

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

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Abstract

Despite substantial advancements in nanomedicine, the clinical translation of synthetic drug delivery systems remains severely hindered by biological barriers, including rapid immune clearance, off-target toxicity, and limited targeting efficacy. To bridge the gap between synthetic pharmacokinetics and biological complexity, cell-membrane camouflaged nanocarriers have emerged as a transformative biomimetic platform. By encloaking synthetic nanoparticle cores with intact natural cell membranes derived from erythrocytes, platelets, leukocytes, cancer cells, or engineered hybrids this top-down nanotechnology endows delivery vehicles with unparalleled, naturally evolved functionalities. This comprehensive review critically examines the latest fabrication and characterization methodologies of these bio-inspired platforms, highlighting how specific membrane sources dictate their unique physiological behaviors, such as CD47-mediated immune evasion and multi-receptor homotypic targeting. We systematically explore their multifunctional capabilities within complex biological environments, emphasizing active targeting, stimuli-responsive drug release, and theranostic integration. Furthermore, we evaluate the profound therapeutic potential of membrane-camouflaged nanocarriers across diverse clinical domains, including precision oncology, immunotherapy, infectious disease neutralization, and cardiovascular interventions. Finally, we provide a critical perspective on current translational bottlenecks manufacturing scale-up, long-term preservation, and regulatory complexities and discuss the future trajectory of the field, driven by artificial intelligence and synthetic biology, toward realizing next-generation, personalized nanomedicines.

Keywords: Biomimetic nanocarriers; Cell-membrane coating; Targeted drug delivery; Immune evasion; Theranostics; Translational nanomedicine.

How to cite this article: Kundu A, Dixit R, Majumdar S, Barik A, Maity A, Sarkar S, Das PP. Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity. *Int J Drug Deliv Technol.* 2026;16(10s): 274-289; DOI: 10.25258/ijddt.16.10s.39

1. Introduction

1.1 Evolution of Nanomedicine

Nanomedicine has profoundly transformed the landscape of therapeutic delivery by offering nanoscale vehicles capable of encapsulating diverse

pharmacological agents, protecting them from premature degradation, and localizing their action.

Over the past few decades, a vast array of synthetic nanocarriers has been developed, ranging from early lipid-based vesicular systems (liposomes) to advanced

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

polymeric nanoparticles (poly(lactic-co-glycolic acid) or PLGA), dendrimers, and inorganic nanomaterials (Blanco, Shen, & Ferrari, 2015). Historically, the rationale for utilizing these nanocarriers, particularly in oncology, heavily relied on the enhanced permeability and retention (EPR) effect. First described by Matsumura and Maeda (1986), this concept posited that nanoparticles preferentially accumulate in tumor tissues due to leaky vasculature and impaired lymphatic drainage. Despite the successful clinical translation of several nanoformulations most notably PEGylated liposomal doxorubicin—the broad clinical efficacy of synthetic nanocarriers remains severely bottlenecked by complex biological barriers. Upon intravenous administration, synthetic nanoparticles rapidly undergo opsonization, a process where serum proteins readily adsorb onto the particle surface to form a protein corona. This corona flags the foreign entities for rapid recognition and phagocytic clearance by the mononuclear phagocyte system (MPS), predominantly sequestering the therapeutic cargo in the liver and spleen rather than the target tissue (Yoo, Irvine, Discher, & Mitragotri, 2011). To circumvent MPS clearance, surface modification with polyethylene glycol (PEG) has long been the gold standard to create a steric hydration layer and confer "stealth" properties. However, the ubiquitous use of PEG is increasingly challenged by clinical evidence of the accelerated blood clearance (ABC) phenomenon. Repeated administrations of PEGylated carriers can trigger the production of anti-PEG antibodies, leading to rapid elimination, potential hypersensitivity reactions, and compromised therapeutic efficacy (Liu & Su, 2023). Furthermore, the complex "bottom-up" functionalization of synthetic nanoparticles with specific targeting ligands often suffers from low conjugation efficiency, protein denaturation, and altered physicochemical properties. These inherent limitations have catalyzed a critical need for alternative, highly biocompatible strategies that can seamlessly interface with the human immune system.

1.2 Bio-Inspired Paradigm Shift

To bridge the persistent gap between synthetic drug delivery systems and complex biological environments, researchers have increasingly turned toward nature for inspiration, initiating a bio-inspired paradigm shift in nanomedicine. The human body naturally produces highly specialized cells such as red blood cells (RBCs), platelets, and immune cells that effortlessly navigate physiological barriers, circulate for extended periods, and precisely home in on specific tissues. In 2011, this biological elegance was harnessed

to create a novel class of delivery vehicles: cell-membrane camouflaged nanoparticles (Hu et al., 2011). Cell-membrane coating is a "top-down" biomimetic nanotechnology that involves extracting the natural plasma membrane from source cells and completely encloaking a synthetic nanoparticle core (Fang, Kroll, Gao, & Zhang, 2018). Unlike traditional bottom-up bioconjugation, which typically mounts only a single or a few types of synthesized ligands onto a nanoparticle surface, this top-down approach faithfully translocates the entire intact cell membrane. Consequently, the nanocarrier inherits the complex lipid bilayer, transmembrane proteins, glycans, and antigens exactly as they exist in their natural spatial conformation, bypassing the need to artificially synthesize structurally complex membrane proteins. The foundational breakthrough of this technology was the RBC membrane-coated nanoparticle. By adopting the RBC's exterior, the synthetic core successfully bypassed immune surveillance. A primary driver of this immune evasion is the preservation of CD47, a transmembrane protein widely expressed on mammalian cells that functions as a critical "don't eat me" signal. When the CD47-functionalized nanocarrier encounters a macrophage, it binds to the signal regulatory protein alpha (SIRP α) receptor on the macrophage's surface, actively inhibiting phagocytosis and extending the circulation half-life of the nanoparticle to mirror that of natural erythrocytes (Hu et al., 2011; Liu & Su, 2023). Building on the success of RBC camouflage, this paradigm has rapidly expanded into a versatile platform technology. Researchers are now exploiting the unique surface proteomes of various nucleated and non-nucleated cells. For instance, cancer cell membranes are utilized for their homotypic adhesion molecules to achieve highly specific tumor targeting, while platelet membranes are leveraged for their innate ability to adhere to damaged vasculature and pathogens (Fang et al., 2018). By seamlessly fusing the highly tunable, cargo-loading capacity of synthetic cores with the sophisticated biological interfacing capabilities of natural cell membranes, camouflaged nanocarriers represent a transformative leap toward truly multifunctional and precision therapeutic delivery.

