface — that marks the particles for phagocytic clearance by Kupffer cells in the liver, splenic macrophages, and circulating monocytes of the mononuclear phagocyte system (MPS). This rapid immunological clearance removes the majority of intravenously injected nanoparticles from circulation within minutes to hours, limiting their accumulation at tumor sites or other therapeutic targets to a median of only 0.7% of the injected dose in human tumors as quantified by the landmark meta-analysis of Wilhelm and colleagues [3,4].

PEGylation — the covalent coating of nanoparticle surfaces with polyethylene glycol chains — became the dominant strategy for extending nanoparticle circulation time by creating a hydrophilic steric barrier that reduces protein adsorption and phagocytic recognition, achieving circulation half-lives of hours compared to minutes for uncoated nanoparticles. However, PEGylation has significant limitations: the accelerated blood clearance (ABC) phenomenon, in which repeated dosing stimulates production of anti-PEG IgM antibodies that dramatically accelerate clearance of PEGylated nanoparticles on subsequent doses; the inability of PEG coating to confer active targeting specificity; and immunological reactions associated with anti-PEG antibodies that are now found in a significant proportion of the general population due to widespread exposure to PEG in foods, cosmetics, and medical products [5,6].

Biomimetic nanocarriers — nanoparticles whose surfaces are functionalized with natural biological materials derived from cell membranes, extracellular vesicles, or purified membrane proteins — address the limitations of both conventional synthetic nanoparticles and PEGylated systems by cloaking synthetic nanoparticle cores within biological membranes that the immune system recognizes as self rather than foreign. The concept, first demonstrated by Hu and colleagues in 2011 who coated polymeric nanoparticles with red blood cell membranes and showed extended circulation comparable to natural red blood cells, has since expanded to encompass membranes from platelets, white blood cells, cancer cells, stem cells, macrophages, and hybrid combinations thereof [7,8].

This review provides a systematic and critical examination of the biomimetic nanocarrier field, covering the biological rationale for cell membrane coating, the diversity of membrane source cells and their distinctive biological properties conferred to coated nanoparticles, preparation and characterization methodologies, mechanisms of immune evasion and targeted delivery, therapeutic applications across oncology, cardiovascular disease, neurological disorders, and infectious disease, and a critical analysis of the key translational barriers that must be overcome for biomimetic nanocarriers to achieve clinical adoption.

2. Scientific Background

2.1 The Mononuclear Phagocyte System and Nanoparticle Clearance

The mononuclear phagocyte system comprises tissue-resident macrophages, circulating monocytes, and dendritic cells that collectively perform the biological function of surveilling the vasculature and tissues

for foreign particles, dead cells, and cellular debris, removing them by phagocytosis. Kupffer cells in the hepatic sinusoids and splenic red pulp macrophages are the quantitatively dominant MPS components for nanoparticle clearance following intravenous injection, collectively removing more than 90% of injected nanoparticles from circulation. Macrophage recognition of nanoparticles is mediated by pattern recognition through multiple receptor systems: Fc receptors recognizing immunoglobulin-opsonized particles, complement receptors recognizing complement-coated particles, scavenger receptors recognizing particles coated with specific proteins, and mannose receptors recognizing nanoparticles with sugar-rich surfaces [9,10].

The CD47 glycoprotein, expressed on the surface of erythrocytes, platelets, and many other cell types, is the molecular mediator of the don't-eat-me signal that prevents phagocytic clearance of self cells. CD47 engages SIRPalpha receptors on macrophage surfaces and activates an inhibitory signaling cascade that suppresses phagocytic machinery. Tumor cells frequently upregulate CD47 expression as an immune evasion mechanism, and therapeutic anti-CD47 antibodies that block CD47-SIRPalpha signaling to restore tumor cell phagocytosis represent an actively investigated cancer immunotherapy. Cell membrane-coated nanoparticles that retain native CD47 from source cell membranes inherit the don't-eat-me signal, gaining macrophage evasion capacity without synthetic PEGylation [11,12].

2.2 Homotypic Targeting and Biological Homing

A distinctive property of cell membrane-coated nanocarriers is their capacity to exhibit the natural homing behavior of the source cell — the ability of certain cell types to preferentially accumulate in specific tissues or bind to specific cell types through surface protein-receptor interactions. Cancer cell membrane-coated nanoparticles exhibit homotypic targeting to tumors of the same cancer cell type through surface adhesion molecules including E-cadherin and EpCAM that mediate cancer cell-cancer cell adhesion. Platelet membrane-coated nanoparticles home to damaged vasculature through platelet adhesion receptors (GPIb, GPVI, integrin alphaIIb-beta3) that recognize exposed collagen and von Willebrand factor at sites of endothelial injury. Macrophage membrane-coated nanoparticles traffic to sites of inflammation through CXCR2 and Mac-1 integrin-mediated chemotaxis and adhesion [13,14].

3. Classification of Biomimetic Nanocarrier Systems

3.1 Red Blood Cell Membrane-Coated Nanocarriers

Red blood cell (RBC) membrane-coated nanocarriers were the first biomimetic cell membrane coating system to be demonstrated, exploiting the extraordinary longevity of natural erythrocytes in circulation (approximately 120 days) and their surface expression of CD47 and other self-recognition molecules that prevent macrophage phagocytosis. RBC membrane is isolated from packed erythrocytes by hypotonic lysis, repeated centrifugation, and extrusion through nanoporous membranes to produce RBC membrane-derived vesicles that are then fused with synthetic nanoparticle cores by co-extrusion or sonication. RBC membrane-coated PLGA nanoparticles demonstrated sixfold longer circulation compared to bare PLGA and twofold longer than equivalent PEGylated PLGA nanoparticles in mouse studies [15,16].

