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Review

Engineering Cell Membrane-Coated Nanoparticles: A Route for Enhanced Therapeutic Efficacy

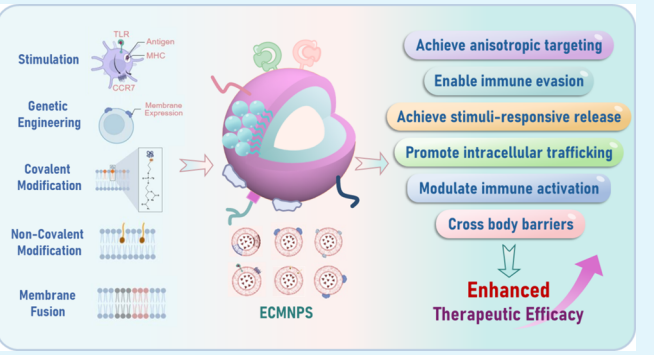
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ABSTRACT: Cell membrane-coated nanoparticles (CMNPs) have emerged as versatile biomimetic nanoplatforms that inherit native membrane biofunctions, such as immune evasion, specific molecular recognition, and prolonged systemic circulation. Nevertheless, conventional CMNPs suffer from low surface ligand density and weak microenvironment responsiveness, leading to unsatisfactory functional homogeneity and restricted translational applicability. These limitations directly translate into key clinical challenges, including poor active targeting capability, rapid in vivo clearance, and insufficient tumor penetration. To tackle these material engineering limitations, engineered (ECMNPs) have been developed through modular membrane engineering to enable precise and programmable surface functionalization. This review systematically summarizes five mainstream membrane modification strategies for ECMNP construction, including stimuli-responsive functionalization, genetic engineering, covalent conjugation, noncovalent assembly, and membrane fusion. By integrating endogenous membrane bioactivity with artificially optimized nanostructures, ECMNPs exhibit tunable targeting capability, stimuli-triggered drug release, immunomodulatory effects, and enhanced transbarrier delivery for treating intractable diseases. We further discuss key translational bottlenecks regarding membrane sourcing, extraction procedures, structural stability, and biological safety. This work highlights membrane engineering-enabled biological regulation of nanomaterials, offering rational guidelines for the design and scalable fabrication of next-generation biomimetic nanotherapeutics.



KEYWORDS: *cell membrane-coated nanoparticles, anisotropic targeting, immune evasion, stimuli-responsive release, intracellular trafficking, immunomodulatory activation, transbarrier transport*

1. INTRODUCTION

Cell membrane-coated nanoparticles (CMNPs), as an innovative paradigm in biomimetic nanotechnology, have evolved into a groundbreaking therapeutic strategy to bypass biological barriers inherent in conventional nanomedicine.[1−3] These nanosystems feature a distinctive shell-core architecture, integrating an endogenous cell membrane exterior with an engineered nanoparticle core.[4,5] This biomimetic design endows them with exceptional adaptive capabilities within complex physiological environments and demonstrates superior efficacy in systemic drug delivery.[6−10] Importantly, CMNPs preserve both the membrane protein composition and bioactive signaling functions of their original cells. For example, erythrocytes possess the capability to circulate within the body for extended periods. Platelets have developed specialized mechanisms that enable them to target specific disease sites to facilitate wound healing. Cancer cells often exhibit immune evasion properties that enhance their survival.[11−13] However, limitations in natural cell membranes currently pose significant challenges for clinical application.[14,15] Stochastic redistribution of membrane components during synthesis may lead to a reduction in ligand presentation density below optimal thresholds,[16,17] whereas the native characteristics of biological membranes appear inadequate for the integration of stimuli-responsive drug release mechanisms.[18,19] Additionally, biological variability in donor cell populations introduces batch-specific differences in membrane protein organization and surface characteristics, creating obstacles for standardized manufacturing.[20] These observations underscore the critical need for the development of advanced membrane engineering strategies designed to overcome current limitations while preserving the inherent biocompatibility of donor cells.

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To address these limitations, multidisciplinary bioengineering strategies have been developed for precision membrane functionalization. Emerging chemical-biological hybrid techniques, encompassing stimulation,[21,22] genetic engineering,[23] covalent modification,[24] noncovalent modification,[25] and membrane fusion,[26,27] provide comprehensive approaches for controlled membrane engineering. These approaches allow the rational incorporation of bioactive components and stimuli-responsive moieties without compromising native membrane architecture. By employing these engineering methods, engineered CMNPs (ECMNPs) can not only achieve precise regulation of the molecular composition of the membrane surface but also enable the construction of "intelligent" nanocarriers through the integration of functional modules. For example, engineered membranes incorporating CD47 (cluster of differentiation 47) exhibit a significant suppression of macrophage phagocytosis, while pH-responsive membrane modifications enable tumor microenvironment-triggered drug release.[28] These engineered technological advancements have substantially enhanced the delivery efficacy and therapeutic specificity of CMNPs in pathophysiological contexts, demonstrating considerable translational potential for precision medicine applications across various disease conditions.

Currently, the biomaterials field lacks a systematic framework linking membrane engineering strategies to tailored biomimetic biofunctions and corresponding therapeutic applications. To fill this gap, this review proposes a unifying conceptual framework that explicitly maps five principal cell membrane engineering approaches (stimuli-responsive modification, genetic engineering, covalent conjugation, noncovalent assembly, and membrane fusion) onto six distinct biofunctional orientations: anisotropic targeting, immune evasion, stimuli-responsive release, optimized intracellular trafficking, immunomodulatory activity, and facilitated trans-barrier transport. This framework establishes clear connections among material engineering strategies, biomaterial functional outcomes, and disease applications by elucidating how each engineering approach directly endows membrane-coated nanoplatforms with specific biofunctions and contextualizing these material performances within pathological settings including tumors, inflammatory disorders, autoimmune conditions, neurological diseases, thrombosis, and infections. This work is anticipated to facilitate cross-disciplinary efforts toward advancing clinically viable biomimetic ECMNP biomaterials.

2. CELL MEMBRANE SOURCES: TYPES, FEATURES, AND NATIVE LIMITATIONS

The strategic selection of cellular membrane sources constitutes a critical design parameter in ECMNP systems, as distinct membrane subtypes exhibit characteristic biological signatures. However, the inherent limitations of native cell membranes, rather than the diversity of membrane categories, have become the key bottleneck restricting the therapeutic performance of ECMNPs. Erythrocytic membranes, neoplastic cell membranes, macrophage-derived membranes, and T-lymphocyte membranes are most popular candidates,[29] each utilizing intrinsic epitopes to mediate biological processes, including immune evasion, extended circulatory persistence, pathological targeting, and immunoregulatory modulation.[30−32] Nevertheless, the native properties of single membrane subtypes are often mismatched with complex clinical requirements, with unavoidable functional shortcomings. Beyond these, additional membrane variants derived from dendritic cells, prokaryotic organisms, platelets, and monocytic cells further expand the repertoire of biointerfacial characteristics, yet they similarly fail to escape the common limitations of native membranes.[33,34]

Although native cell membranes retain partial biological functions from their source cells, their inherent structural and functional constraints pose considerable application challenges. Erythrocyte membranes rely on a CD47 protein-dependent self-identification mechanism to prolong the in vivo circulatory persistence of nanoparticles to some extent, making them candidates for sustained-release delivery systems.[35,36] However, their inherent lack of endogenous targeting machinery results in extremely low accumulation efficiency at lesion sites, which severely narrows their therapeutic application scenarios. Comparatively, cancer cell-derived membranes achieve moderate tissue-specific tropism through homologous recognition pathways, but their surface-displayed tumor-associated antigens are susceptible to adaptive immune phagocytosis, leading to premature clearance of nanoparticles before reaching target lesions, along with uncontrollable in vivo immunogenicity risks.[37−39] Macrophage membranes exhibit chemotactic properties toward inflammatory lesions and neoplastic niches via CCR2 receptor-mediated migration and phagocytic modulation, yet the native expression of Fc receptors readily triggers off-target cellular uptake. Precise regulation of Fc receptor expression is mandatory; otherwise, targeting specificity will be drastically compromised.[40−42] T-lymphocyte membranes enable site-specific recognition through TCR-CD3 complex interactions, but their intrinsic immunostimulatory potential via immune synapse formation tends to provoke systemic immune responses, requiring more sophisticated membrane engineering strategies to enhance therapeutic specificity while preserving systemic tolerance.

Alternative membrane systems also present intractable native defects that prevent direct adaptation to diverse therapeutic demands. Dendritic cell membranes bearing MHC-antigen complexes can prime adaptive immunity, but they carry a high risk of cytokine hyperactivation syndromes, raising serious concerns about immunological safety.[43] Bacterial membranes enriched in pathogen-associated molecular patterns serve as potent innate immune activators for vaccine development, yet they are associated with high endotoxin residue risks and require stringent endotoxin depletion protocols, leading to complicated preparation, high cost, and poor batch consistency. Platelet membranes enable tumor-selective adhesion through P-selectin-mediated vascular interactions, yet their intrinsic membrane rigidity substantially impedes payload encapsulation and reduces drug loading efficiency.[44−46] Monocyte-derived membranes enable targeted localization to pathological sites via the CCL2/CCR2 chemokine axis, but the substantial functional heterogeneity among monocyte subsets causes large batch-to-batch variations in membrane composition, hindering standardized preparation and quality control.[47]

The aforementioned common and type-specific limitations of native cell membranes demonstrate that screening natural membrane sources alone is insufficient to meet complex therapeutic needs. Accordingly, the core focus of contemporary research has shifted from cataloging membrane types to rational membrane design and engineering modification. On one hand, researchers are committed to developing rational membrane selection matrices that integrate targeting mechanisms,

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immunogenic profiles, and disease microenvironmental parameters to define the applicable boundaries of different membranes.[48−50] In addition, in recent years, a small number of other cell types have been applied in this field, such as osteoblasts. Osteoblast-derived membranes inherit the bone-homing property and osteogenic bioactivity of source cells and have emerged as a promising membrane material for bone defect regeneration, osteosarcoma targeted therapy, and other bone-related disease interventions.[51] However, they also face the universal challenges of native membranes and require engineering optimization to further improve performance. The diversity and limitations of these biological properties underscore both the critical importance of aligning membrane selection with specific clinical objectives and the necessity of membrane engineering. Table 1 provides a foundational framework for membrane source selection, upon which the five major engineering strategies described in the following sections can be applied to further enhance or repurpose these intrinsic functionalities for specific therapeutic needs.