2. Fabrication and Characterization Strategies

The successful translation of cell-membrane camouflaged nanoparticles hinges on precise, reproducible fabrication techniques that seamlessly integrate biological membranes with synthetic cores. Typically, the top-down fabrication of these biomimetic platforms involves three critical stages:

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

core nanomaterial synthesis, cell membrane extraction, and the final coating or fusion process (Zhai et al., 2017). Each step must be meticulously optimized to ensure the structural integrity and biological functionality of the resulting core-shell nanocarriers.

2.1 Core Nanomaterial Selection

The selection of the inner synthetic core is primarily dictated by the desired therapeutic payload and the specific clinical application. A vast array of materials has been successfully employed, including organic polymers, inorganic nanoparticles, and hybrid metal-organic frameworks (MOFs). Poly(lactic-co-glycolic acid) (PLGA) remains the most extensively utilized polymeric core due to its FDA-approved status, excellent biodegradability, and sustained drug-release kinetics (Fang et al., 2018). For therapies requiring high loading capacities of hydrophilic drugs, mesoporous silica nanoparticles (MSNs) are frequently selected (Zhai et al., 2017). Alternatively, inorganic cores such as gold nanoparticles, iron oxide (Fe₃O₄), and upconversion nanoparticles are preferred when incorporating theranostic modalities like magnetic resonance imaging (MRI) or photothermal therapy (PTT) (Xuan et al., 2019). Crucially, the physicochemical properties of the core specifically its surface charge, size, and geometry dictate the efficiency of the membrane coating process. Natural cell membranes possess an asymmetric charge distribution, typically presenting a net negative charge due to sialic acid residues. Consequently, negatively charged cores like PLGA facilitate a coating process driven by the minimization of electrostatic repulsion, which encourages the membrane vesicles to self-assemble and thermodynamically stabilize around the core (Kroll et al., 2016). While spherical nanoparticles ranging from 65 to 340 nm are most common, recent advancements have demonstrated that even nonspherical templates, such as gold nanocages or MOFs, can be successfully cloaked if the surface energy dynamics are appropriately managed (Xuan et al., 2019).

Table 2: Main Cell Membrane Sources, Retained Surface Markers, and Biological Utilities

Cell Membrane Source	Key Preserved Surface Markers /Receptors	Primary Biological Function	Target Application Niche	Reference(s)
Red Blood	CD47, CD59,	Acts as a “don’t	Prolonged	Hu et al.,

Cell (RBC)	CD55, Glycophorin A	eat me” signal (CD47–SIRPα axis), suppresses complement activation, and prevents opsonization.	systemic circulation; long-acting drug delivery; systemic detoxification (nanosponges).	2011; Luk & Zhang, 2015
Platelet	P-selectin, CD44, GPIIb/IIIa, GPIbα, and CD47	Adhesion to damaged endothelium and subendothelial collagen; natural affinity for circulating tumor cells (CTCs) and specific bacteria.	Targeted thrombolysis; atherosclerosis plaque stabilization; anti-metastasis therapy.	Hu et al., 2015; Wei et al., 2018
Cancer Cell	EpCAM, N-cadherin, Thomsen-Friedenreich antigen, Galectin-3, specific mutant TAAs	Homotypic binding (self-recognition and cellular adhesion); presentation of tumor-associated antigens (TAAs) to the	Personalized and homotypic targeted tumor drug delivery; autologous multi-antigenic cancer	Fang et al., 2014; Kroll et al., 2017

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

		immune system.	vaccines.	
Macrophage / Leukocyte	LFA-1, Mac-1, PSGL-1, CD14, Toll-like receptors (TLRs), CD126	Chemotaxis toward inflammatory gradients; transendothelial migration; broad-spectrum binding and neutralization of endotoxins and cytokines.	Targeted delivery to inflamed tissues (rheumatoid arthritis, stroke); crossing the BBB; sepsis and cytokine storm management.	Parodi et al., 2013; Thampai et al., 2017
Mesenchymal Stem Cell (MSC)	CD29, CD44, CD73, CD90, CXCR4	Intrinsic tumor tropism; homing to sites of injury and ischemia; inherent low immunogenicity and immunosuppressive signaling.	Targeted oncology (tumor homing); ischemic tissue repair; regenerative nanomedicine.	Gao et al., 2016; Zhao et al., 2021
Bacterial (Outer Membrane Vesicles - OMVs)	Lipopolysaccharides (LPS), Pathogen-associated molecular patterns	Highly immunogenic; rapid recognition by host antigen-presenting cells	Non-replicating, self-advantaging antibacterial vaccines;	Gao et al., 2015; Li et al., 2020

	(PAMPs), OmpA	(APCs); functions as a natural, potent immunological adjuvant.	localized cancer immunotherapy.	
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2.2 Membrane Extraction Protocols

Extracting intact cell membranes without denaturing their associated proteins is arguably the most sensitive step in the fabrication process. The protocol diverges depending on whether the source cells are anucleated (red blood cells, platelets) or nucleated (cancer cells, macrophages, stem cells). For anucleated cells, extraction is relatively straightforward. Red blood cells (RBCs) are typically subjected to hypotonic lysis, in which low osmotic pressure causes the cells to swell and rupture, releasing intracellular hemoglobin and yielding empty RBC “ghosts” (Liu et al., 2022). Platelets, conversely, are often subjected to repeated freeze–thaw cycles to disrupt their cellular structures (Liu et al., 2022). Extracting membranes from nucleated cells requires more rigorous protocols to eliminate mitochondrial and nuclear contamination. Harvested cells are first suspended in an ice-cold hypotonic buffer containing protease inhibitor cocktails to prevent enzymatic degradation of membrane proteins (Chugh et al., 2021). Mechanical disruption is then performed using a Dounce homogenizer or a high-pressure homogenizer. Following lysis, the mixture undergoes differential centrifugation. Low-speed centrifugation (e.g., 800 × g) is first used to pellet intact nuclei and unbroken cells, followed by a medium-speed step to remove mitochondria. Finally, the supernatant is subjected to ultracentrifugation (typically at 100,000 × g) or discontinuous sucrose density gradient centrifugation to isolate pure plasma membrane fragments (Chugh et al., 2021).