3.2 Platelet Membrane-Coated Nanocarriers

Platelet membrane-coated nanocarriers exploit the natural adhesive properties of platelets for damaged vascular endothelium and their homing to cancer cell surfaces through P-selectin-mediated interactions. Platelet membrane retains a repertoire of surface glycoproteins (GPIb, GPVI, integrin alpha2-beta1, integrin alphaIIb-beta3) that mediate binding to collagen, von Willebrand factor, fibrinogen, and cancer cell surface CD44 and mucins. Platelet membrane-coated nanoparticles demonstrated selective accumulation at sites of arterial injury in mouse models of atherosclerosis and vascular thrombosis, delivering thrombolytic agents or anti-restenosis drugs specifically to the site of vessel damage. In oncology applications, platelet membrane-coated nanoparticles exploited P-selectin-CD44 interactions to target circulating tumor cell clusters, achieving superior capture compared to antibody-coated nanoparticles [17,18].

3.3 White Blood Cell Membrane-Coated Nanocarriers

White blood cell (leukocyte) membrane-coated nanocarriers exploit the natural tissue-trafficking properties of leukocytes — their ability to roll on inflamed endothelium, adhere through integrin-selectin interactions, and transmigrate across the endothelial barrier through diapedesis — to achieve nanoparticle delivery to inflamed tissues including tumors, atherosclerotic plaques, and infected organs. Neutrophil membrane-coated nanoparticles were shown to home specifically to tumor-associated neutrophil-enriched

inflammatory microenvironments and penetrate tumor interstitium through neutrophil-like extravasation. Macrophage membrane-coated nanoparticles retain CXCR2, CD11b, and LFA-1 surface proteins that mediate inflammation-directed chemotaxis, enabling tumor and inflammatory tissue targeting [19,20].

3.4 Cancer Cell Membrane-Coated Nanocarriers

Cancer cell membrane-coated nanocarriers exploit homotypic targeting — the preferential adhesion of cancer cells to other cancer cells of the same type through shared surface adhesion molecules including E-cadherin, EpCAM, CD44, and N-cadherin — to achieve source tumor cell-specific drug delivery. HeLa cell membrane-coated nanoparticles showed superior uptake by HeLa cervical cancer cells compared to other cancer cell lines, while 4T1 mouse breast cancer cell membrane-coated nanoparticles preferentially accumulated in 4T1 tumors in syngeneic mouse models. Cancer cell membranes also express PD-L1 and other immune checkpoint molecules, raising the possibility that cancer cell membrane-coated nanocarriers delivering immunostimulatory payloads could simultaneously target tumors and co-deliver PD-L1 for immune checkpoint engagement [21,22].

3.5 Stem Cell and Macrophage Membrane-Coated Nanocarriers

Mesenchymal stem cell membrane-coated nanocarriers exploit MSC's natural tumor tropism — the tendency of MSCs to home to tumor microenvironments through CXCR4-SDF-1 axis chemotaxis — as a biological targeting mechanism for tumor-directed drug delivery without the risks and manufacturing challenges of live cell therapy. MSC membrane coatings preserve CXCR4 and other chemokine receptors that mediate tumor tropism, enabling nanoparticles to follow the same migration pathways as natural MSCs toward tumor-secreted SDF-1 gradients. Exosome membranes from diverse source cells have also been applied as nanoparticle coatings, combining the natural membrane composition and targeting proteins of exosomes with the superior drug loading capacity of synthetic nanoparticle cores [23,24].

3.6 Hybrid Membrane Systems

Hybrid membrane nanocarriers combine membrane components from two or more distinct cell types to create designer biomimetic surfaces with combined biological functions not present in any single cell membrane. The most extensively investigated hybrid systems include RBC-platelet hybrid membranes combining RBC's long circulation CD47-mediated immune evasion with platelet's tumor adhesion properties; cancer cell-macrophage hybrid membranes combining cancer cell homotypic targeting with macrophage inflammation tropism for enhanced tumor penetration; and neutrophil-cancer cell hybrid membranes combining neutrophil extravasation capacity with cancer cell tumor recognition for more efficient tumor delivery. Hybrid membranes are prepared by co-extrusion of membrane vesicles from the two source cell types, producing hybrid vesicles containing membrane proteins from both sources [25,26].

Table 1: Classification of cell membrane-coated biomimetic nanocarriers by source cell, key surface molecules, biological properties conferred, and therapeutic applications

Membrane Source	Key Surface Molecules	Biological Properties	Targeting Mechanism	Therapeutic Applications
Red blood cell (RBC)	CD47, CD55, CD59, glycophorin	Long circulation (t1/2 6× bare NP)	Immune evasion via CD47-SIRPα	Cancer drug delivery, toxin adsorption, vaccine
Platelet	GPIb, GPVI, integrin αIIbβ3, P-selectin	Vascular injury homing, cancer adhesion	Collagen/vWF binding; P-sel–CD44	Atherosclerosis, thrombosis, circulating tumor cells
Neutrophil / leukocyte	CXCR2, Mac-1, LFA-1, L-selectin	Inflammation-directed trafficking	Selectin-mediated rolling + integrin adhesion	Tumor, ischemia, infected tissue drug delivery
Cancer cell	E-cadherin, EpCAM, CD44, N-cadherin	Homotypic tumor targeting	Same-type cancer cell adhesion molecules	Homotypic cancer drug delivery, immunotherapy
Macrophage	CD11b, CXCR2, SRA, CD14, PD-L1	Tumor and inflammation tropism	CXCR2-ligand; scavenger receptor	Tumor delivery, atherosclerosis, sepsis
Mesenchymal stem cell	CXCR4, CD44, CD90, integrin α4β1	Tumor tropism via SDF-1 gradient	CXCR4-SDF-1 chemotaxis	Pancreatic cancer, glioma drug delivery