3. CELL MEMBRANE ENGINEERING STRATEGIES

The essence of ECMNPs lies in the engineered functionalization of native cellular membranes. Through physical manipulation, chemical conjugation, or biological modification, these biomimetic constructs acquire augmented functionalities that surpass the characteristics of native membranes.[62−65] Established engineering methodologies encompass a variety of approaches designed to modify membrane properties while retaining their biocompatibility and structural integrity. These approaches include stimulation, genetic engineering, covalent modification, noncovalent modification, and membrane fusion (Figure 1). Each of these engineering approaches aims to achieve precise control over targeting specificity, therapeutic payload delivery, and responsiveness to the microenvironment while maintaining the intrinsic properties of the original cell membrane.[66,67]

3.1. Stimulation

In ECMNP research, controlled modulation of membrane protein expression through biochemical stimuli represents a promising strategy for enhancing nanocarrier functionality. This approach relies on the targeted activation of intracellular signaling cascades to promote biosynthesis and surface enrichment of selective transmembrane proteins. Chemical stimulation can directly modulate cellular processes through small-molecule-mediated metabolic or signaling pathway interactions, thereby inducing the expression or post-translational modification of membrane proteins.[68,69] In practical applications, TNF-α stimulation is employed to induce overexpression of lymphocyte function-associated antigen 1 (LFA-1) on the surface of neutrophils.[70] The administration of IFN-γ in combination with rapamycin has been shown to effectively upregulate the coexpression of three critical immune regulatory molecules in fibroblast-like synoviocytes: programmed cell death 1 ligand 1 (PD-L1), Galectin-9 (Gal-9) and Fas Ligand (Fasl).[71] Furthermore, retinoic acid treatment has been shown to promote α4β7 integrin overexpression in primary leukocytes.[72] Beyond chemical strategies, biological stimulation can also

Table 1. Decision for Membrane Selection Based on Therapeutic Objectives

therapeutic objective and clinical scenario	target tissue/ pathological site	desired core biofunction	recommended membrane source	core inherent advantage	critical limitations	ref
systemic circulation and sustained drug delivery (systemic chronic diseases, disseminated tumors)	blood circulation, disseminated lesions	long circulatory retention, immune evasion, sustained drug release	erythrocyte, cancer cell	CD47-mediated self-recognition, high biocompatibility, low immunogenicity	no endogenous targeting capacity; extremely low lesion enrichment efficiency	52,53
homologous tumor targeted therapy (homologous primary and metastatic tumors)	homologous tumor tissue	tumor homologous targeting, tumor antigen presentation	cancer cell, bacterial	spontaneous tumor tropism via homologous recognition	prone to immune phagocytic clearance; high batch-to-batch heterogeneity	54,55
inflammatory lesion and tumor microenvironment targeting (inflammatory diseases, tumor inflammatory microenvironment)	inflammatory lesions, tumor stroma	inflammatory chemotaxis, tissue infiltration, immune regulation	macrophage, bacterial	CCR2-mediated inflammatory targeting, strong tissue penetration	Fc receptor-induced off-target uptake; poor functional stability	56,57
precise tumor immunotherapy (solid tumors, immune dysfunction diseases)	tumor immune microenvironment	specific immune recognition, immune synapse activation	T lymphocyte, nephrocyte	precise antigen recognition via TCR-CD3 complex	risk of systemic immune overactivation; poor membrane structural stability	58
immune priming and immunotherapy (tumor immunotherapy, infectious diseases)	lymph nodes, immune activation sites	antigen presentation, adaptive immune priming	dendritic cell, monocyte	intact MHC-antigen presentation machinery	high risk of cytokine hyperactivation syndrome	47,59
vascular injury and metastatic tumor targeting (vascular injury, metastatic tumors)	damaged blood vessels, tumor neovasculature	vascular adhesion, lesion anchoring	platelet	P-selectin-mediated vascular targeting and tumor adhesion	high membrane rigidity; low payload encapsulation efficiency	60
infectious disease intervention and vaccine adjuvant (infectious diseases, prophylactic vaccines)	immune organs, systemic circulation	potent innate immune activation, vaccine adjuvant effect	bacterial, monocyte, nephrocyte	strong innate immune activation driven by pathogen-associated molecular patterns	high endotoxin contamination risk; complex purification process	47,61
bone tissue repair and bone disease targeting (bone defects, osteoporosis, osteosarcoma)	bone tissue, bone remodeling sites	bone homing, osteogenic bioactivity, bone tissue targeting	osteoblast	specific bone tissue affinity and osteogenic functional adaptability	narrow disease adaptation range; immature application system	51

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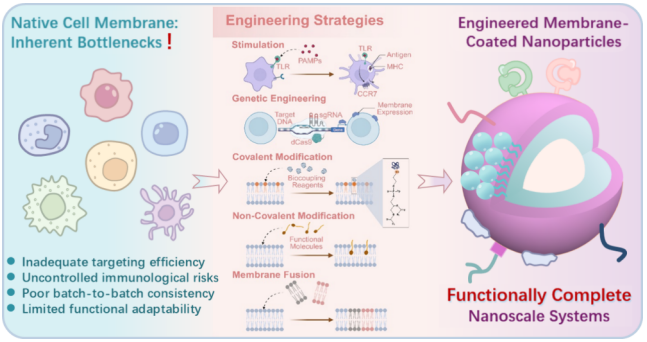


Figure 1. Engineering strategies for cell membranes. Stimulation, genetic engineering, covalent modification, noncovalent modification, and membrane fusion represent five widely adopted engineering strategies for functionalizing nanoparticle surfaces with biological membranes. These approaches enable precise modulation of key physicochemical properties, thereby addressing critical limitations associated with straightforward coatings and significantly improving the therapeutic performance of biomimetic nanoparticle systems.

modulate membrane protein expression through the application of native biological mediators.[73] For instance, exposure to *Staphylococcus aureus* significantly increases the expression levels of TLR2 and TLR4 on macrophage membranes during cocultivation. This enhanced receptor expression contributes to improved bacterial targeting when nanoparticles are coated with membranes from these preconditioned macrophages.[74] Stimulation with IL-4 promotes the polarization of M0 macrophages toward the M2 phenotype. During this polarization process, key surface membrane markers such as CD206 and CD163 are significantly upregulated, which is associated with the acquisition of M2-type functional characteristics.[75] Similarly, RAW264.7 cells can be induced to differentiate into M1-type macrophages through treatment with lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), thereby enabling their membranes to acquire tumor-targeting capabilities.[76]

3.2. Genetic Engineering

Genetic engineering serves as a pivotal technology for reconfiguring organismal functions through precise genome editing, enabling the rational design of engineered cellular membranes.[77,78] When native physiological capacities fail to meet demands, this approach demonstrates particular promise for ECMNPs.[79−81] Its core lies in the strategic modulation of membrane-associated genes *via* overexpression, knockout, or site-directed editing, thereby precisely controlling transmembrane protein composition and receptor density. By enabling surface display of functional molecules while avoiding compromising its integrity or cell viability, these modifications have achieved notable progress in multiple domains including precision targeting enhancement and immune-modulatory function regulation.[82,83]

Current engineering of ECMNPs primarily relies on self-replicating plasmid vectors combined with low-toxicity viral delivery systems, such as lentiviruses, for efficient gene transfection. To achieve targeted genetic modifications, CRISPR-Cas9, transcription activator-like effector nucleases (TALENs), and zinc finger nucleases (ZFN) constitute the primary genome-editing toolkit. Among these, CRISPR-Cas9 has become the predominant choice due to its operational efficiency, editing precision, and cost-effectiveness. In contrast, while TALEN and ZFN systems demonstrate comparable specificity advantageous for specialized applications, their practical implementation faces constraints associated with intricate design requirements and elevated operational costs. By selecting appropriate target genes for transfection, the targeting capabilities of ECMNPs can be enhanced through molecular customization. For instance, incorporation of the rabies virus glycoprotein-derived rabies virus glycoprotein (RVG) peptide confers blood-brain barrier (BBB) penetration and neural targeting properties to ECMNPs.[84] Genetically introducing integrin α4 into mouse leukemia cells (which already express high levels of β1 integrin) allows formation of functional very late antigen-4 (VLA-4) heterodimers. These heterodimers bind to vascular cell adhesion molecule-1 (VCAM-1), enabling inflammation-specific homing.[85] Furthermore, implementation of glypican-3 (GPC3)-targeting chimeric antigen receptor (CAR) systems demonstrates precise cancer-targeting. Through T-cell membrane modification with GPC3-specific single-chain antibodies, the resulting CAR-T membrane-functionalized ECMNPs exhibit selective recognition of hepatocellular carcinoma cells expressing this oncofetal antigen, while substantially reducing off-target interactions with healthy hepatic tissue.[86] Zhang et al. genetically engineered Expi293 cells (a human embryonic kidney cell line) to express CARs targeting both T-cell CD3 and breast cancer HER2 epitopes, with subsequent membrane isolation enabling nanoparticle coating for targeted activation of cytotoxic T lymphocytes against HER2-expressing malignancies.[87] Recent studies have demonstrated that the stable integration of high-affinity SIRPα variants (CV1) into tumor cells using lentiviral vectors can effectively disrupt endogenous SIRPα-CD47 interactions, thereby attenuating the phagocytosis-inhibitory "don't eat me" signaling and enhancing macrophage-mediated tumor clearance.[88,89]