2.3 Coating Methodologies

Once the core nanoparticles and pure membrane vesicles are prepared, they must be fused into a stable core-shell architecture. Several techniques have been developed to achieve this, each with distinct advantages and translatability challenges.

- **Extrusion:** This remains the gold-standard mechanical method. The core nanoparticles and membrane vesicles are co-extruded multiple times through a polycarbonate porous membrane (typically stepping down

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

from 400 nm to 100 nm pores) using an Avanti micro-extruder. The mechanical shear force and the inherent fluidity of the lipid bilayer compel the membrane to reorganize and completely wrap around the solid cores (Zhai et al., 2017). While extrusion yields highly uniform size distributions and faithful "right-side-out" membrane orientations, it is labor-intensive, prone to material loss on the filters, and difficult to scale up for industrial production.

- **Sonication:** As a higher-throughput alternative to extrusion, co-incubation paired with ultrasonic waves (bath sonication) is widely used. The ultrasonic energy temporarily disrupts the cell membrane bilayer, initiating electrostatic attraction between the cores and the membrane fragments, which subsequently reassemble into a lower-entropy, stable core-shell structure (Zhai et al., 2017). Although scalable, sonication parameters (intensity, duration, and temperature) must be tightly controlled, as excessive energy can generate localized heat that denatures heat-sensitive surface proteins (Liu et al., 2022).
- **Microfluidic Electroporation:** To circumvent the mechanical and thermal degradation associated with extrusion and sonication, microfluidic electroporation has emerged as a cutting-edge technique. This continuous-flow method applies calibrated electrical pulses to a mixture of cells and nanoparticles moving through microchannels. The electric field creates transient pores in the cell membrane, allowing intracellular contents to escape while driving the nanoparticles inside, ultimately forming the coated structure (Shi et al., 2021). This strategy significantly improves the retention of the membrane's structural integrity and functional proteins, offering superior scale-up potential and reproducibility (Xuan et al., 2019; Shi et al., 2021).

2.4 Physicochemical and Biological Characterization

Rigorous characterization is mandatory to validate the successful formation and functionality of the biomimetic camouflage. Physicochemically, dynamic light scattering (DLS) is utilized to monitor changes in hydrodynamic size and surface charge. A successful coating typically results in an increase of 10 to 20 nm

in the nanoparticle's diameter corresponding to the thickness of a lipid bilayer and a shift in the core's zeta potential to precisely match the surface charge of the source membrane vesicles (Fang et al., 2014). Transmission electron microscopy (TEM), coupled with negative staining (using uranyl acetate), is indispensable for visual confirmation; it reveals a distinct core-shell spherical morphology characterized by a highly electron-dense core surrounded by a lighter, ~5-10 nm thick lipid membrane halo (Chugh et al., 2021; Fang et al., 2014). Biologically, it is imperative to verify that the complex proteome of the source cell has been translocated without degradation. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) is routinely employed to demonstrate that the protein profile of the camouflaged nanoparticles perfectly mirrors that of the source cell lysates, with no significant loss of major protein bands (Fang et al., 2018). Furthermore, Western blotting is utilized to confirm the presence and orientation of specific functional markers essential for therapeutic efficacy, such as the CD47 "don't eat me" signal from RBC membranes or EpCAM adhesion molecules from cancer cell membranes (Fang et al., 2018; Zhai et al., 2017).

3. Diverse Cell Membrane Sources and Their Unique Biological Utilities

The versatility of cell-membrane coating nanotechnology stems from the diverse array of source cells available. By carefully selecting the biological donor, researchers can endow synthetic nanocarriers with highly specific, naturally evolved functionalities that dictate their physiological fate, targeting capabilities, and therapeutic efficacy.

3.1 Red Blood Cell (RBC) Membranes

The erythrocyte, or red blood cell (RBC), represents the foundational and most extensively investigated source for membrane camouflage. The primary rationale for utilizing RBC membranes is to confer exceptional systemic circulation longevity. Nature has optimized RBCs to circulate in the human bloodstream for approximately 120 days, a feat achieved through a unique constellation of surface proteins. The most critical of these is the transmembrane protein CD47, which acts as a robust "don't eat me" signal. When an RBC-camouflaged nanoparticle encounters a macrophage of the mononuclear phagocyte system (MPS), CD47 engages with the signal regulatory protein alpha (SIRP α) receptor on the macrophage's surface. This interaction triggers an intracellular signaling cascade that actively inhibits actin cytoskeleton reorganization, thereby thwarting

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

phagocytosis (Hu et al., 2011). Beyond CD47, the complex glycan profile and acidic sialic acid residues on the RBC surface further prevent protein opsonization and complement activation. Consequently, RBC-coated nanocarriers exhibit a significantly extended pharmacokinetic half-life compared to traditional PEGylated systems, making them ideal for sustained drug delivery and systemic detoxification therapies (Fang, Kroll, Gao, & Zhang, 2018).

3.2 Platelet Membranes

While RBCs provide passive stealth, platelet membranes offer a sophisticated degree of active targeting deeply rooted in natural hemostatic and inflammatory pathways. Platelets inherently circulate in a resting state but rapidly adhere to sites of vascular injury, atherosclerotic plaques, and invasive pathogens. This tropism is governed by an array of specialized surface receptors, notably P-selectin, CD44, and integrins such as GPIIb/IIIa and GPIba (Hu et al., 2015). By translocating these specific binding moieties onto polymeric or inorganic cores, platelet-camouflaged nanocarriers can autonomously navigate to damaged endothelium for targeted delivery of thrombolytics or restenosis-preventing agents. Furthermore, platelets possess a well-documented affinity for circulating tumor cells (CTCs) and bacteria (*Staphylococcus aureus*). In oncology, platelet-coated nanoparticles exploit this natural affinity to bind to CTCs in the bloodstream, neutralizing them before they can establish distant metastatic niches (Wang et al., 2020).