Hybrid (RBC + platelet)	CD47 + GPIb + P-selectin	Long circ. + tumor adhesion	Combined: immune evasion + targeting	Improved cancer delivery vs single-membrane

RBC: red blood cell; NP: nanoparticle; vWF: von Willebrand factor; SDF-1: stromal cell-derived factor 1; CXCR4: C-X-C chemokine receptor type 4; GPIb: glycoprotein Ib; GPVI: glycoprotein VI; EpCAM: epithelial cell adhesion molecule.

4. Formulation Design and Development

4.1 Nanoparticle Core Selection

The selection of the synthetic nanoparticle core for cell membrane coating is governed by the required drug loading capacity, drug release kinetics, core biocompatibility, and compatibility with the membrane coating process. PLGA nanoparticles are the most widely used cores for cell membrane coating, offering biodegradable drug release kinetics ranging from days to months depending on polymer molecular weight and composition, established pharmaceutical safety, and compatibility with extrusion-based membrane coating. Gold nanoparticles, iron oxide nanoparticles, mesoporous silica nanoparticles, and lipid nanoparticles have also been investigated as cores, each offering distinctive properties — gold nanoparticles for photothermal therapy, iron oxide for magnetic targeting and MRI contrast, mesoporous silica for high drug loading capacity [27,28].

The size and surface properties of the core nanoparticle must be compatible with the membrane coating process. PLGA cores of 100 to 200 nanometers are most extensively used, as this size range is appropriate for extrusion-based membrane coating through 200-nanometer pore size membranes, falls within the size range for efficient MPS evasion in combination with the membrane's CD47-mediated don't-eat-me signaling, and is small enough for extravasation at tumor and inflamed tissue sites [29].

4.2 Cell Membrane Sourcing and Characterization

The source cell type, growth conditions, and membrane extraction protocol collectively determine the protein composition and biological activity of the membrane coating applied to nanoparticles. For RBC membrane, freshly collected whole blood from the intended patient (autologous) or from blood bank supplies (allogeneic) can be used; allogeneic RBC membrane raises potential immunogenicity concerns if major blood group antigens present on the RBC surface are recognized by recipient antibodies. For cancer cell membrane, cultured cancer cell lines or freshly excised primary tumor tissue are the membrane sources; tumor-derived membranes contain the full complement of tumor-specific antigens including neoantigens, mutant proteins, and overexpressed tumor markers [30].

4.3 Membrane-to-Core Ratio Optimization

The ratio of cell membrane material (measured as membrane protein content or membrane vesicle area) to nanoparticle core surface area must be optimized to ensure complete and uniform membrane coating while minimizing uncoated membrane vesicle contamination in the final preparation. Insufficient membrane-to-core ratio produces incompletely coated nanoparticles with exposed synthetic core surfaces that are recognized by the MPS, while excess membrane produces free membrane vesicles that compete with coated nanoparticles for cell uptake. Optimization is typically performed by varying the membrane vesicle-to-nanoparticle weight ratio and monitoring coating completeness by zeta potential (complete coating produces a zeta potential approaching that of the source cell membrane) and morphological assessment by cryo-EM [31].

5. Preparation Methods

5.1 Cell Membrane Extraction

Cell membrane extraction begins with cell lysis to release membrane fragments while minimizing cytoplasmic protein contamination. Hypotonic lysis (for RBCs — incubation in 0.2x PBS) or mechanical disruption (nitrogen cavitation, Dounce homogenization, or freeze-thaw cycling) for nucleated cells ruptures the plasma membrane and releases cytoplasmic contents. Sequential differential centrifugation (300 to 500 × g to remove intact cells, 3,000 to 10,000 × g to remove nucleus and organelles, 10,000 to 20,000 × g to collect large membrane fragments, and 100,000 × g to pellet plasma membrane vesicles) enriches plasma membrane components while depleting cytoplasmic and organelle contamination. The membrane pellet is washed and resuspended in buffer for membrane vesicle formation [32,33].

5.2 Membrane Coating by Co-Extrusion

Co-extrusion is the most widely used method for cell membrane coating of nanoparticles, mixing membrane vesicles with the nanoparticle core dispersion and extruding the mixture sequentially through polycarbonate membranes of decreasing pore size (400 nm, 200 nm, 100 nm) using a mini-extruder under controlled pressure. The mechanical shearing forces applied during extrusion disrupt membrane vesicle integrity, generating membrane fragments that fuse with and wrap around the nanoparticle core surface. Multiple extrusion cycles (10 to 20 passes) improve coating completeness and size uniformity. The right-side-out orientation of the membrane coating — preserving the extracellular-facing surface of the source cell membrane on the outside of the coated nanoparticle — is critical for retention of biological targeting function and is partially achieved by co-extrusion but requires verification by inside-out protein detection [34,35].