3.3. Covalent Modification

Covalent modification of cell membranes has emerged as an important strategy for engineering precise functionalities in synthetic cellular systems, primarily through the stable anchoring of exogenous functional molecules. Owing to the inherently high bond energy of covalent interactions, these modifications exhibit exceptional resistance to molecular detachment, thereby conferring enhanced stability and controllable functionality to the resulting composite systems.[90] Recent progress has yielded a panel of highly efficient chemical reactions to implement covalent membrane modification under mild physiological conditions. Amide-bond formation represents one of the most widely adopted approaches to link amino and carboxyl moieties, compatible with mild carbon diazide-based catalysis.[91] In this approach, nucleophilic substitution between carboxyl/iminodiacetate groups on exogenous molecules and membrane-surface amino groups facilitates stable amide conjugation.[92] Complementing this, click chemistry, known for its efficiency, specificity, and bio-orthogonality, enables spatiotemporally controlled coupling under physiological conditions. For instance, azide-modified membranes can conjugate with the target functional groups *via* copper-free azide-alkyne cycloaddition, a process that preserves native protein conformation and activity

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through its mild reaction parameters (physiological pH/temperature).[93,94] Meanwhile, sulfhydryl-directed strategies exploit native or engineered -SH groups on platelet membranes. Using a maleimide-PEG-NHS (maleimide-polyethylene glycol-*N*-hydroxysuccinimide) heterobifunctional linker, thioether bonds form with membrane -SH groups while NHS esters simultaneously couple to recombinant tissue plasminogen activator (rt-PA) *via* amide linkages. Notably, this covalent conjugation minimizes premature drug dissociation during circulation, retaining > 90% activity even after 18-day lyophilized storage.[60] Beyond static linkages, dynamic covalent chemistry expands design possibilities. Borate ester bonds are formed through interactions between phenylboronic acid and diols present in yeast surface polysaccharides, such as β-glucan and chitin. In contrast, reversible disulfide bonds are established *via* thiol-disulfide exchange reactions occurring between liposomes and T cell membranes.[95] Importantly, these redox-responsive linkages enable intracellular glutathione-triggered dissociation, serving as a representative example of environmentally adaptive design strategies.[96]

Collectively, these covalent strategies provide a hierarchical toolkit for engineering membrane-coated nanosystems. Through synergistic integration, they may advance precision biomedicine applications ranging from targeted delivery to bioimaging.

3.4. Noncovalent Modification

Noncovalent modification also serves as a fundamental strategy in cell membrane engineering, achieved through physical adsorption or intermolecular interactions that integrate exogenous functional molecules.[97,98] Among all engineering strategies, noncovalent binding has gained particular interest as it optimally preserves both native membrane protein activity and the structural dynamicity of the lipid bilayer, both of which are essential for maintaining biological function.[99,100] Nevertheless, various noncovalent modification approaches exhibit distinct trade-offs among binding affinity, modification specificity, and physiological stability, which largely determine their practical application feasibility, operational durability, and targeting accuracy in complex physiological microenvironments. A comprehensive parametric comparison and critical discussion of different noncovalent strategies is essential for rational strategy selection and performance optimization.

Typical noncovalent membrane modification strategies primarily encompass electrostatic adsorption, specific recognition via receptor-ligand or antigen-antibody interactions, and hydrophobic lipid anchoring. Each approach exhibits distinct kinetic characteristics and application limitations, particularly regarding quantifiable surface retention half-life, environmental tolerance, and targeting specificity. First, electrostatic adsorption relies on charge complementarity between cationic exogenous molecules and the anionic phospholipid outer layer of cell membranes, enabling rapid, reversible, and facile molecule anchoring.[101−103] Typically, cationic molecules bind *via* electrostatic interactions to the anionic cell surface, though this strategy is highly susceptible to fluctuations of ionic strength and pH in physiological fluids, resulting in frequent ligand dissociation and short surface retention time. In contrast, receptor-ligand and antigen-antibody systems leverage molecular recognition for targeted modifications, providing enhanced specificity.[104−106] Benefiting from highly matched molecular steric conformation, biomolecular recognition effectively avoids nonspecific binding, realizing precise anchoring of functional molecules on target cell membranes. However, this specific binding strategy faces prominent trade-offs between specificity and physiological stability as well as binding affinity variability. While weak, reversible noncovalent recognition favors biosafety, it only delivers moderate binding affinity. Affinity varies markedly with ligand bioactivity, receptor abundance, and local microenvironments, which yields unstable modification performance inside complex biological milieus. In addition, such transient molecular interactions shorten surface-retention half-lives; dynamic ligand shedding further triggers off-target effects and compromises in-vivo durability. Moreover, the limited biocompatibility and batch-to-batch variability of natural ligands further hinder the large-scale, standardized application of this specific modification strategy. Among alternative methods, hydrophobic insertion strategies demonstrate particular promise: amphiphilic functional molecules can spontaneously insert their hydrophobic alkyl or lipid moieties into the hydrophobic core of phospholipid bilayers, while exposing hydrophilic functional groups outside the cell membrane, achieving stable and long-term membrane integration without disrupting the intrinsic fluidity and protein activity of cell membranes.[107−109] Compared with electrostatic adsorption and biomolecular recognition, hydrophobic anchoring exhibits significantly enhanced binding stability and longer surface retention time. For instance, streptavidin embeds effectively into erythrocyte membranes via hydrophobic domain-lipid layer interactions, establishing platforms for subsequent functionalization.[110] Similarly, distearoyl phosphatidylethanolamine (DSPE) spontaneously integrates into exosome membranes through hydrophobic interactions between its dual alkyl chains and the lipid bilayer, thereby facilitating the covalent attachment of functional proteins.

In recent years, lipid anchoring functionalization strategies have achieved innovative progress in structural optimization and performance improvement. Emerging studies have developed multi-chain lipid anchors, galloylated lipid modified modules, and amphiphilic polymer-lipid conjugates, which further enhance the hydrophobic intercalation strength and anti-interference ability in complex environments. Different from traditional single-chain lipid anchoring, dual-chain and multi-chain lipid molecules can form synergistic hydrophobic interactions with lipid bilayers, effectively resisting the interference of ionic fluctuation and protein adsorption in body fluids, realizing long-term stable modification of cell membranes.[111,112] Galloylated lipid-modified modules represent an advanced dual-function anchoring strategy. The hydrophobic alkyl tail of galloylated-lipid inserts into the phospholipid bilayer for stable membrane integration, while the exposed galloyl head-group provides additional noncovalent binding sites via hydrogen-bonding, hydrophobic and electrostatic interactions for secondary anchoring of functional ligands.[113] As a widely used family of lipid-insertion materials, amphiphilic polymer-lipid conjugates are typically constructed from one or more hydrophobic lipid tails covalently linked to hydrophilic polymer segments. These molecules can spontaneously insert their lipid moieties into phospholipid bilayers for noncovalent cell-surface anchoring. Their membrane retention stability is strongly governed by

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molecular architecture: longer alkyl lipid tails markedly slow ligand dissociation from cell membranes, whereas extended hydrophilic polymer chains tend to accelerate shedding.[114] However, this strategy still has inherent trade-offs: the improvement of binding stability will slightly reduce the dynamic adjustability of membrane surface molecules, and excessive hydrophobic modification may affect the lateral diffusion of partial membrane lipids. Therefore, rational design of lipid anchor hydrophobicity and molecular density is critical to balance modification stability, membrane dynamic activity, and biological safety.

3.5. Membrane Fusion

Cell membrane fusion technology addresses functional constraints of single biological interfaces by strategically integrating diverse membrane components.[115,116] This approach preserves native functionalities inherited from donor cells, including targeted recognition and immune evasion, while conferring novel synergistic capabilities.[117] Multimembrane systems critically surpass single-membrane architectures in some biomedical applications, demonstrating enhanced programmability for tasks such as multilevel drug delivery and adaptive immune modulation.[75,118] Fusion strategies typically combine membranes from distinct species or cell types, exemplified by immune-tumor cell hybrids or erythrocyte-tumor composites, through physical engineering methods.[119] Commonly employed techniques involve controlled sonication to compromise membrane integrity, iterative extrusion through nanoporous membranes, or combined protocols integrating both methodologies. These processes promote reorganization of the phospholipid bilayer, leading to the formation of stable fused membrane structures. When native protein compositions prove insufficient, modular supplementation with additional membrane proteins (typically requiring two or more distinct types) enables functional customization.[120,121] For instance, nanoparticles cloaked with hybrid membranes incorporating cancer cells and DC have shown efficacy in suppressing tumor recurrence and metastatic dissemination.[59]

3.6. Cross-Comparison of Engineering Strategies

Each of the five membrane engineering strategies presents distinct advantages and inherent performance trade-offs, and rational selection should be tailored to specific disease-related therapeutic goals. Their cross-comparison is detailed in Table 2. Stimulation is the simplest and fastest method, suitable for acute-inflammation targeting and short-term immune-modulation therapy, but it yields only transient membrane remodeling and is subject to significant donor-to-donor variability, which limits its use for chronic repeated treatments. Genetic engineering enables precise and stable receptor expression, making it the preferred approach for intractable-disease scenarios such as BBB penetration and checkpoint regulation; however, its dependence on viral vectors and prolonged cell culture limits its utility in rapid prototyping. Covalent modification provides highly stable surface functionalization resistant to vascular shear stress, ideal for vascular-targeted and stimuli-triggered therapy, yet chemical reactions may inadvertently denature membrane proteins. Noncovalent modification is the mildest approach and best preserves native membrane functions for immune-evasion applications, yet its reversible nature raises concerns about ligand dissociation in serum-rich environments. Membrane fusion uniquely integrates multiple membrane types to achieve synergistic therapeutic functions, but the poorly controlled process results in inconsistent product quality and low yield. No single strategy is universally optimal; researchers must balance modification stability, bioactivity retention and fabrication complexity to select the appropriate workflow for a given disease model.