Table 3: Recent Advances in Therapeutic Delivery using Membrane-Camouflaged Nanocarriers (2020–2024)

Disease Target / Application	Core Nanomaterial	Membrane Source	Encapsulated Payload / Stimuli	Therapeutic Outcomes	Reference
COVID-19 (SARS-CoV-2 Infection)	Poly(lactic-co-glycolic acid) (PLGA)	Human Macrophage or Lung Epithelial	None (Acts as a therapeutic decoy / Nanospunge)	Successfully neutralized SARS-CoV-2 viral entry by acting as	Zhang et al., 2020

		Cell Membranes		decoy receptors (ACE2/CD147); competitively blocked host cell infection.	
Cerebral Ischemia (Stroke)	Mesoporous Prussian Blue Nanozymes (MPBZs)	Macrophage Membrane	ROS-scavenging catalytic core (No external drug payload)	Exploited inflamed endothelium (VCAM-1) to cross the blood-brain barrier (BBB); effectively scavenged reactive oxygen species (ROS) and suppressed neuroinflammation.	Ma et al., 2020
Bacterial Bone Infection (Osteomyelitis)	PLGA Nanoparticles	Macrophage Membrane	Vancomycin (Broad-spectrum antibiotic)	Targeted the localized inflammatory microenvironment; eradicated	Shi et al., 2021

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

				ted intracellular <i>Staphylococcus aureus</i> hiding within host macrophages; reduced bone destruction.					e quantities of pro-inflammatory cytokines (IL-6, TNF- α), preventing lethal cytokine storms.	
Solid Tumor & Metastasis	Polymeric Nanoparticles (PLGA)	Platelet Membrane	Doxorubicin (DOX) (Chemotherapeutic)	Mimicked platelet affinity for circulating tumor cells (CTCs) and damaged vasculature; significantly enhanced tumor accumulation and inhibited lung metastasis.	Wang et al., 2020					
Systemic Hyperinflammation (Sepsis / COVID-19)	Polymeric Nanoparticles (PLGA)	Human Macrophage Membrane	None (Nanosponge decoy)	Concurrently sequestered SARS-CoV-2 virions and massiv	Rao et al., 2020					
Rheumatoid Arthritis	Mesoporous Silica Nanoparticles (MSNs)	Neutrophil Membrane	Celastrrol (Anti-inflammatory agent)						Targeted inflammation synovial tissue via chemotaxis; neutralized synovial cytokines; effectively prevented cartilage degradation and joint swelling in vivo.	Deng et al., 2021
Solid Tumors (Synergistic)	Hollow Mesoporous	Cancer Cell Membrane	Doxorubicin (DOX) + Near-Infrared						Homotypic targeting facilitates	Chen et al., 2020

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

Theranostics)	Copper Sulfide (\$CuSS\$)	ane (MCF-7)	d (NIR) Light	ed precise tumor accumulation; localized NIR irradiation triggered core hyperthermia, releasing DOX for synergistic photothermal-chemotherapy.
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cadherin, galectin-3, and various mutated integrins) that facilitates highly specific self-recognition and homologous adhesion. This mechanism naturally drives multicellular tumor spheroid formation and metastasis (Fang et al., 2014). When coated onto a synthetic core, cancer cell membranes direct the nanocarriers to selectively accumulate in the source tumor tissue and, crucially, in its homotypic metastases. This allows for personalized oncological interventions where a patient's own biopsied tumor cells could theoretically be used to synthesize highly specific delivery vehicles. Beyond drug delivery, these camouflaged particles present a dense, natural array of tumor-associated antigens (TAAs) to the immune system. When combined with immunological adjuvants in the synthetic core, they serve as potent, multi-antigenic nanovaccines capable of eliciting robust, tumor-specific cytotoxic T-lymphocyte responses without the need for complex antigen identification (Kroll et al., 2017).

3.3 Leukocyte/Macrophage Membranes

Leukocytes, including macrophages, neutrophils, and T-cells, are the primary sentinels of the immune system. Their membranes are richly decorated with chemokine receptors and adhesion molecules such as LFA-1, Mac-1, and PSGL-1 that allow them to undergo chemotaxis, marginate along blood vessel walls, and extravasate into inflamed tissues and the tumor microenvironment (TME) (Parodi et al., 2013). Nanoparticles cloaked in leukocyte membranes effectively inherit this dynamic "homing" capability. Macrophage membrane-coated nanocarriers, for instance, naturally gravitate toward inflammatory gradients and actively bind to inflamed endothelium expressing VCAM-1 and ICAM-1. This targeted accumulation has shown immense promise in treating localized inflammation, sepsis, and rheumatoid arthritis. Moreover, because macrophages express receptors capable of binding endotoxins (like Toll-like receptors), their membrane-coated counterparts can act as nanoscale "sponges," sequestering inflammatory cytokines and bacterial toxins to mitigate cytokine storms (Zhang et al., 2018).

3.4 Cancer Cell Membranes

The concept of utilizing cancer cell membranes for nanocarrier camouflage introduces a powerful strategy known as homotypic targeting. Cancer cells possess a unique surface antigen profile (e.g., EpCAM, N-

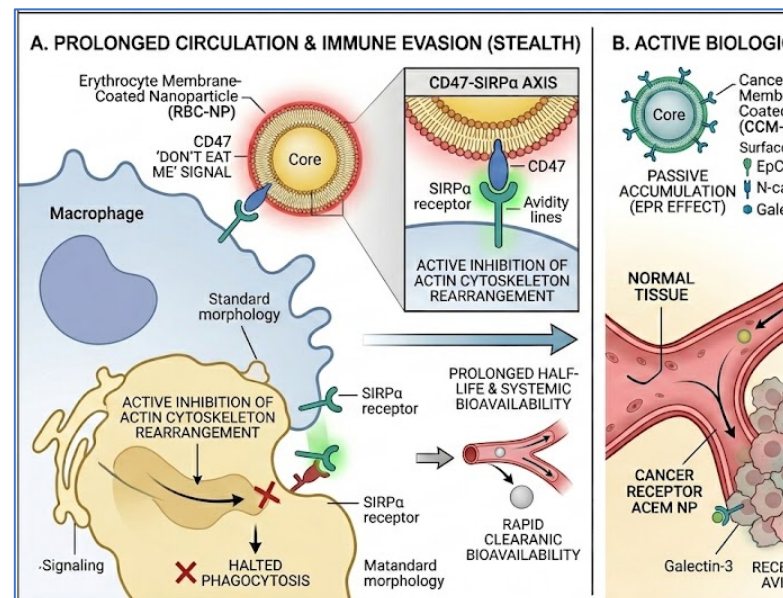


Figure 1: Biological Mechanisms - Stealth & Active Targeting.