5.3 Membrane Coating by Sonication

Sonication-assisted membrane coating uses probe or bath sonication to disrupt membrane vesicles in the presence of nanoparticle cores, generating membrane fragments that reassemble around the nanoparticle surface. Sonication provides more rapid processing than co-extrusion and is compatible with temperature-sensitive biological membranes where the elevated mechanical energy of extrusion might cause membrane protein denaturation. However, sonication can cause fragmentation of delicate membrane proteins and generate heat that may affect heat-sensitive surface proteins. Optimal sonication parameters (amplitude, duration, pulse frequency, temperature control) must be empirically determined for each membrane-nanoparticle combination [36].

5.4 Electrostatic Assembly and Click Chemistry Methods

Alternative membrane coating strategies include electrostatic self-assembly of negatively charged membrane vesicles onto positively charged nanoparticle cores, and click chemistry conjugation of purified membrane proteins onto nanoparticle surfaces through bioorthogonal reaction pairs (DBCO-azide, tetrazine-trans-cyclooctene). Electrostatic assembly is simple and scalable but produces nanoparticles with partially inverted membrane orientation and potential membrane instability at physiological ionic strength. Click chemistry conjugation enables precise control of membrane protein density and orientation on the nanoparticle surface but requires prior chemical modification of the membrane protein and the nanoparticle surface, adding complexity and potential for protein denaturation [37].

6. Characterization and Evaluation

6.1 Physicochemical Characterization

Biomimetic cell membrane-coated nanoparticles are characterized by size and PDI (dynamic light scattering), zeta potential, and morphology (cryo-electron microscopy). Successful membrane coating is indicated by a shift in zeta potential from the value of the bare nanoparticle core toward the value of the source cell membrane vesicles. Core PLGA nanoparticles typically have zeta potentials of approximately -40 to -50 mV, while RBC membranes have zeta potentials of approximately -18 to -25 mV; RBC membrane-coated PLGA nanoparticles should show a zeta potential in the range of -20 to -25 mV, confirming membrane incorporation. Cryo-EM images show the characteristic lipid bilayer surrounding the nanoparticle core, distinguishable from bare nanoparticles by the electron-dense bilayer visible at the particle periphery [38].

6.2 Membrane Protein Verification

The retention of key functional membrane proteins is verified by western blotting, ELISA, and flow cytometry for specific protein markers. For RBC membrane-coated nanoparticles, detection of CD47, CD55, CD59, and glycophorin A by western blot confirms membrane protein transfer. The relative enrichment of membrane proteins versus cytoplasmic protein contamination is assessed by detecting cytoplasmic markers (hemoglobin for RBCs, actin for nucleated cells) alongside membrane markers — a favorable membrane-to-cytoplasmic protein ratio indicates enriched plasma membrane coating with minimal intracellular protein contamination. Proteomics analysis of the membrane coat by LC-MS/MS provides comprehensive protein identification, confirming the presence of targeting molecules and the absence of undesired intracellular proteins [39,40].

6.3 In Vitro Macrophage Evasion and Phagocytosis Assays

The immune-evasive properties of cell membrane-coated nanoparticles are assessed by in vitro phagocytosis assays using human or murine macrophages (RAW264.7, THP-1 differentiated, or primary

bone marrow-derived macrophages). Fluorescently labeled nanoparticles are incubated with macrophages at physiologically relevant particle-to-cell ratios, and phagocytic uptake is quantified by flow cytometry or fluorescence microscopy after removing non-internalized particles by washing. Bare nanoparticles and PEGylated nanoparticles serve as controls. CD47-mediated evasion is confirmed by repeating the assay with anti-CD47 antibody blockade, which should restore phagocytosis of membrane-coated nanoparticles to the level of bare nanoparticles [41].

6.4 In Vivo Pharmacokinetics and Biodistribution

In vivo circulation half-life of cell membrane-coated nanoparticles is measured by intravenous injection of fluorescently or radiolabeled nanoparticles in mice, with blood sampling at defined time points and nanoparticle concentration quantification by fluorescence spectroscopy or liquid scintillation counting. Biodistribution studies quantify nanoparticle accumulation in major organs (liver, spleen, lung, kidney, heart, tumor) at 24 to 72 hours post-injection by ex vivo organ fluorescence imaging or tissue extraction and quantification. RBC membrane-coated nanoparticles consistently demonstrate two- to sixfold longer circulation half-lives compared to PEGylated nanoparticles in mouse studies, with corresponding reduction in liver and spleen accumulation [42].

7. Mechanism of Immune Evasion and Targeted Delivery

7.1 CD47-Mediated Phagocytosis Inhibition

CD47, expressed at densities of approximately 25,000 to 50,000 molecules per erythrocyte surface, engages SIRPalpha receptors on macrophage surfaces through extracellular immunoglobulin-like domain interactions. SIRPalpha engagement activates its cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs), which recruit SHP-1 and SHP-2 phosphatases that dephosphorylate and inactivate myosin IIA — a molecular motor required for phagocytic cup formation. Without myosin IIA activity, the macrophage cannot complete the phagocytic engulfment of CD47-presenting particles or cells. Cell membrane-coated nanoparticles inherit the native CD47 density and spatial orientation of the source cell membrane, providing the same molecular SIRPalpha engagement that protects natural RBCs from phagocytosis [43].

7.2 Complement Evasion

Beyond CD47, cell membranes express a complement regulatory protein repertoire including CD55 (decay-accelerating factor, DAF) and CD59 (protectin) that collectively inhibit complement deposition on cell surfaces. CD55 accelerates the decay of C3/C5 convertases on the membrane surface, preventing C3b deposition and opsonin accumulation. CD59 inhibits the membrane attack complex (MAC) formation at the terminal complement cascade, preventing membrane perforation. RBC membrane-coated nanoparticles retain CD55 and CD59 in active conformations, providing complement evasion that is absent from synthetic nanoparticles and inadequately provided by PEGylation alone [44].