4. FUNCTIONS OF ECMNPS

Conventional synthetic nanocarriers are inherently restricted by poor immune compatibility and insufficient pathological targeting. In contrast, ECMNPs achieve functional reconstruction and performance breakthroughs through artificial membrane remodeling. By rationally introducing exogenous functional motifs, optimizing endogenous protein expression, or constructing hybrid membrane architectures, membrane engineering endows nanoparticles with multiple newly acquired or significantly enhanced capabilities. Such artificially upgraded biointerfacial properties fundamentally break through the functional bottlenecks of both traditional nanocarriers and primitive membrane-camouflaged nanoparticles.[122]

4.1. Achieve Anisotropic Targeting

Native cell membranes only possess passive, low-precision recognition ability relying on inherent surface adhesion molecules, which cannot actively adapt to complex pathological microenvironments or achieve customizable disease targeting. Membrane

Table 2. Cross-Comparison of Five Cell Membrane Engineering Strategies

engineering strategy	core principle	advantages	disadvantages	difficulty	suitable scenarios
stimulation	biochemical or biologically triggered increases in membrane protein levels	mild, preserves native structure; easy to operate; low cost	low controllability; protein expression varies; weak targeting enhancement	low	inflammation targeting; immune modulation
genetic engineering	plasmid/virus transfection/CRISPR editing and other technologies to achieve regulation of protein expression	high precision; strong targeting; stable; customizable	time-consuming; biosafety concerns; hard to scale	high	BBB penetration; CAR-T targeting; checkpoint regulation
covalent modification	amide/click chemistry/disulfide bond covalent linkage	ultra-stable; high ligand density; stimuli-responsive possible; high stability	may denature membrane proteins; reaction conditions critical	high	targeted delivery; stimuli-triggered release
noncovalent modification	electrostatic/hydrophobic/antigen-antibody binding	best biocompatibility; no protein damage; fast	easy to dissociate in vivo; low stability	low	immune evasion; quick surface functionalization
membrane fusion	combining two or more different membranes via ultrasound/extrusion methods	combines multiple functions; overcomes single-membrane limits	complex preparation; poor batch consistency; hard to standardize	medium	homotypic targeting; long circulation; immune activation

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engineering strategies, including biochemical stimulation, metabolic modification, and genetic editing, actively reshape the surface molecular fingerprint of cell membranes, thereby significantly improving targeting accuracy and expanding the spectrum of treatable diseases (Figure 2).[58,123−125]

Compared with the passive homing of primitive membrane nanoparticles, artificially engineered functional moieties enable active and controllable pathological recognition. For instance, metabolic glycoengineering can introduce bioorthogonal reactive groups on T-cell membrane surfaces, enabling precise covalent anchoring of nanoparticles on tumor cell membranes through click chemistry and achieving tumor-specific spatial targeting that cannot be realized by natural membrane proteins.[126] Biochemical stimulation further optimizes membrane targeting phenotypes: Endothelin-1 stimulation upregulates integrin α4β1 expression, facilitating VCAM-1 binding at atherosclerotic endothelial sites.[127] The inherent chemotactic properties of macrophage membranes are preserved in the membrane fusion system, enabling the targeted delivery of therapeutic payloads into plaques through leukocyte-like migration.[128] Similarly, peptide-modified erythrocyte membranes acquire artificial tumor vascular targeting capability via c(RGDyK) functionalization, enabling selective endothelial inhibition and tumor nutrient deprivation therapy.[110]

Genetic engineering further achieves stable and long-term targeting optimization. By integrating neuronal-targeting RVG29 with mitochondria-directing triphenylphosphonium (TPP) on membrane surfaces, dual-organelle targeting can be achieved for spatially controlled drug delivery.[129] Through genetic modification of progenitor cells, artificially overexpressed VLA-4 integrin endows membrane nanoparticles with specific inflammatory pulmonary endothelium targeting, improving local anti-inflammatory drug accumulation while reducing systemic renal toxicity.[87] In addition, genetically engineered umbilical vein endothelial cell membranes simultaneously acquire tumor macrophage targeting and inflammatory cytokine neutralization functions, realizing dual therapeutic effects that are unavailable in native membrane systems.[130]

Overall, different membrane engineering methods enable precise customization of targeting motifs. Such artificially upgraded active targeting mechanisms effectively overcome the low specificity and single-function limitations of natural membrane homing, providing versatile design principles for precise disease intervention.[131]

4.2. Enable Immune Evasion

Traditional synthetic nanoparticles, which are widely utilized in biomedical applications such as drug delivery and diagnostic imaging,[132] often encounter a major obstacle during systemic circulation: they are readily identified and subsequently removed by the body's immune defenses.[133−135] However, natural cell membranes yield genetically hard-wired protein profiles, which offer only limited, nontunable antiphagocytic capacity. Membrane-engineering workflows overcome this constraint by artificially upregulating or re-engineering

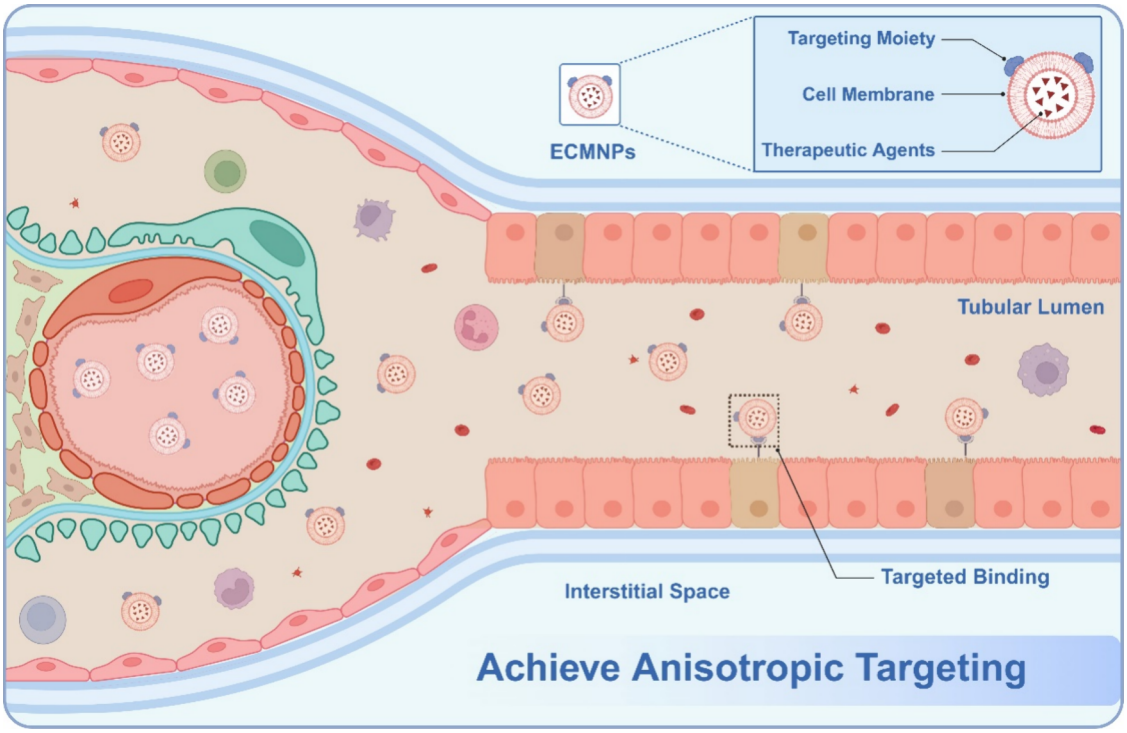


Figure 2. ECMNPs with anisotropic targeting capability. ECMNPs exhibiting anisotropic targeting capabilities are typically developed using a biomimetic engineering strategy. In this approach, a therapeutic agent such as a chemotherapeutic drug, nucleic acid, or bioactive molecule forms the core of the nanoparticle structure. This core is then enveloped by an engineered biologically derived cell membrane isolated from specific cell sources, including red blood cells, platelets, or immune cells, which naturally possess biocompatibility and functional surface proteins. To achieve targeted delivery, the outer surface of the ECMNPs is engineered with targeting moieties such as peptides, polysaccharose, or ligands that are designed to recognize and bind to specific biomarkers. These biomarkers often include overexpressed receptors, adhesion molecules, or altered glycoproteins that appear on the surface of diseased cells during the progression of pathological states, including inflammation, infection, or cancer.

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self-recognition moieties to achieve programmable, boosted immune evasion. (Figure 3).[136−138]

Membrane component optimization represents a facile engineering approach to improve circulation performance. Hybrid membrane engineering verifies that erythrocyte membrane proportion positively correlates with in vivo retention time; full erythrocyte membrane engineering achieves the longest circulation half-life (8.1 h). These values were significantly higher than those observed for unmodified nanoparticles (2.6 h) and cancer CMNPs (4.4 h).[52] The observed trend was further supported by quantitative biodistribution data, which demonstrated increased blood retention levels—rising from 8.7% ID/g in cancer CMNPs to 14.2 and 18.6% ID/g in the hybrid and erythrocyte-exclusive formulations, respectively. More importantly, genetic engineering achieves quantitative enhancement of immune evasion capability. Artificial overexpression of CD47 on macrophage membranes strengthens the binding affinity with SIRPα, continuously activates "don't eat me" signaling, and effectively inhibits phagocytic clearance. This engineered immune modification strategy significantly prolongs systemic circulation time and improves lesion accumulation, exhibiting unique advantages for chronic inflammatory disease treatment.[56] In short, immune evasion based on native membrane proteins is passive and limited, while membrane engineering realizes active performance enhancement, effectively resolving the insufficient circulation stability of traditional biomimetic nanoparticles.