3.5 Stem Cell and Bacterial Membranes

Exploring more specialized biological niches, stem cell and bacterial membranes have emerged for distinct applications. Mesenchymal stem cell (MSC) membranes provide a unique combination of low inherent immunogenicity, exceptional tumor tropism, and intrinsic tissue regeneration signaling (Gao et al., 2016). They are increasingly investigated for targeted delivery in regenerative medicine and ischemic stroke recovery. Conversely, bacterial cell membranes, specifically outer membrane vesicles (OMVs) derived from Gram-negative bacteria, are highly immunogenic.

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

While unsuitable for stealth drug delivery, they are heavily loaded with pathogen-associated molecular patterns (PAMPs). Coating nanoparticles with OMVs creates highly stable, non-replicating bacterial mimics that serve as potent self-adjuvating vaccines, driving powerful prophylactic immune responses against infectious diseases without the systemic toxicity risks of live-attenuated pathogens (Gao et al., 2015).

3.6 Hybrid and Engineered Cell Membranes

As the field advances, the inherent limitations of single-membrane systems such as the lack of active targeting in RBCs or the rapid clearance of cancer cell membranes have catalyzed the development of hybrid and engineered cell membranes. This cutting-edge approach involves the fusion of two distinct membrane types to yield a singular nanocarrier with synergistic, multi-pronged capabilities. For example, fusing RBC and platelet membranes creates a chimeric camouflage that possesses both the extended circulatory half-life of an erythrocyte (via CD47) and the specific targeting capabilities of a platelet (via integrins) (Dehaini et al., 2017). Beyond hybridization, source cells or isolated membranes can be artificially engineered prior to coating. Lipid-insertion techniques can be used to anchor targeting aptamers into the membrane bilayer, while genetic engineering of the parent cells can force the overexpression of specific therapeutic ligands or checkpoint inhibitors (PD-1). This dynamic engineering bridges the gap between natural biological complexity and synthetic programmability, representing the future trajectory of biomimetic nanomedicine (Chen et al., 2020).

4. Multifunctional Capabilities in Biological Environments

The true translational value of cell-membrane camouflaged nanocarriers lies not merely in their structural novelty, but in their profound functional versatility. By marrying the highly tunable physicochemical properties of synthetic cores with the sophisticated biochemical interfaces of natural cell membranes, these platforms exhibit unprecedented multifunctional capabilities. Once introduced into complex biological environments, they simultaneously execute immune evasion, precise biological targeting, stimuli-responsive payload release, and advanced theranostic functions.

4.1 Prolonged Systemic Circulation & Stealth Properties

The foremost hurdle for any intravenously administered nanomedicine is the rapid recognition and clearance by the mononuclear phagocyte system (MPS). Traditional strategies to mitigate this, such as

PEGylation, rely on steric hindrance to reduce protein opsonization. However, biomimetic camouflage introduces a paradigm shift by utilizing active biological signaling to achieve systemic stealth. When a synthetic nanoparticle is encloaked in a red blood cell (RBC) or leukocyte membrane, it inherits a dense canopy of endogenous surface proteins and a highly hydrated glycocalyx. The fundamental mechanism of this stealth behavior is predominantly governed by the CD47 transmembrane protein, ubiquitously present on erythrocyte and immune cell membranes. CD47 functions as an active "don't eat me" signal by binding to the signal regulatory protein alpha (SIRP α) receptor on host macrophages (Hu et al., 2011). This receptor-ligand engagement triggers the phosphorylation of immunoreceptor tyrosine-based inhibitory motifs (ITIMs) on SIRP α , which subsequently recruits and activates SHP-1 and SHP-2 phosphatases. These enzymes dephosphorylate multiple downstream targets, ultimately paralyzing the macrophage's actin cytoskeleton remodeling and halting phagocytosis (Luk & Zhang, 2015). Furthermore, the translocation of natural sialic acids and homologous complement regulatory proteins (e.g., CD59, CD55) onto the nanocarrier surface actively suppresses the alternative pathway of the complement cascade. This orchestrated, multi-tiered evasion strategy enables membrane-camouflaged nanoparticles to achieve circulation half-lives that vastly outperform their artificially functionalized counterparts, ensuring sustained bioavailability of the encapsulated therapeutics (Rao et al., 2015).

4.2 Active, Homotypic, and Multi-Receptor Targeting

Beyond passive immune evasion, cell-membrane coating endows nanocarriers with the intrinsic ability to actively navigate to specific disease foci. Traditional active targeting relies on the bottom-up conjugation of a single targeting ligand (folic acid or antibodies), which often suffers from low avidity and off-target binding. In stark contrast, cell-membrane camouflage transfers an intact, multi-receptor array, enabling synergistic binding kinetics that mirror natural cellular tropism. Cancer cell membrane-camouflaged nanoparticles excel in homotypic targeting the biological phenomenon where tumor cells recognize and adhere to identical cells. This behavior drives natural tumor spheroid formation and metastasis, mediated by a complex interplay of surface antigens such as EpCAM, N-cadherin, Thomsen-Friedenreich antigen, and various galectins (Fang et al., 2014). By replicating this surface signature, synthetic cores can

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

selectively bind to both the primary source tumor and its disseminated metastases. Similarly, leukocyte-camouflaged carriers exploit inflammation targeting. The presence of lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1) on the biomimetic surface enables robust binding to intercellular adhesion molecule-1 (ICAM-1), which is uniquely overexpressed on inflamed endothelial cells in the tumor microenvironment (TME) or localized infection sites (Parodi et al., 2013). This multi-receptor avidity guarantees high-fidelity, tissue-specific accumulation while bypassing healthy, non-inflamed tissues.