7.3 Homotypic Targeting Mechanisms

Cancer cell membrane-coated nanoparticles achieve homotypic tumor targeting through molecular recognition between surface adhesion molecules present on the membrane coat and their binding partners on tumor cells of the same type. E-cadherin homotypic adhesion (E-cadherin on the coated nanoparticle membrane binding to E-cadherin on tumor cells through Ca2+-dependent extracellular domain interactions), CD44-hyaluronic acid receptor interactions, and EpCAM-EpCAM homotypic binding collectively mediate selective nanoparticle retention and uptake at homotypic tumor cells. The specificity of homotypic targeting has been demonstrated by comparing tumor accumulation in syngeneic tumor models with matched versus mismatched cancer cell membrane coatings, showing two- to fourfold greater accumulation in matched tumors [45].

8. Therapeutic Applications

8.1 Cancer Drug Delivery

Cancer cell membrane-coated nanoparticles for homotypic tumor-targeted drug delivery represent the most extensively investigated therapeutic application of biomimetic nanocarriers. MCF-7 breast cancer cell membrane-coated PLGA nanoparticles loaded with doxorubicin demonstrated fivefold higher tumor accumulation compared to bare PLGA nanoparticles and twofold higher than PEGylated PLGA nanoparticles in MCF-7 tumor xenograft mouse models, translating to superior tumor growth inhibition

and improved survival at equivalent doses. The combination of cancer cell membrane's homotypic targeting with the immune evasion provided by retained CD47 and CD55 created synergistic delivery advantages not achievable by either biological property alone [46,47].

For cancer immunotherapy applications, cancer cell membrane-coated nanoparticles delivering immunostimulatory payloads (TLR agonists, STING agonists, siRNA against immune checkpoint molecules) simultaneously provide tumor antigen delivery (from membrane surface tumor antigens) and immune activation, functioning as a combined cancer vaccine and immunotherapy delivery system. Cancer cell membrane-coated iron oxide nanoparticles delivering anti-PD-L1 siRNA achieved significantly greater tumor immune infiltration and anti-tumor immune response compared to equivalent free siRNA in a mouse melanoma model, attributed to the combined tumor-targeting and antigen-presentation functions of the cancer cell membrane coat [48].

8.2 Cardiovascular Drug Delivery

Platelet membrane-coated nanoparticles for cardiovascular drug delivery exploit platelet's natural adhesion to sites of vascular injury to achieve localized drug delivery to atherosclerotic plaques, thrombotic lesions, and post-angioplasty restenosis sites. Platelet membrane-coated nanoparticles loaded with thrombus-dissolving tissue plasminogen activator (tPA) demonstrated superior thrombus accumulation and faster thrombolysis at lower doses compared to free tPA in mouse models of arterial thrombosis, attributed to platelet membrane GPIb-mediated binding to von Willebrand factor at the thrombus surface. The ability to reduce the effective tPA dose while achieving equivalent thrombolysis reduces the hemorrhagic complication risk that currently limits systemic tPA use in stroke and myocardial infarction [49].

8.3 Neurological Disease and Brain Drug Delivery

RBC membrane-coated nanoparticles and macrophage membrane-coated nanoparticles have been investigated for brain-targeted drug delivery in neurological diseases, exploiting different biological mechanisms. RBC membrane-coated nanoparticles demonstrate extended circulation that increases the probability of blood-brain barrier transcytosis events occurring over the longer plasma residence time. Macrophage membrane-coated nanoparticles leverage macrophage natural neuroinflammation tropism — macrophages migrate to brain inflammatory sites in response to chemokine gradients — to achieve preferential accumulation in regions of neuroinflammation including ischemic stroke, traumatic brain injury, and neurodegeneration-associated neuroinflammation. Macrophage membrane-coated curcumin nanoparticles demonstrated threefold greater brain accumulation in a neuroinflammation mouse model compared to PEGylated nanoparticles [50].

8.4 Toxin Adsorption and Anti-Infective Applications

An innovative application of RBC membrane-coated nanoparticles is toxin adsorption — using the nanoparticle membrane coating to absorb pore-forming bacterial toxins that target cell membranes, neutralizing their cytotoxic activity before they can lyse natural cells. Because pore-forming toxins including staphylococcal alpha-hemolysin, streptolysin, and pneumolysin attack by inserting into lipid bilayer membranes, RBC membrane-coated nanoparticles act as decoy membrane targets that absorb and neutralize these toxins. In mouse models of methicillin-resistant Staphylococcus aureus (MRSA) infection and alpha-hemolysin poisoning, RBC membrane-coated nanoparticle 'nanosponges' demonstrated protection against lethal toxin doses by absorbing toxin molecules, preventing hemolysis and organ damage [51,52].

8.5 Cancer Vaccine Delivery

Cancer cell membrane-coated nanoparticles function as whole-tumor antigen cancer vaccines when combined with immunostimulatory adjuvants, delivering the complete tumor antigen landscape — including patient-specific neoantigens, tumor-associated antigens, and cancer-specific post-translational modifications — to antigen-presenting cells in a form that generates antigen-specific T cell responses. The natural tumor antigen display on the nanoparticle membrane surface, including correct glycosylation and protein folding that may be critical for generating protective immune responses, may provide advantages over defined peptide antigen vaccines that are limited by the need to identify and synthesize specific immunogenic epitopes. Cancer cell membrane plus adjuvant nanoparticle cancer vaccines induced CD8+ T cell responses and tumor growth inhibition in multiple syngeneic mouse tumor models [53].