4.3. Achieve Stimuli-Responsive Release

Traditional nanocarriers and primitive membrane-camouflaged nanoparticles lack precise spatiotemporal drug release capability, often causing premature drug leakage and systemic side effects.[10,139,140] Natural cell membranes do not possess pathological microenvironment responsiveness. Membrane engineering endows nanoparticles with artificially constructed multistimuli responsive characteristics, realizing on-demand controlled release triggered by tumor acidity, intracellular redox environment, or exogenous physical stimulation (Figure 4).[141,142]

Through artificial modification of membrane physicochemical properties, engineered membranes can achieve microenvironment-adaptive drug release. Acid-sensitive membrane engineering enables rapid payload dissociation in the acidic tumor microenvironment (pH 6.5), while maintaining stable encapsulation under normal physiological pH, which effectively improves tumor-selective drug activation compared with unmodified membrane nanoparticles.[110,119,143] Redox-responsive release is another artificially introduced functional characteristic. By constructing disulfide-bond-modified membrane structures, engineered nanoparticles can respond to high intracellular GSH levels in tumor tissues, triggering carrier degradation and controlled drug release.[144,145] Furthermore, exogenous responsive function can be artificially implanted via membrane engineering. Tumor cell membranes loaded with

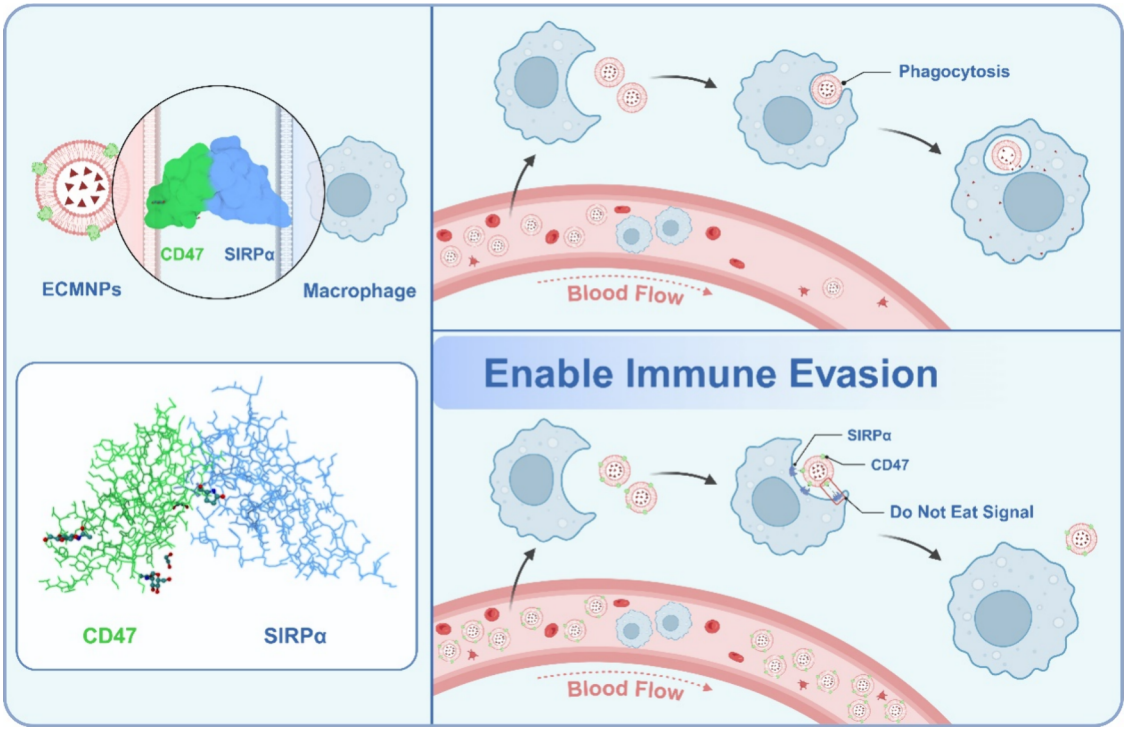


Figure 3. ECMNPs with immune evasion capability. CD47 has been identified on the cell membrane surface as a critical self-recognition marker that inhibits phagocytic activity through its interaction with the SIRP-α receptor. As a transmembrane glycoprotein, CD47 plays an essential role in preserving immune tolerance by transmitting a "do not eat me" signal to phagocytic cells, particularly macrophages, which are key mediators of innate immune responses. This signaling mechanism is crucial for preventing the inappropriate destruction of healthy cells and maintaining tissue homeostasis. The overexpression of CD47 on the surface of ECMNPs can trigger a downstream signaling cascade that effectively suppresses phagocytic engagement. This functional mimicry of natural cell surface markers allows ECMNPs to evade premature recognition and clearance by the MPS, thereby significantly extending nanoparticle circulation time in the bloodstream and improving their capacity to accumulate at targeted pathological sites.

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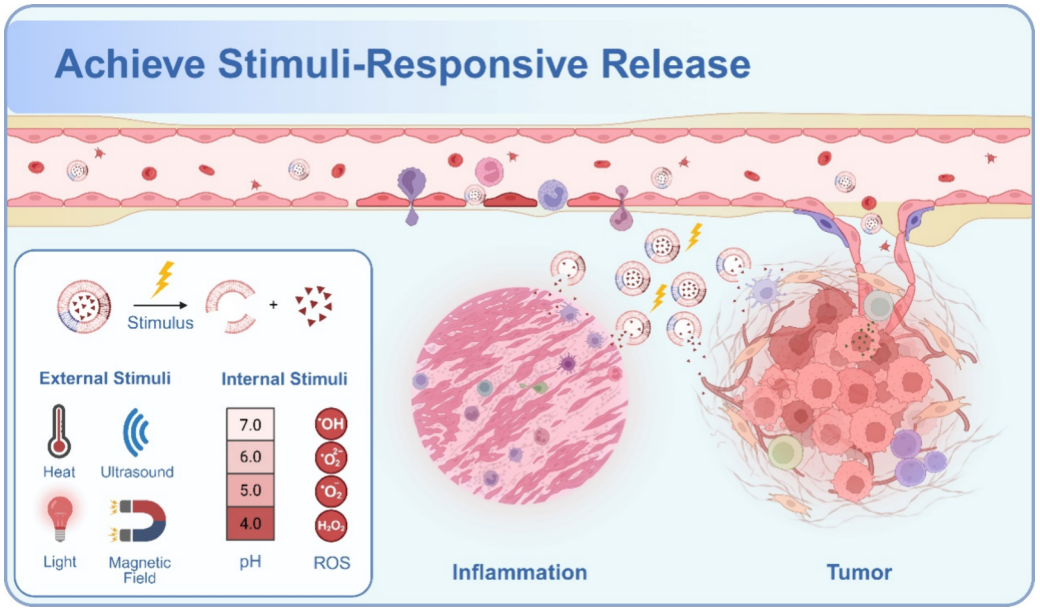


Figure 4. ECMNPs with stimuli-responsive release capability. The wide range of stimuli that can be utilized to control the spatiotemporal aspects of drug delivery and release, combined with the diversity of responsive materials available, enables significant flexibility in the design of stimuli-responsive ECMNPs. These nanoparticles can be tailored to respond to specific environmental cues, allowing for precise control over when and where the therapeutic payload is released. This level of control is particularly valuable in targeted therapies, such as those used in cancer treatment or inflammatory disease management, where minimizing off-target effects is crucial. Internal stimuli that influence the behavior of ECMNPs include physiological changes within the local microenvironment, such as fluctuations in pH levels and the presence of reactive oxygen species associated with oxidative stress. In addition to internal cues, external stimuli also play a key role in modulating the function of stimuli-responsive ECMNPs. These include physical triggers such as heat, ultrasound, light, and magnetic fields. Unlike internal stimuli, external triggers can be applied from outside the body, offering clinicians direct control over the activation of drug release.

ICG realize laser-triggered photothermal therapy, achieving spatiotemporally precise tumor ablation without damaging normal tissues.[146] In summary, stimuli-responsive release is a newly acquired function entirely derived from membrane engineering, which effectively compensates for the nonresponsive defect of natural membrane carriers and greatly improves therapeutic safety and precision.

4.4. Promote Intracellular Trafficking

Primitive membrane-coated nanoparticles can achieve cellular internalization relying on natural membrane fusion, but they lack active subcellular regulation ability and are easily trapped in lysosomes, resulting in low therapeutic utilization.[147,148] Engineering the membrane coatings of nanoparticles has been shown to markedly enhance cellular internalization by selectively activating these endocytic signaling cascades.[149] Moreover, the synergistic interplay between engineered membrane components and the nanoparticle core enables the modulation of intracellular trafficking pathways, directing therapeutic payloads to specific subcellular compartments such as the nucleus or mitochondria (Figure 5).[150]

Native membrane-mediated cell uptake is random and uncontrollable. In contrast, artificially functionalized membrane ligands can actively initiate receptor-mediated endocytosis. For example, cyclic RGD-engineered cancer cell membranes significantly enhance tumor cell recognition and membrane fusion. The engineered pH-responsive core further achieves lysosomal escape under ultrasound assistance, realizing efficient cytoplasmic release of mRNA drugs.[151] In a separate investigation, researchers functionalized erythrocytic membranes with the c(RGDyK) peptide to confer nanoparticles with the ability to enhance transcellular transport and deep tumor penetration.[110] This ligand-receptor interaction activates receptor-mediated endocytosis, thereby significantly enhancing both the transcellular transport and intracellular accumulation of the drug delivery system in tumor cells as well as endothelial cells lining tumor-associated vasculature. Moreover, dual-targeting membrane engineering based on c-Met peptide modification combines native tumor tropism with artificially enhanced receptor uptake, achieving nuclear drug accumulation that cannot be realized by natural membranes.[152]

4.5. Modulate Immune Activation

Natural cell membranes only possess weak, passive immune regulatory effects determined by inherent cell phenotypes, lacking adjustable and controllable immune intervention capability. Membrane engineering can artificially edit immune-related membrane proteins, enabling programmable activation or blockade of immune signaling pathways, which realizes active immunomodulatory therapy beyond native membrane functions.[125,153,154] Of particular translational significance is the capacity to orthogonally regulate immune checkpoint interactions *via* precision engineering of antigen-presenting complexes and cytokine receptor clusters, demonstrating therapeutic potential in immunomodulation contexts spanning neoplastic and inflammatory pathologies (Figure 6).