4.3 Stimuli-Responsive Therapeutics

While the biological membrane facilitates secure transport and precise localization, the therapeutic efficacy ultimately depends on the spatiotemporal release of the payload. To optimize this, researchers engineer the synthetic core to act as a "smart" reservoir, unleashing its cargo strictly in response to specific triggers within the TME or via external physical stimuli. Internally, the TME is characterized by mild hypoxia, acidic pH (pH 6.5-6.8), elevated concentrations of glutathione (GSH), and specific overexpressed enzymes (e.g., matrix metalloproteinases). By utilizing pH-sensitive polymers or structurally incorporating disulfide/diselenide bonds within the core matrix, the biomimetic nanoparticle remains stable during systemic circulation but rapidly degrades upon endosomal uptake (pH ~5.0) or exposure to the highly reductive intracellular environment of tumor cells, triggering a burst release of chemotherapeutics (Zhai et al., 2017). Externally, stimuli-responsive modalities are often paired with inorganic cores. For instance, gold nanocages or hollow mesoporous copper sulfide nanoparticles can be cloaked in cell membranes. Upon accumulation at the tumor site, external irradiation with near-infrared (NIR) light penetrates deep into the tissue. The inorganic core rapidly converts this photonic energy into localized heat, effectively rupturing the encompassing lipid membrane to release encapsulated drugs while simultaneously inducing photothermal ablation of the surrounding cancer cells (Chen et al., 2016).

4.4 Theranostics

The integration of diagnostic imaging and therapeutic intervention into a single platform, termed theranostics, represents a critical frontier in personalized nanomedicine. Cell membrane-camouflaged nanocarriers are exceptionally well suited for this application, as the lipid bilayer acts as a highly

effective barrier that prevents the premature leakage of contrast agents and protects delicate imaging probes from enzymatic degradation in blood plasma. For high-resolution anatomical imaging, contrast agents such as gadolinium (Gd) chelates or superparamagnetic iron oxide nanoparticles (SPIONs) can be embedded within the core to achieve highly sensitive T₁- or T₂-weighted magnetic resonance imaging (MRI) (Luk & Zhang, 2015). For functional and optical imaging, near-infrared fluorescent dyes (indocyanine green, ICG) or semiconducting polymer nanoparticles are encapsulated to facilitate real-time fluorescence and photoacoustic imaging (PAI). The natural biomimetic coating greatly enhances the tumor-to-background signal ratio by minimizing nonspecific accumulation in the liver and skin. Consequently, clinicians can utilize PAI and MRI to dynamically track the *in vivo* biodistribution of the nanocarriers, verify their targeted accumulation at the disease site, and subsequently trigger therapeutic mechanisms (such as photothermal or photodynamic therapy), thereby directly monitoring treatment efficacy in real time (Chen et al., 2016; Zhai et al., 2017). This unified approach paves the way for highly precise, visually guided oncological interventions.

5. Applications in Therapeutic Delivery

The convergence of synthetic nanotechnology and biological mimicry has catalyzed paradigm-shifting advancements across multiple therapeutic domains. By effectively bypassing biological barriers that historically hindered synthetic nanocarriers, cell-membrane camouflaged platforms have demonstrated profound clinical potential in oncology, immunology, infectious diseases, and cardiovascular medicine.

5.1 Precision Oncology

The fundamental challenge in conventional chemotherapy is the lack of tumor specificity, which precipitates severe dose-limiting off-target toxicities and the rapid onset of multidrug resistance (MDR). Cell-membrane coated nanoparticles directly address these bottlenecks through highly specific biological routing and altered cellular internalization mechanisms. When utilizing cancer cell membranes, the resulting nanocarriers exploit homotypic binding mechanisms mediated by surface adhesion molecules such as EpCAM, galectin-3, and N-cadherin to preferentially accumulate in both the primary tumor and homologous metastatic niches (Fang et al., 2014). Crucially, biomimetic nanocarriers bypass traditional membrane diffusion by entering cancer cells via receptor-mediated endocytosis. This distinct internalization pathway prevents the therapeutic cargo

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

from being immediately recognized and extruded by P-glycoprotein (P-gp) efflux pumps, a primary mechanism of MDR (Zhai et al., 2017). Furthermore, these platforms excel in combinatorial precision oncology. By encapsulating photosensitizers (Indocyanine green) or utilizing photothermal inorganic cores (gold nanoshells) alongside chemotherapeutics, researchers can achieve spatiotemporally controlled photothermal and photodynamic therapies (PTT/PDT). Upon near-infrared (NIR) irradiation, the localized hyperthermia not only physically ablates tumor tissue but also disrupts the nanoparticle's lipid coating, triggering a burst release of the chemotherapeutic agent precisely within the tumor microenvironment (TME), yielding synergistic anti-tumor efficacy (Chen et al., 2016).

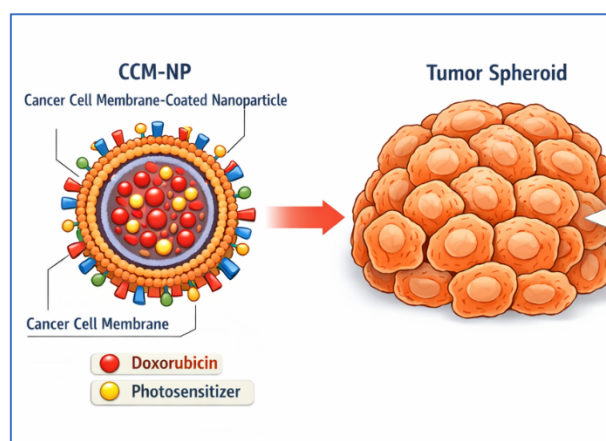


Figure 2: Broad Therapeutic Applications of Cell-Membrane Camouflaged Nanocarriers.

5.2 Immunotherapy and Vaccines

In the realm of immunotherapy, biomimetic nanocarriers serve dual yet distinct roles: as highly immunogenic nanovaccines and as immunosuppressive nanoscale decoys. For cancer vaccination, extracting membranes from a patient's own biopsied tumor cells yields an autologous, multi-antigenic coating. When this membrane is cloaked over a polymeric core loaded with immunological adjuvants (such as Toll-like receptor agonists like CpG oligodeoxynucleotides), the resulting nanoparticle closely mimics an invading pathogen. Upon subcutaneous administration, these nanovaccines efficiently drain into local lymph nodes, where they are actively taken up by dendritic cells. This process enhances antigen cross-presentation and subsequently primes a robust, tumor-specific CD8⁺ cytotoxic T-lymphocyte response, effectively suppressing tumor growth and preventing metastatic relapse (Kroll et al.,

2017). Conversely, when hyperinflammation threatens host survival, such as in autoimmune disorders or sepsis, cell membrane-coated nanoparticles can act as therapeutic “nanosponges.” Macrophage membrane-camouflaged nanoparticles inherit a dense array of cytokine receptors (e.g., CD14, CD126). When injected systemically, these biologically inert nanosponges circulate freely and function as decoy targets, intercepting and sequestering large quantities of pro-inflammatory cytokines (such as IL-6 and TNF- α) as well as bacterial endotoxins before they can engage with native cellular targets, thereby abruptly halting the lethal cascade of a cytokine storm (Wei et al., 2016).