9. Recent Advances

9.1 Genetically Engineered Cell Membrane Coatings

Genetic engineering of source cells before membrane extraction enables production of biomimetic nanocarriers with enhanced or novel surface properties not present in native cell membranes. Overexpression of targeting molecules, fusion proteins combining natural membrane anchors with synthetic ligands, and CRISPR-mediated knockout of immunosuppressive surface proteins in cancer cell membrane-coated cancer vaccine nanoparticles have been reported in 2023 and 2024 publications. Engineered macrophage membranes overexpressing CXCR2 or integrin alpha4 demonstrated enhanced tumor inflammatory site targeting compared to wild-type macrophage membrane, and engineered RBC membranes with added GE11 peptide-lipid fusion anchors targeting EGFR-expressing tumors achieved active tumor targeting superimposed on native RBC immune evasion [54].

9.2 Bacterial Outer Membrane Vesicle-Based Biomimetic Systems

Bacterial outer membrane vesicles (OMVs) — nanosized vesicles naturally secreted by gram-negative bacteria from their outer membrane — have been investigated as biomimetic nanocarrier coatings for cancer immunotherapy, exploiting their natural immunostimulatory properties (containing LPS, peptidoglycan fragments, and surface-displayed bacterial proteins that potently activate innate immune TLR pathways) while delivering tumor antigen cargo. OMV-coated nanoparticles delivering tumor-associated antigen demonstrated strong cytotoxic T cell responses and tumor growth inhibition in mouse models, with the OMV coat providing built-in adjuvant activity that eliminated the need for separate adjuvant co-formulation. The immunostimulatory potency of OMVs must be carefully managed to avoid systemic inflammatory toxicity [55].

9.3 Synthetic Cell Mimics and Protocells

Protocells — lipid-based nanostructures designed to incorporate selected functional membrane proteins from purified sources rather than whole cell membrane extracts — represent a reductionist approach to biomimetic nanocarrier design that provides greater compositional control than whole membrane coating while retaining key biological functions. Reconstituted phospholipid bilayer nanoparticles incorporating purified CD47 at defined densities, purified integrin complexes, and specific CXCR4 chemokine receptors enable systematic investigation of the contribution of individual membrane proteins to circulation time, targeting specificity, and cellular uptake efficiency, providing mechanistic insights that whole-membrane preparations cannot. Protocell technology bridges the gap between fully synthetic nanocarriers and biologically complex whole-membrane systems [56].

9.4 Exosome Membrane-Coated Nanoparticles

Exosome membrane-coated nanoparticles, combining the biological membrane properties of cell-derived exosomes with the drug loading capacity of synthetic nanoparticle cores, have been developed as an alternative to direct cell membrane coating that exploits the established exosome isolation infrastructure in cell biology laboratories. Tumor-derived exosome membrane-coated PLGA nanoparticles demonstrated homotypic tumor targeting comparable to cancer cell membrane-coated nanoparticles while offering slightly higher batch-to-batch reproducibility due to the more standardized nature of exosome production from defined culture conditions. The integration of exosome membranes with synthetic cores addresses the drug loading limitation of natural exosomes while preserving the biological targeting and immune evasion properties of the exosomal membrane [57,58].

10. Comparative Analysis

Biomimetic cell membrane-coated nanocarriers occupy a distinct position in the nanocarrier landscape, offering biological immune evasion and targeting properties that PEGylated nanoparticles cannot match, while providing greater drug loading capacity than natural exosomes and avoiding the manufacturing and regulatory complexity of live cell therapy. The most relevant comparisons are with PEGylated synthetic nanoparticles (the current clinical standard for extended-circulation nanocarriers), natural exosomes (direct competitors for biological immune evasion), and antibody-conjugated targeted nanoparticles (the primary alternative for actively targeted drug delivery) [59].

PEGylated nanoparticles provide consistent, well-characterized immune evasion through steric exclusion of opsonin proteins but cannot replicate the multifaceted biological immune recognition evasion provided by CD47, CD55, and CD59 acting in concert. The ABC phenomenon limits the utility of PEGylated nanoparticles in repeat-dosed settings, a limitation not shared by cell membrane-coated nanoparticles whose biological membrane components may be less immunogenic than synthetic PEG. Antibody-conjugated targeted nanoparticles achieve highly specific active targeting through antigen-

antibody recognition but are restricted to single-antigen targeting, whereas cell membrane coatings provide multi-molecule targeting through the full complement of source cell adhesion molecules [60].

Table 2: Comparative analysis of biomimetic cell membrane-coated nanocarriers versus synthetic nanocarrier platforms

Parameter	Bare PLGA NP	PEGylated NP	Antibody-NP	Cell Membrane NP
Circulation half-life	Very short (min)	Moderate (hours)	Moderate (hours)	Long (days) — CD47
MPS evasion mechanism	None	Steric PEG barrier	Steric PEG barrier	CD47/CD55/CD59 — biological
Active targeting	None	None (passive EPR)	Antigen-specific (1 target)	Multi-molecule biological
Repeat-dose immunogenicity	High	ABC phenomenon (anti-PEG)	Potentially (anti-antibody)	Lower (self antigens)
Manufacturing complexity	Low	Moderate	High	High (cell sourcing)
Batch-to-batch consistency	Excellent	Good	Good	Moderate (biological variability)

NP: nanoparticle; MPS: mononuclear phagocyte system; PEG: polyethylene glycol; ABC: accelerated blood clearance; EPR: enhanced permeability and retention.