Native tumor cell membranes cannot initiate effective antitumor immune responses, while engineered hybrid tumor-erythrocyte membranes actively reshape the tumor immune microenvironment, upregulating cytotoxic T cells and inhibiting

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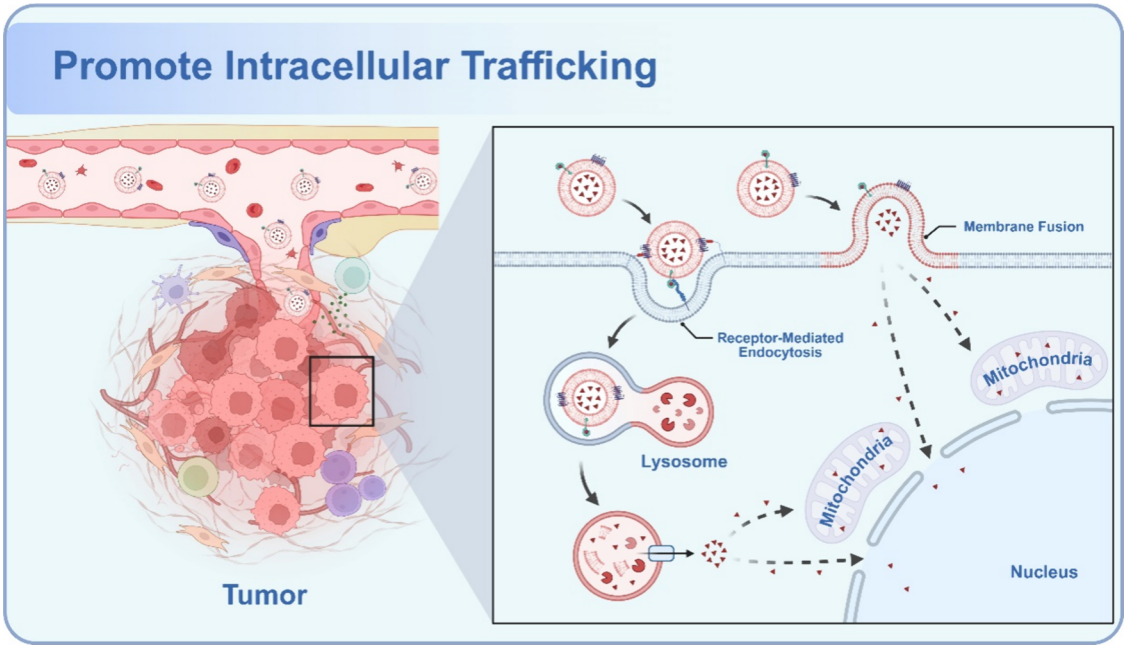


Figure 5. ECMNPs with intracellular trafficking capability. Engineering the membrane coatings of nanoparticles can markedly enhance cellular internalization by selectively activating specific endocytic signaling cascades. This enhancement is primarily attributed to receptor-mediated endocytosis, a highly regulated cellular process that enables cells to internalize extracellular materials through the binding of specific ligands on the ECMNPs surface to corresponding cell membrane receptors. Moreover, the biomimetic nature of ECMNPs allows their membrane to not only engage in receptor-mediated uptake but also to physically fuse with the plasma membrane of target cells. This fusion mechanism provides an alternative and highly efficient pathway for intracellular delivery, bypassing conventional endosomal trafficking and thereby reducing the risk of lysosomal degradation. As a result, the therapeutic cargo carried by ECMNPs can be more effectively delivered to specific subcellular compartments, such as the nucleus or mitochondria.

regulatory T cells to suppress primary and metastatic tumors.[53] The introduction of exogenous co-stimulatory molecules (CD80/CD86) via genetic engineering provides artificial secondary immune activation signals, breaking tumor immune tolerance and achieving full T-cell activation.[59] Besides, it is also reported that ECMNP can be designed to incorporate bacteria, utilizing immune molecules present in bacterial outer membrane vesicles to activate immature dendritic cells and initiate a subsequent immune response.[54] Moreover, artificially modified SIRPα variant membrane proteins can actively block the CD47-SIRPα immune checkpoint, restoring macrophage phagocytic function and triggering robust antitumor immune responses, which cannot be achieved by unmodified cell membranes.[55] Different from the passive immune regulation of natural membranes, engineered membrane modification endows nanoparticles with initiative and programmable immunotherapeutic functions, greatly expanding the application potential of biomimetic nanomedicine in tumor and inflammatory immunotherapy.

4.6. Cross Body Barriers

Natural cell membranes lack specific barrier-penetrating motifs and cannot cross dense physiological barriers such as the BBB, severely limiting the delivery of nanomedicines to central nervous system diseases.[155] These barriers are composed of tightly connected cells that form complex junctional structures, which prevent the unrestricted passage of molecules, pathogens, and toxins.[156−158] Membrane engineering can artificially implant barrier-targeting and transcytosis functional motifs, enabling ECMNPs to break through the transport limitations of natural biomimetic nanoparticles.[159−161] ECMNPs provide an innovative strategy that integrates the biomimetic interfacial properties of natural cell membranes with the precisely engineered functionalities of synthetic nanocarriers to cross these biological barriers (Figure 7).

Native macrophage and erythrocyte membranes cannot cross the BBB, while RVG peptide engineering enables specific binding to central nervous system acetylcholine receptors, mediating efficient transcytosis and brain accumulation.[129,162] Their experimental results indicated that RVG-modified nanoparticles achieved significant drug accumulation in the brain within one-hour post-injection, whereas nanoparticles without RVG modification showed no such effect. Combined with TPP mitochondrial targeting modification, the dual-engineered membrane platform further achieves subcellular mitochondrial delivery in neuronal tissue, providing a new strategy for neurodegenerative disease treatment. Similarly, RVG-modified exosome membranes and RGD-engineered glioblastoma cell membranes both obtain artificial BBB penetration capabilities, enabling targeted therapy for brain tumors and neurological diseases that are inaccessible for unmodified nanoparticles.[151,163] In summary, physiological barrier penetration is an exclusive artificially engineered function. Membrane engineering successfully overcomes the tissue delivery limitation of natural biomimetic carriers, realizing precise deep-tissue drug delivery.

Collectively, primitive cell membrane coatings only provide passive and inherent biomimetic properties, while various membrane engineering strategies actively upgrade nanoparticle biointerfacial performance. By endowing novel targeting, responsive, intracellular regulatory, immunomodulatory and

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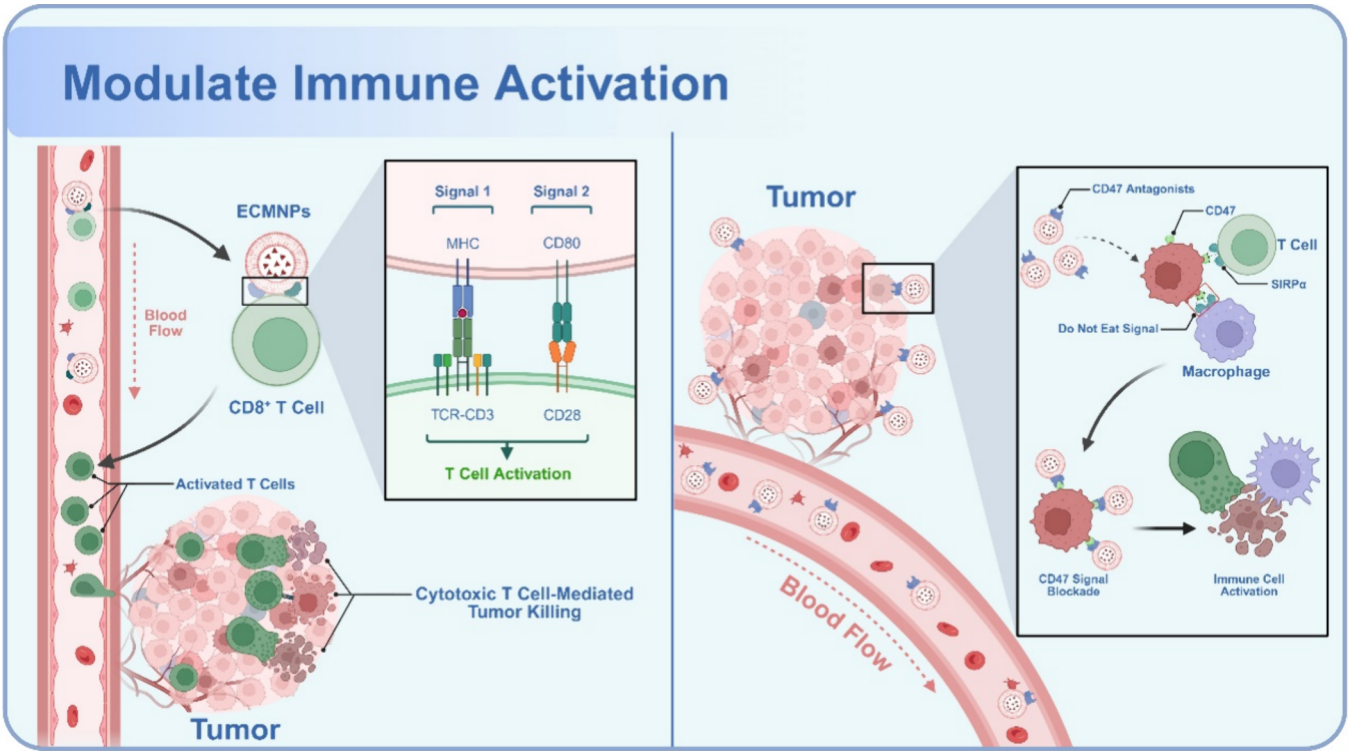


Figure 6. ECMNPs with immune activation capability. CD47 overexpression is a prevalent phenomenon in both solid and hematologic malignancies, including acute leukemia, non-Hodgkin's lymphoma, colorectal cancer, and ovarian cancer. Elevated expression levels of CD47 have been strongly correlated with aggressive tumor phenotypes, such as enhanced invasiveness and reduced therapeutic responsiveness. CD47 serves as a critical immune checkpoint molecule by acting as a "don't eat me" signal, which enables tumor cells to evade phagocytosis by immune effector cells, particularly macrophages. Therapeutic blockade of this signaling pathway has been shown to restore macrophage-mediated immune surveillance and improve tumor cell clearance. Preclinical studies demonstrate that inhibition of CD47 signaling through the application of ECMNPs significantly enhances macrophage phagocytic activity, leading to reduced tumor growth and decreased metastatic potential.

barrier-crossing functions, engineered modification realizes performance optimization that cannot be achieved by natural cell membranes. Such mechanism-driven functional upgrades constitute the core innovative superiority of ECMNPs, providing systematic design guidelines for the development of next-generation high-performance biomimetic nanotherapeutics (Table 3).