5.3 Infectious Diseases

The escalating global crisis of antimicrobial resistance necessitates non-traditional therapeutic interventions. Cell-membrane camouflaged nanocarriers are at the forefront of this effort, offering both targeted antimicrobial delivery and pathogen neutralization strategies that operate independently of traditional antibiotic mechanisms (Fang, Kroll, Gao, & Zhang, 2018). Neutrophil and macrophage membranes, inherently programmed to seek out sites of infection via chemotaxis and inflammation-driven homing, can be utilized to deliver high payloads of broad-spectrum antibiotics directly to bacterial abscesses or intracellular reservoirs, effectively overcoming the poor tissue penetration of free drugs (Shi et al., 2021; Thamphiwatana et al., 2017). More innovatively, the nanosponge concept has been aggressively adapted to neutralize viral pathogens, a strategy most notably demonstrated during the COVID-19 pandemic. SARS-CoV-2 initiates host cell infection by binding its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor, while also relying on coreceptors like CD147. By fabricating nanocarriers coated with human lung epithelial cell membranes or engineered macrophage membranes, researchers created viral decoys that present a high density of functional ACE2 and CD147 receptors. These nanosponges aggressively bind to the circulating SARS-CoV-2 virions, competitively blocking them from infecting healthy host cells (Zhang et al., 2020). Furthermore, macrophage-derived nanosponges not only sequester the virions for systemic clearance but concurrently absorb pro-inflammatory cytokines, mitigating the associated immune overreaction and cytokine storm (Rao et al., 2020). Because this biomimetic intervention targets the fundamental host-pathogen interaction rather than specific viral epitopes, it remains highly resilient against future viral mutations.

5.4 Cardiovascular and Cerebrovascular Diseases

The targeted delivery of therapeutics to the cardiovascular and central nervous systems presents unique hydrodynamic and anatomical challenges, particularly navigating the high shear stress of flowing blood and penetrating the formidable blood-brain barrier (BBB) (Blanco, Shen, & Ferrari, 2015). Platelet-membrane camouflaged nanoparticles have emerged as the premier vehicle for cardiovascular interventions due to their natural hemostatic tropism. In the context of atherosclerosis or acute thrombosis, the endothelial lining is damaged, exposing subendothelial collagen and von Willebrand factor (vWF). Platelet-coated nanocarriers, inherently decorated with a dense array of active integrins and receptors (e.g., GPIIb/IIIa, GPIb α , and P-selectin), possess an intrinsic, high-avidity affinity for these exposed substrates (Hu et al., 2015; Wei et al., 2018). By encapsulating thrombolytic agents such as urokinase or tissue plasminogen activator (tPA), these biomimetic carriers concentrate the drug specifically at the site of the blood clot. This targeted accumulation vastly improves local thrombolysis efficiency while drastically minimizing the risk of systemic hemorrhagic complications traditionally associated with free tPA administration (Song et al., 2019; Xu et al., 2018). In cerebrovascular events such as ischemic stroke, the intact BBB fundamentally prevents most neuroprotective agents from reaching the damaged brain parenchyma. However, during acute ischemia, the local brain endothelium undergoes severe inflammation, drastically upregulating adhesion molecules such as VCAM-1 and ICAM-1 (Parodi et al., 2013). Neutrophil and macrophage membrane-coated nanoparticles are uniquely positioned to exploit this pathological shift. By utilizing their native leukocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1), these nanocarriers can firmly adhere to the inflamed brain endothelium, actively undergo transendothelial migration, and successfully cross the compromised BBB (Dong et al., 2019). Once within the ischemic penumbra, they can deliver high concentrations of neuroprotectants, reactive oxygen species (ROS) scavengers, or anti-apoptotic agents directly to the degenerating neurons, thereby effectively halting secondary neural degeneration and improving functional recovery (Ma et al., 2020; Zhang et al., 2018).

6. Current Challenges and Translational Perspectives

Despite the profound pre-clinical success and unprecedented biological capabilities of cell-

membrane camouflaged nanocarriers, their journey from the laboratory bench to bedside clinical application is obstructed by a formidable "valley of death." Transitioning these highly complex, bio-hybrid systems into commercially viable, regulatory-approved therapeutics requires overcoming significant bottlenecks in large-scale manufacturing, formulation stability, and regulatory compliance.

6.1 Manufacturing and Scale-up Bottlenecks

The most immediate impediment to the clinical translation of biomimetic nanocarriers is the lack of standardized, scalable manufacturing protocols compliant with Good Manufacturing Practice (GMP) guidelines. The top-down fabrication process relies heavily on multi-step, labor-intensive procedures that are inherently difficult to scale. Currently, membrane isolation predominantly utilizes mechanical homogenization followed by repeated cycles of differential and density-gradient ultracentrifugation (Bose et al., 2018). While effective for synthesizing milligram quantities in pre-clinical settings, ultracentrifugation is a batch process with notoriously low yields and cannot be seamlessly integrated into continuous industrial production lines. To bridge this gap, engineers are actively exploring Tangential Flow Filtration (TFF) and microfluidic-based isolation techniques, which offer continuous, high-throughput processing and superior reproducibility (Chugh, Vijaya Krishna, & Pandit, 2021). Furthermore, batch-to-batch variation presents a critical quality control challenge. Unlike purely synthetic nanomaterials, biological membranes are inherently heterogeneous. The proteomic and lipidomic profiles of source cells can fluctuate significantly based on the donor's age, sex, metabolic state, and the specific cell-culture conditions (in the case of expanded nucleated cells). For instance, cultivating enough patient-derived cancer cells or mesenchymal stem cells requires massive, highly controlled bioreactors. Ensuring that the structural integrity and precise ratio of functional membrane proteins such as CD47 or specific integrins remain consistent across industrial-scale batches is paramount, as minute deviations can drastically alter the pharmacokinetic profile and targeting efficacy of the final nanomedicine (Fang, Kroll, Gao, & Zhang, 2018).