11. Advantages and Limitations

11.1 Advantages

- CD47-mediated don't-eat-me signaling from source cell membrane provides biological immune evasion equivalent to natural self-cell recognition, substantially extending nanoparticle circulation compared to PEGylated systems without the anti-PEG immunogenicity concerns
- Multi-molecule biological targeting through the complete adhesion molecule repertoire of the source cell membrane provides cell-type-specific delivery specificity that synthetic single-ligand targeting cannot replicate, enabling delivery to specific cell types within heterogeneous tissue environments
- Complement regulatory proteins CD55 and CD59 retained from cell membranes provide complement evasion that synthetic nanoparticles lack, reducing complement-mediated inflammatory adverse effects associated with nanoparticle administration
- Cancer cell membrane coatings deliver the complete tumor antigen repertoire — including neoantigens, tumor-associated antigens, and patient-specific mutations — enabling personalized cancer vaccine formulation without the need for antigen identification and synthesis
- RBC nanosponge technology exploits the inherent pore-forming toxin susceptibility of lipid bilayer membranes to create decoy membrane targets that neutralize bacterial toxins and venoms with broad-spectrum activity against membrane-targeting virulence factors
- Hybrid membrane systems combining biological properties from two cell types create designer biomimetic surfaces with combined immune evasion and targeting functions that exceed what any single cell type can provide, demonstrating the tunability of the biomimetic approach
- Autologous cell membrane sourcing from patient's own cells (RBCs, tumor cells, immune cells) eliminates allogeneic immunogenicity concerns and enables truly personalized nanocarrier design matched to the individual patient's immunological context

11.2 Limitations

- Cell membrane extraction and nanoparticle coating processes are complex, multi-step biological manufacturing operations that are difficult to standardize across batches, cell donors, and manufacturing facilities, producing batch-to-batch variability in membrane protein composition and density

- The quality control of biological membrane preparations requires proteomics-level characterization to confirm membrane protein retention and orientation, at a cost and complexity that substantially exceeds the analytical burden of synthetic nanoparticle characterization
- Scale-up of cell membrane-coated nanoparticle production to the quantities required for clinical trials and commercial manufacturing has not been demonstrated for most cell membrane types, with current yields from laboratory protocols insufficient for patient-scale production without significant process engineering investment
- The regulatory classification of cell membrane-coated nanoparticles — as drug products, biological products, or combination products — is not established in most regulatory jurisdictions, creating uncertainty about the preclinical safety, efficacy, and quality requirements for IND-enabling studies and clinical development
- Long-term storage stability of cell membrane-coated nanoparticles is constrained by the biological nature of the membrane coating, with membrane protein degradation, membrane reorganization, and lipid oxidation potentially altering the biological properties of the coating over the product's required shelf life
- Allogeneic cell membrane sourcing raises immunogenicity concerns if blood group antigens, minor histocompatibility antigens, or other allotypic membrane proteins present on the coating are recognized as foreign by the recipient's immune system, potentially triggering immune reactions analogous to blood transfusion incompatibility

12. Clinical Translation and Marketed Products

Biomimetic cell membrane-coated nanocarriers represent an emerging technology in the early stages of clinical translation, with no approved pharmaceutical products as of 2024. The field is currently concentrated in preclinical proof-of-concept studies and early IND-enabling safety assessments, with a small number of investigational programs advancing toward first-in-human clinical trials. The first clinical translation programs have focused on RBC membrane-coated nanoparticles for cancer drug delivery and platelet membrane-coated nanoparticles for cardiovascular indications, where the biological rationale is strongest and the manufacturing challenges are most tractable [61].

The primary translational barriers are manufacturing scalability and regulatory pathway clarity. Published research programs have demonstrated proof-of-concept at laboratory scale using milligram quantities of nanoparticles and milliliter volumes of cell membrane, but clinical trial quantities typically require gram-scale nanoparticle production with hundreds of milliliters of membrane coating material from thousands of donor cells. The regulatory landscape for cell membrane-coated nanoparticles — spanning aspects of drug product chemistry manufacturing and controls, biological product characterization, and potentially combination product regulatory pathways depending on the classification decision — has not yet been definitively resolved by any major regulatory agency [62].

Table 3: Selected preclinical applications and early clinical development programs for biomimetic cell membrane-coated nanocarriers (as of 2024)

Programme / System	Membrane Source	Drug Cargo	Indication	Development Status / Key Data
RBC membrane nanosponge (UCSD/Zhang)	RBC	Toxin absorption (no drug)	MRSA toxin poisoning	Preclinical — mouse model efficacy; first IND evaluation
Cancer cell membrane NP (multiple groups)	Homologous cancer cells	Doxorubicin, paclitaxel	Solid tumors (matched)	Preclinical — 3–5× tumor accumulation vs PEG-NP
Platelet NP-tPA (multiple groups)	Platelets	Tissue plasminogen activator	Arterial thrombosis / stroke	Preclinical mouse model — reduced tPA dose for thrombolysis
Macrophage NP (neuroinflammation)	Macrophage RAW264.7	Curcumin / anti-inflammatory	Neuroinflammation / TBI	Preclinical — 3× brain accumulation vs PEG-NP
Cancer vaccine NP (UCSD)	Autologous tumor cells	Adjuvant (MPLA) +	Personalized cancer vaccine	Preclinical — CD8+ T cell response + tumor

		tumor antigen		inhibition
MSC membrane NP (glioma)	Mesenchymal stem cells	Temozolomide	Glioblastoma	Preclinical — CXCR4-mediated tumor tropism demonstrated

RBC: red blood cell; NP: nanoparticle; MRSA: methicillin-resistant Staphylococcus aureus; tPA: tissue plasminogen activator; TBI: traumatic brain injury; MSC: mesenchymal stem cell; MPLA: monophosphoryl lipid A.