5. CHALLENGES AND FUTURE PERSPECTIVES

ECMNPs represent a significant advancement in bionic nanotechnology, presenting a strategic approach to mitigate the delivery constraints of conventional nanomedicine by synergistically integrating natural membrane biofunctions with the design versatility of synthetic nanomaterials. From a technical perspective, the systematic incorporation of stimuli-responsive systems, genetic reprogramming modalities, and covalent or noncovalent surface engineering facilitates the precise spatial organization of molecular motifs on nanoparticle interfaces. This methodological refinement advances beyond the inherent stochasticity associated with traditional membrane coating techniques, thereby establishing a robust molecular framework for developing functionalized carriers with tailored biointerfacial properties. Functionally, ECMNPs exhibit distinct synergistic merits: geometrically optimized ligand presentation improves pathological recognition fidelity, adaptable biomimetic architectures facilitate dynamic navigation across physiological barriers, and atomically tuned surface energetics help balance circulatory persistence with cellular internalization efficiency.

Notwithstanding the considerable progress achieved in ECMNP development, their clinical translation remains impeded by multifaceted challenges spanning biological, engineering, and translational domains. Biologically, surface-engineered cell-membrane carriers introduce several unique biological risks absent in unmodified membrane-coated nanoparticles. Current engineering strategies largely rely on membrane materials derived from a limited repertoire of cell lineages—such as cancer cells, macrophages, erythrocytes, and platelets. After artificial functionalization, engineered membranes may acquire unexpected immunogenic profiles: ligands, recombinant receptors or chemical tags introduced via genetic, covalent or metabolic modification can generate neoepitopes, triggering adaptive immune clearance after repeated intravenous administration. Meanwhile, donor-cell clonal heterogeneity produces variable baseline membrane-protein expression; post-modification inconsistency is further amplified across batches, making it difficult to reproduce targeted-binding performance. In addition, oncogenic- or bacterial-derived starting membranes still carry intrinsic safety hazards, as residual pathogenic components may provoke adverse immune responses, even after surface engineering. Although detergent-free extraction and microfluidic-purification techniques can mitigate protein denaturation risks during membrane isolation, these isolation

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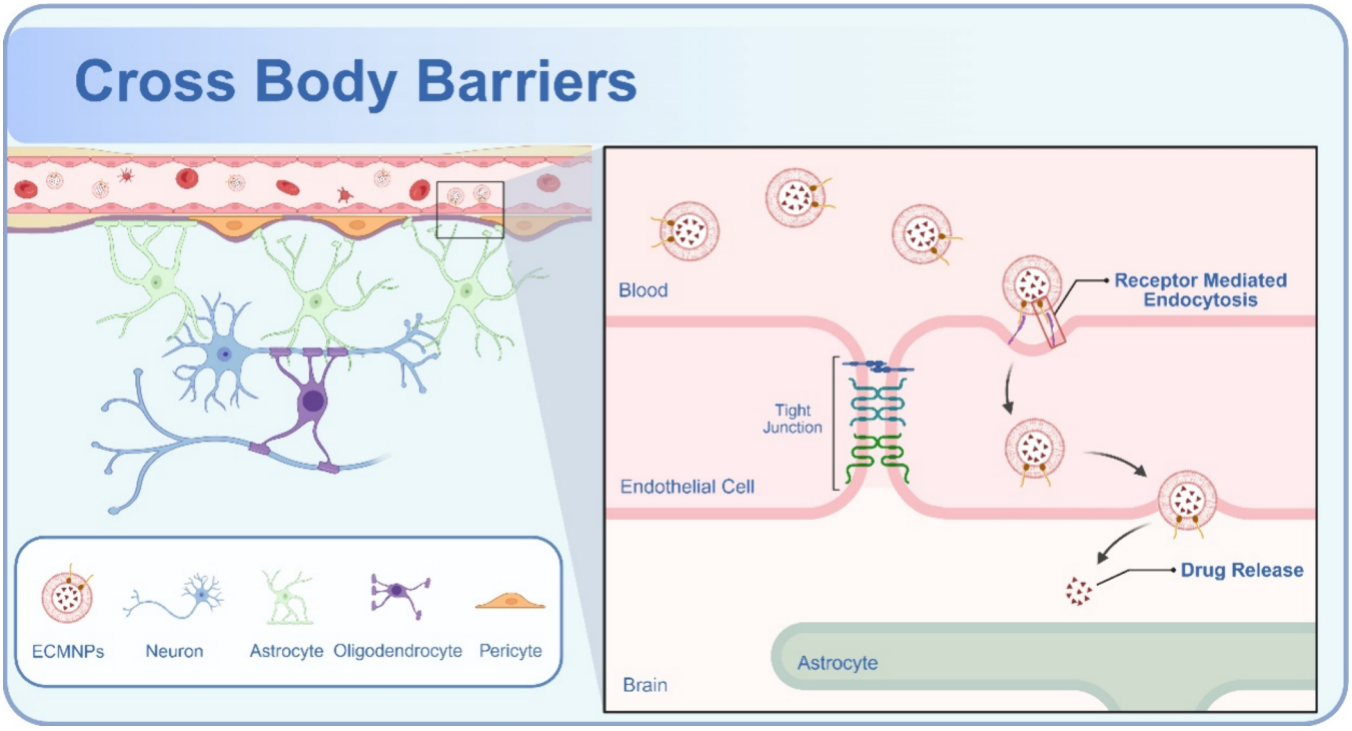


Figure 7. ECMNPs with body barriers crossing capability. The natural presence of various physiological barriers is indispensable for the functional efficiency and structural integrity of multiple organs within the body. These barriers function as highly selective interfaces that govern the transport of substances between distinct physiological compartments. While they are critical for maintaining internal homeostasis and safeguarding sensitive tissues from potentially harmful substances, they also represent a major obstacle in the effective delivery of therapeutic agents. ECMNPs surface-modified with specialized glycoproteins demonstrate the capacity to selectively bind to specific receptors expressed on barrier tissues. This advanced design enables them to traverse biological barriers through receptor mediated endocytosis, thereby enhancing targeted drug delivery to desired anatomical locations.

workflows cannot eliminate batch variation introduced by subsequent surface-engineering reactions.

Engineering obstacles are equally pronounced and largely originate from the extra surface-modification workflow unique to engineered-cell-membrane nanoparticles. Hybrid membrane-fusion engineering suffers from suboptimal fusion efficiencies (typically 20–50%), yielding a substantial fraction of unmodified single-layer vesicles that fail to achieve the designed synergistic functionality. Noncovalent surface engineering, though mild and easy-to-operate, frequently suffers rapid ligand dissociation within serum-rich biological environments, resulting in the premature loss of artificially introduced targeting moieties. Conversely, covalent coupling can firmly anchor functional ligands, yet cross-linking chemistry may disrupt native membrane-protein conformation and abolish the intrinsic biomimetic properties of ECMNPs. Genetic-engineering-based membrane remodeling enables highly precise customization, yet its long-duration cell-editing workflow severely delays large-batch manufacturing. Furthermore, nearly all existing ECMNP fabrication pipelines remain lab-scale processes; scalable, liter-scale continuous-flow systems integrating both membrane coating and subsequent surface-engineering steps are still missing.

Regarding clinical translation, ECMNPs face interconnected challenges in manufacturing, regulation, and preclinical validation. From a production standpoint, the lack of scalable, sterile, and cost-effective fabrication systems prevents existing methodologies from meeting the stringent batch consistency and yield requirements for clinical use. The biological origin of membrane materials further conflicts with Good Manufacturing Practice (GMP) requirements for injectable products: terminal sterilization typically compromises membrane protein integrity, necessitating aseptic processing and comprehensive donor cell testing (sterility, mycoplasma, endotoxin) throughout the production chain. The Quality by Design (QbD) framework offers a systematic approach to address batch-to-batch variability by prospectively defining critical quality attributes (e.g., membrane protein integrity, coating completeness, particle size, ligand density) and linking them to critical process parameters. However, the absence of unified, standardized methods for quantitatively assessing cell membrane surface engineering efficiency hinders the objective comparison of modification strategies and the establishment of reliable release criteria. On the regulatory front, ECMNPs present a classification dilemma due to their hybrid nature as biologics, drugs, and medical devices; the lack of dedicated guidelines for membrane-coated nanoparticles under existing frameworks creates ambiguity that discourages biopharmaceutical investment. Compounding these hurdles, preclinical validation relies heavily on immunodeficient or syngeneic murine models that inadequately recapitulate human immune responses to engineered membranes. Furthermore, maximum tolerated doses (MTDs) and no-observed-adverse-effect levels (NOAELs) for ECMNP platforms have not been systematically established, leaving safety margins undefined. Bridging these translational gaps requires comprehensive toxicological evaluations in non-human primates aligned with

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Table 3. Recently Proposed Engineering Functionalizations of ECMNPs