6.2 Preservation and Shelf-life

A critical, yet often underreported, challenge in the translation of biomimetic nanocarriers is their long-term preservation and thermodynamic stability. Cell membranes are biologically labile constructs; their lipid bilayers are highly susceptible to lipid peroxidation and hydrolysis, while their embedded

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

transmembrane proteins can easily undergo irreversible denaturation and conformational degradation when removed from their native physiological environment (Zou et al., 2020). In an aqueous suspension, core-shell nanoparticles are prone to gradual membrane detachment, aggregation, and premature leakage of encapsulated therapeutics, rendering long-term liquid storage unfeasible. To achieve a commercially viable shelf-life, cryopreservation via lyophilization (freeze-drying) is mandatory. However, the freezing and subsequent dehydration processes generate immense physical stress, primarily through ice crystal formation and the removal of the protein hydration shell, which can collapse the biomimetic architecture. To mitigate this, lyoprotectants and cryoprotectants typically non-reducing disaccharides such as trehalose or sucrose are introduced into the formulation. These sugars undergo glass transition, replacing water molecules via hydrogen bonding to stabilize the lipid-protein domains during desiccation (Liu et al., 2022). Nevertheless, optimizing the precise type and concentration of these excipients is highly empirical. Developing universal, robust lyophilization protocols that guarantee 100% morphological recovery and retained biological avidity upon reconstitution at the patient's bedside remains an active and necessary area of investigation.

6.3 Safety, Toxicity, and Regulatory Hurdles

The regulatory landscape for biomimetic nanomedicines is highly complex and currently lacks dedicated frameworks. Agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) typically evaluate therapeutics as either drugs, biologics, or medical devices. Cell-membrane camouflaged nanoparticles fundamentally blur these lines, existing as complex "combination products." Establishing universal Chemistry, Manufacturing, and Controls (CMC) standards for products containing both a synthetic chemical core and an intact, biologically derived cellular membrane is a daunting regulatory hurdle (Mitchell et al., 2021). Safety and immunotoxicity profiles are deeply intertwined with the source of the cellular membrane. While autologous sourcing (using a patient's own cells) theoretically bypasses immune rejection, it represents a highly personalized, exorbitant, and time-consuming logistical challenge, similar to the current hurdles facing CAR-T cell therapies. Conversely, allogeneic (donor-derived) or xenogeneic (animal-derived) membranes offer promising "off-the-shelf" scalability but carry severe

risks of immunogenicity. Introducing mismatched Major Histocompatibility Complex (MHC) molecules or foreign blood group antigens into a patient's systemic circulation can trigger severe hypersensitivity, complement activation, and accelerated immune clearance (Fang et al., 2018). Furthermore, incomplete purification during membrane extraction can result in the retention of residual intracellular components, such as nuclear DNA or mitochondrial proteins, which may act as dangerous autoantigens and inadvertently trigger autoimmune pathologies. Strict regulatory criteria defining the acceptable limits of intracellular impurities will be essential for clinical approval.

6.4 Future Perspective

To overcome these translational barriers, the future trajectory of cell-membrane camouflaged nanocarriers will increasingly rely on interdisciplinary convergence, specifically integrating advanced computational modeling and synthetic biology. Artificial Intelligence (AI) and Machine Learning (ML) algorithms are poised to revolutionize the design phase. By processing vast datasets of lipidomic profiles and core physicochemical properties, predictive AI models and molecular dynamics (MD) simulations can rapidly identify the thermodynamically optimal core-membrane combinations, precisely predicting formulation stability and coating efficiency prior to any physical synthesis (Mitchell et al., 2021). Moreover, the field is rapidly shifting toward engineered, "designer" cell membranes. Rather than relying solely on the natural, wild-type state of source cells, researchers are utilizing CRISPR/Cas9 genetic editing to force parent cells to artificially overexpress specific homing ligands, therapeutic checkpoints (e.g., PD-1), or highly specific catalytic enzymes prior to membrane harvesting (Liu et al., 2022). This synergy of synthetic biology with biomimetic nanotechnology promises to yield highly uniform, super-functionalized, and personalized nanocarriers. As manufacturing technologies mature and regulatory pathways crystallize, these bio-inspired platforms possess the unprecedented potential to fully bridge the gap between synthetic pharmacology and physiological complexity, redefining the limits of precision medicine.

7. Conclusion

The advent of cell-membrane camouflaged nanocarriers represents a transformative leap in targeted therapeutic delivery, effectively bridging the gap between synthetic pharmacokinetics and physiological complexity. By seamlessly encloaking

Bio-Inspired Cell-Membrane Camouflaged Nanocarriers: Bridging the Gap Between Synthetic Delivery Systems and Biological Complexity

synthetic nanoparticle cores within intact natural cell membranes, this bio-inspired paradigm overcomes the critical limitations of traditional nanomedicine, such as rapid immune clearance, poor targeting avidity, and off-target toxicity. Whether utilizing erythrocytes for prolonged systemic circulation, cancer cells for homotypic tumor targeting, or leukocytes for dynamic inflammatory homing, these platforms endow drug delivery vehicles with unparalleled, multi-receptor functionalities that hold immense potential for precision oncology, immunotherapy, and the treatment of infectious and cardiovascular diseases. However, the transition of these highly advanced biomimetic systems from the laboratory bench to the clinical bedside remains obstructed by significant translational bottlenecks. Future research must rigorously address the complex challenges of GMP-compliant large-scale manufacturing, the long-term thermodynamic stability and shelf-life of extracted biological membranes, and the establishment of clear regulatory frameworks for such bio-hybrid combination products. Overcoming these hurdles will necessitate a deeply multidisciplinary approach. By integrating microfluidic engineering for reproducible scale-up, artificial intelligence for predicting optimal core-membrane thermodynamics, and synthetic biology to yield super-functionalized "designer" membranes, researchers can seamlessly navigate these translational barriers. Ultimately, as manufacturing techniques and regulatory pathways mature, cell-membrane camouflaged nanotechnology is poised to redefine the limits of personalized nanomedicine and deliver next-generation therapeutics.

Conflict of interest

None.

Funding

None.

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