13. Critical Analysis

The biomimetic cell membrane-coated nanocarrier field has generated substantial scientific excitement and a rapidly growing publication volume, but shares with many advanced nanocarrier fields a pronounced tendency toward demonstration of proof-of-concept in highly favorable experimental systems without systematic investigation of the translational challenges that would need to be resolved for clinical development. Several methodological issues in the published literature deserve explicit critical examination.

The demonstration of homotypic targeting in cell culture and in xenograft mouse models using human cancer cell lines may not accurately represent the complexity of targeting in clinical tumor environments. In a typical xenograft model, immunodeficient mice bear a tumor of a single defined human cancer cell type in which surface adhesion molecule expression is uniform and stable; the cancer cell membrane-coated nanoparticle achieves homotypic targeting by binding to the identical adhesion molecules present on all cells in the tumor. Human tumors are heterogeneous — different regions express different levels of E-cadherin, EpCAM, and CD44, and some tumor cells undergo epithelial-to-mesenchymal transition that fundamentally alters surface adhesion molecule expression, potentially converting E-cadherin-expressing cells to N-cadherin-expressing mesenchymal cells that would not be targeted by epithelial cancer cell membrane-coated nanoparticles. The translational validity of homotypic targeting in heterogeneous human tumor environments has not been systematically evaluated [63].

The circulation half-life advantages reported for cell membrane-coated nanoparticles — consistently presented as two- to sixfold longer than PEGylated nanoparticles in published mouse studies — must be interpreted in the context of the enormous inter-species differences in MPS clearance kinetics and CD47-SIRPalpha signaling. CD47 on human cells engages human SIRPalpha with specific binding affinity, and mouse CD47 engages mouse SIRPalpha; in xenograft models where human cell membrane-coated nanoparticles are tested in mice, the human CD47 on the membrane coat interacts with mouse SIRPalpha with lower affinity than human SIRPalpha, potentially underestimating the don't-eat-me efficacy in the intended human patient context. Conversely, studies using mouse-sourced cell membranes tested in syngeneic mouse models may overestimate the immune evasion achievable in human patients where the degree of cross-species CD47-SIRPalpha compatibility differs [64].

The membrane orientation problem — the need to maintain the extracellular-facing surface of the source cell membrane on the outside of the coated nanoparticle to preserve the biological function of targeting and immune evasion proteins — has been inadequately addressed in many published studies. Co-extrusion is the standard coating method, and is assumed to produce right-side-out membrane orientation, but this assumption has been rigorously tested by inside-out protein detection in only a minority of published studies. If a substantial fraction of membrane-coated nanoparticles have inverted or mixed membrane orientation, the effective density of functional surface proteins would be lower than expected, and intracellular proteins exposed on the outside of some particles could trigger immune recognition rather than evasion. Systematic quantification of membrane orientation and its impact on biological performance across different membrane types and coating methods is an important methodological gap in the field [65].

14. Conclusion

Biomimetic cell membrane-coated nanocarriers represent one of the most conceptually innovative and biologically sophisticated drug delivery platforms to emerge in the past decade. The fundamental insight — that nanoparticles can inherit the immune-evasive, tissue-homing, and functionally active surface properties of natural cells by coating them with cell-derived biological membranes — addresses the most fundamental limitation of synthetic nanocarrier drug delivery: the inability to fool the immune system's sophisticated surveillance mechanisms that evolved over billions of years to distinguish self from non-self. The demonstrated extensions of nanoparticle circulation time through CD47-mediated phagocytosis inhibition, tumor-specific accumulation through cancer cell membrane homotypic targeting, and vascular

injury-directed delivery through platelet membrane adhesion molecule retention collectively establish that cell membrane coating transfers biologically meaningful functional properties to nanoparticle carriers.

The therapeutic potential of biomimetic nanocarriers extends across oncology (homotypic tumor targeting, cancer vaccine antigen delivery), cardiovascular medicine (platelet membrane-coated thrombolytics), neurology (macrophage membrane-coated neuroinflammation-targeted delivery), and infectious disease (RBC nanosponge toxin adsorption), reflecting the diversity of cell type-specific biological homing behaviors that can be exploited through appropriate membrane source selection. The hybrid membrane concept, combining biological properties from multiple cell types in designer biomimetic surfaces, extends the design space beyond what natural cells provide, opening the possibility of fully engineered biomimetic systems with optimized combinations of immune evasion, targeting specificity, and functional activity.

The pathway from the compelling preclinical demonstrations that populate the current literature to clinically approved biomimetic nanocarrier products requires resolution of challenges that the field has not yet systematically engaged: the manufacturing scalability of biological membrane extraction and nanoparticle coating at clinical-trial quantities; robust quality control assays for membrane protein composition, orientation, and functional integrity at manufacturing scale; regulatory pathway clarification for this novel hybrid bio-synthetic product class; and rigorous assessment of homotypic targeting specificity in the complex heterogeneous microenvironments of human disease rather than the idealized homogeneous systems of laboratory cell culture and xenograft models. Addressing these challenges with the same scientific rigor and creativity that has characterized the biomimetic nanocarrier design innovation described in this review will determine whether this remarkable platform fulfills its considerable therapeutic promise.

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