name	disease	membrane source	engineering strategies	goal	ref.
CMN-ICG	liver cancer	RBC	noncovalent conjugation	stimuli-responsive release	164
3BP@CP NPs	recurrent metastatic triple-negative breast cancer	HEK293T	genetic engineering	immunomodulatory activation; immune evasion	165
Ru-Pt-Ru@PD1	proximal melanoma; distal liver cancer	PD1 cell	genetic engineering	immunomodulatory activation	166
PDA@R@M/K	Alzheimer disease	microglia	noncovalent conjugation	transbarrier transport facilitation	167
AP@CM-Ang	glioblastoma	microglia	genetic engineering; noncovalent conjugation	transbarrier transport facilitation; anisotropic targeting	168
Mg/Ce-MOF@MUFA-PLs	iron accumulation-related diseases	bone marrow stromal cell	stimulation	anisotropic targeting	123
TGN/RAP12-RBC-NPs@Ltn	Alzheimer disease	RBC	noncovalent conjugation	transbarrier transport facilitation; anisotropic targeting	169
PBM@A-BDNF NPs	spinal cord injury	microglia	stimulation	anisotropic targeting	170
CEP@LP-M^{CCR2}	acute lung injury	HEK293T	genetic engineering	anisotropic targeting	171
Hy-gNVs@chol	myocardial infarction	macrophage; artificial liposomes	membrane fusion	immunomodulatory activation; anisotropic targeting	172
PNP-PA	thrombotic	platelet	covalent modification	anisotropic targeting	60
FPVM	bacterial infection	dendritic cell	covalent modification	immunomodulatory activation; anisotropic targeting	173
Cu@MIL	virus infection	HeLa cell	genetic engineering; noncovalent conjugation	anisotropic targeting	174
Sa-M-GSNCs	bacterial infection	macrophage	stimulation	stimuli-responsive release; anisotropic targeting	74
RRM-NVs	vascular complications of diabetes	macrophage	genetic engineering	immunomodulatory activation	175
ARPC	squamous cell carcinoma of the head and neck	RBC	noncovalent conjugation	stimuli-responsive release; immunomodulatory activation	81
PGC@FM	breast cancer; unsaturated fatty acid	breast cancer cell	membrane fusion	anisotropic targeting; immunomodulatory activation	138
Bev@TPNVs	hepatic metastases	HEK293T; platelet	genetic engineering; membrane fusion	anisotropic targeting; immunomodulatory activation	121
NB@CM-H-PD-1	liver cancer	hamster ovary cells	genetic engineering; noncovalent conjugation	stimuli-responsive release; anisotropic targeting	73
iRGD-RBCM@TPOR	neuroblastoma	RBC	noncovalent conjugation	intracellular trafficking; anisotropic targeting	69
FRCZD	breast cancer	RBC	noncovalent conjugation	stimuli-responsive release; anisotropic targeting	124
R837@MfNP	carcinoma of the rectum	CT26; macrophage	membrane fusion	stimuli-responsive release; immunomodulatory activation	143
JE-CM-MNS	cancer	Jurkat cell	genetic engineering	anisotropic targeting	176
MMM/COL-NP	atherosclerosis	macrophage	noncovalent conjugation	anisotropic targeting; immunomodulatory activation	56
CIMs	liver cancer	CAR-T cell	genetic engineering	stimuli-responsive release; anisotropic targeting	86
VLA-DEX-NP	pneumonia	C1498-VLA; C1498-VLAM	genetic engineering	anisotropic targeting	87
hNVs	cancer	B16F10; 4T1 cell	genetic engineering; membrane fusion	immunomodulatory activation	88
gCM-MNs	melanoma; breast cancer	macrophage	genetic engineering	immunomodulatory activation	55
V-NVs/T+A	triple negative breast cancer	4T1 cell	genetic engineering	immunomodulatory activation	77
ACE NPs	virus infection	HEK-293T cell	genetic engineering	anisotropic targeting	61
SIRPα@Zeb	melanoma	macrophage	noncovalent conjugation	immunomodulatory activation	89
MMNPs	myocardial infarction	macrophage	genetic engineering	intracellular trafficking	82
EMNP	osteoarthritis	mesenchymal stem cell	genetic engineering	intracellular trafficking; anisotropic targeting	80
IL-12 mRNA@cRGD-CM-$CaCO)_3$NPs	spongioblastoma	GL261 cell	covalent modification	transbarrier transport facilitation; anisotropic targeting; stimuli-responsive release	151
DPLGA@[RAW-4T1]NPs	lung metastasis of breast cancer	RAW264.7; 4T1 cell	membrane fusion	anisotropic targeting	119

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Table 3. continued

name	disease	membrane source	engineering strategies	goal	ref.
Melanin@RBC-M	cancer	RBC; MCF-7	membrane fusion	immune evasion; anisotropic targeting; stimuli-responsive release	52
PCN@FM	cancer	tumor cell; dendritic cell	membrane fusion	immunomodulatory activation	120
HPDA@[OMV-CC] NPs	melanoma	B16-F10 cell; bacteria	membrane fusion	immune evasion; stimuli-responsive release	54
NEX	acute kidney injury	neutrophil granulocyte; hucMSCs	membrane fusion	anisotropic targeting	115
Fe_3O_4-ICG@IRM	ovarian cancer	tumor cell; RBC	membrane fusion	immune evasion; stimuli-responsive release	53
SPNE	cancer	tumor cells; dendritic cells	membrane fusion	immunomodulatory activation; stimuli-responsive release	59
FIRN	rheumatoid arthritis	fibroblast	stimulation	anisotropic targeting	71
VIN	ischemic stroke	mesenchymal stem cell	stimulation	anisotropic targeting	22
MKNs	intervertebral disc degeneration	adipose-derived stem cells	stimulation	anisotropic targeting	68
RBC-NCs	glioma	RBC	noncovalent conjugation	anisotropic targeting	110
MφM-LPs	bacterial infection	macrophage; artificial liposomes; neutrophile; RBC	membrane fusion	anisotropic targeting	98
cRGD-mPIT	cancer	tumor cells	noncovalent conjugation	anisotropic targeting; stimuli-responsive release	100
V-M@OA	cancer	oncolytic adenoviruses	noncovalent conjugation	immunomodulatory activation	107
PD-1/LAG-3 NVs	carcinoma of the rectum	HEK-293T	noncovalent conjugation	immunomodulatory activation	108
IOCMMNPs	cancer	HEK293	covalent modification	anisotropic targeting	94
RVG/TPP-MASLNs-GS	Alzheimer disease	macrophage	covalent modification	transbarrier transport facilitation	129
RVG-NV-NPs	Alzheimer disease	neural stem cell	genetic engineering	transbarrier transport facilitation; immune evasion; stimuli-responsive release	156
PD-1-MM@PLGA/RAPAs	glioblastoma	macrophage	genetic engineering	transbarrier transport facilitation; anisotropic targeting;	159
NP-D@MP	hepatic metastasis of colonic carcinoma	cancer cell	genetic engineering	Immunomodulatory activation	177
AP-NPs	cancer	cancer cell	genetic engineering	anisotropic targeting; immunomodulatory activation	23
RuPOP@CM	breast cancer	cancer cell	noncovalent conjugation	immune evasion; immunomodulatory activation	133
SIM@TR-NPs	cancer	macrophage	genetic engineering	anisotropic targeting; stimuli-responsive release	154
M1@PLGA–PEG-TMP195	cancer	macrophage	stimulation	anisotropic targeting; immunomodulatory activation	178
N_3-TINPs	cancer	T cell	covalent modification	anisotropic targeting; stimuli-responsive release	126
MNM/siRNA NPs	acute myocardial infarction	neutrophils	genetic engineering; stimulation	immune evasion; anisotropic targeting	42
MEP-D	triple negative breast cancer	macrophage	genetic engineering	anisotropic targeting	152
apM@MOF-Que	osteoarthritis	chondrocyte	stimulation	immune evasion; immunomodulatory activation	134
MPB-3BP@CM NPs	colorectal cancer	HEK-293T	genetic engineering	immune evasion; immunomodulatory activation; anisotropic targeting; stimuli-responsive release	137
HRMSGD	cancer	RBC; Hela cell	membrane fusion	anisotropic targeting; stimuli-responsive release	142
CM@AIE NPs	spongioblastoma	T cell	genetic engineering	transbarrier transport facilitation; stimuli-responsive release	141
IM-MNPs/DXM	systemic lupus erythematosus	CD4 T cell	genetic engineering	anisotropic targeting; stimuli-responsive release	179
IL-11/MM@NPs/Dox	osteosarcoma	macrophage	genetic engineering	stimuli-responsive release	136
αCD3-αHER2 SMART-Exos	breast cancer	T cell	genetic engineering	anisotropic targeting	58
iRINPs	lung cancer	RBC	noncovalent conjugation	anisotropic targeting; intracellular trafficking	36
ARISP	triple negative breast cancer	erythrocyte	noncovalent conjugation	anisotropic targeting	32
DCuS@[RBC–B16]NPs	melanoma	RBC; B16-F10	membrane fusion	anisotropic targeting; immune evasion	117
NP-R@M-M	cancer	cancer cell	noncovalent conjugation	immunomodulatory activation	25

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anticipated clinical dosing regimens, coupled with early, proactive engagement with regulatory agencies to delineate critical quality attributes and establish product-specific quality standards.

Looking ahead, addressing the multifaceted challenges spanning biological, engineering, and translational domains will necessitate sustained interdisciplinary collaboration. As the field advances, the continued refinement of standardized protocols for quality control and safety assessment is anticipated to further bolster the translational potential of ECMNPs. Such progress may ultimately facilitate the transition of nanomedicine from preclinical research to clinical application, thereby contributing to the realization of precision medicine and individualized therapeutic strategies.

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H.Y.: Writing—original draft, investigation. X.Z.: Resources. Y.W.: Writing—review and editing, supervision. J.Y.: Writing—review and editing, Supervision. X.F.: Investigation.

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ABBREVIATIONS

CMNPs	Cell membrane-coated nanoparticles
ECMNPs	Engineered cell membrane-coated nanoparticles
CD47	Cluster of Differentiation 47
LFA-1	Lymphocyte function-associated antigen 1
PD-L1	Programmed cell death 1 ligand 1
Gal-9	Galectin-9
Fasl	Fas ligand
LPS	Lipopolysaccharide
IFN-γ	Interferon-gamma
TALENs	Activator-like effector nucleases
ZFN	Zinc finger nucleases
RVG	Rabies virus glycoprotein
BBB	Blood-brain barrier
VLA-4	Very late antigen-4
VCAM-1	Vascular cell adhesion molecule-1
GPC3	Glypican-3
CAR	Chimeric antigen receptor
SIRPα	Signal regulatory protein α
DSPE	Distearoyl phosphatidylethanolamine
TCRs	T cell receptors
PEG	Polyethylene glycol
NHS	N-Hydroxysuccinimide
rt-PA	Recombinant tissue plasminogen activator
MHC	Major histocompatibility complex
CD3	Cluster of Differentiation 3
TPP	Triphenylphosphonium
UVEC	Umbilical vein endothelial cell
HUVEC	Human umbilical vein endothelial cell
MPS	Mononuclear phagocyte system
GSH	Glutathione
ICG	Indocyanine green
ICNPs	Indocyanine green-encapsulated nanoparticles
c-Met	Mesenchymal-epithelial transition factor receptor
CaCO3	Calcium carbonate
SLNs	Solid lipid nanoparticles
Exo-AuNPs	Exosome-encapsulated gold nanoparticles
NOAELs	No-observed-adverse-effect levels
GMP	Good Manufacturing Practice
QbD	Quality by Design

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