



Biomimetic Cell Membrane-Coated Nanoparticles for Precision Cancer Therapy: Recent Advances and Clinical Translation

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ABSTRACT

Biomimetic cell membrane-coated nanoparticles (CMNPs) have emerged as promising nanoplatforams for precision cancer therapy by combining the biological functions of natural cell membranes with the therapeutic advantages of nanoparticles. CMNPs consist of a nanoparticle core, cell membrane coating, and therapeutic or diagnostic cargo, providing immune evasion, prolonged circulation, biocompatibility, and enhanced tumor targeting. This review discusses different cell membranes and nanoparticle cores used in CMNPs, their preparation and fabrication strategies, membrane engineering approaches, and key characterization parameters. The mechanisms of precision tumor targeting, including passive and active targeting, homotypic targeting, immune-cell-mediated targeting, and tumor microenvironment targeting, are highlighted. Therapeutic applications including chemotherapy, gene therapy, photothermal and photodynamic therapy, radiotherapy, immunotherapy, and combination therapies are reviewed. The potential of CMNPs for cancer theranostics, imaging-guided therapy, and applications against different cancer types is also discussed. Emerging approaches such as hybrid membranes, stimuli-responsive systems, AI/ML-assisted design, personalized nanomedicine, and multidrug-resistance targeting are highlighted. Finally, major challenges related to membrane standardization, reproducibility, toxicity, stability, scalability, GMP manufacturing, pharmacokinetics, and regulatory requirements are addressed. Overall, CMNPs represent a promising approach for targeted, multifunctional, and personalized cancer therapy with significant potential for clinical translation.

Keywords: Cell membrane-coated nanoparticles; Biomimetic nanoparticles; Precision cancer therapy; Nanomedicine; Tumor targeting; Theranostics; Clinical translation.

1.Introduction

1.1Global cancer burden

Cancer remains one of the major global health challenges and is a leading cause of morbidity and mortality worldwide. According to the International Agency for Research on Cancer (IARC), approximately 20 million new cancer cases and 9.7 million cancer-related deaths were estimated globally in 2022. Furthermore, nearly one in five individuals is expected to develop cancer during their lifetime, highlighting the substantial and continuously increasing global burden of the disease [1]. Despite considerable advances in cancer diagnosis, surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, the effective and selective eradication of malignant cells remains a major therapeutic challenge. The complex biological characteristics of tumors and differences in treatment response among patients have created a need for more precise and efficient therapeutic strategies.[2]

1.2 Limitations of conventional cancer therapy

Conventional cancer therapies, particularly chemotherapy, are frequently associated with limited selectivity toward malignant tissues. Most cytotoxic anticancer drugs act on rapidly proliferating cells and therefore may also damage normal tissues, resulting in systemic adverse effects. In addition, inadequate drug accumulation at the tumor site, premature drug degradation or clearance, dose-limiting toxicity and the development of therapeutic resistance can compromise treatment efficacy. Although targeted therapies have improved treatment selectivity for specific molecular alterations, their effectiveness may be restricted by variations in tumor biology and the emergence of resistant cancer-cell populations. These limitations have stimulated the development of advanced drug-delivery approaches capable of improving tumor-specific drug accumulation while minimizing exposure to healthy tissues [2,3]

1.3 Challenges in precision cancer therapy: tumor heterogeneity, poor penetration, off-target toxicity, drug resistance and immunosuppressive tumor microenvironment

Precision cancer therapy aims to provide individualized and selective treatment by exploiting molecular, cellular and biological characteristics of tumors. However, several barriers complicate the successful implementation of precision drug delivery. Tumor heterogeneity is one of the major challenges because tumors consist of genetically and phenotypically diverse cell populations that may express different receptors, antigens and therapeutic targets. Consequently, a therapeutic system designed against one tumor-associated target may not effectively recognize all malignant cell populations. In addition, the abnormal tumor vasculature, dense extracellular matrix, elevated interstitial fluid pressure and heterogeneous blood flow can restrict the penetration and distribution of therapeutic agents within solid tumors [4,5].

1.4 Emergence of nanomedicine

The emergence of nanomedicine has provided new opportunities for addressing some of these limitations. Nanoparticles can function as drug-delivery vehicles capable of encapsulating or carrying therapeutic molecules and modifying their pharmacokinetic and biodistribution profiles. Depending on their composition and design, nanocarriers can improve drug solubility and stability, protect therapeutic molecules from premature degradation, facilitate controlled drug release and enhance delivery to tumor tissues. Nanomedicine has consequently been extensively investigated for chemotherapy, gene therapy, immunotherapy, photothermal therapy, photodynamic therapy and combination cancer treatments [3,4]. Nanoparticles may also undergo recognition and clearance by the mononuclear phagocyte system, limiting their circulation time and reducing the amount of therapeutic payload available for tumor delivery. In addition, insufficient tumor specificity, biological instability, limited tumor penetration and potential immunological interactions can restrict the therapeutic performance and clinical translation of conventional nanomedicines [5,6].

1.5 Limitations of conventional synthetic nanoparticles

These limitations have encouraged researchers to develop nanocarriers that possess more biologically compatible and naturally functional interfaces. An emerging strategy to overcome these challenges is the development of biomimetic cell membrane-coated nanoparticles (CMNPs). In this approach, a synthetic or biologically engineered nanoparticle core is coated with a naturally derived cell membrane.[5] The resulting hybrid nanostructure combines the physicochemical and drug-delivery advantages of the nanoparticle core with the biological characteristics of the source cell membrane. Depending on the membrane source, cell membrane-coated nanoparticles may acquire properties such as improved biocompatibility, prolonged circulation, immune evasion, cellular recognition and tumor-targeting capability. Commonly investigated membrane sources include red blood cells, platelets, leukocytes, cancer cells, stem cells and hybrid membranes[7,8]

1.6 Concept and rationale of biomimetic cell membrane coating

The rationale behind cell membrane coating is based on biomimicry, in which naturally occurring membrane proteins and surface components are utilized to improve the interaction of nanoparticles with the biological environment. For example, red blood cell membranes have been investigated for their ability to provide prolonged circulation characteristics, whereas cancer-cell membranes can facilitate homotypic recognition and tumor-associated interactions. Platelet and immune-cell membranes have also been investigated for their potential tumor-homing and biological targeting properties. Thus, the membrane source can be selected according to the desired therapeutic function, making cell membrane coating a versatile strategy for designing multifunctional nanocarriers [9–10].

Cell membrane-coated nanoparticles are particularly attractive for precision cancer therapy because they integrate two complementary components: the engineered functionality of the nanoparticle core and the naturally derived biological functionality of the cell membrane. The nanoparticle core can be engineered for drug loading, controlled release, imaging or combination therapy, while the membrane coating can provide biological recognition and interaction with the tumor microenvironment. This biomimetic design may improve tumor targeting and therapeutic efficiency while potentially reducing nonspecific interactions and systemic toxicity. Recent studies and reviews have demonstrated the potential of cell membrane-coated nanoparticles in chemotherapy, immunotherapy, phototherapy, gene delivery and cancer theranostics [10,11].

1.7 Significance, objectives and scope of the review

Despite these promising characteristics, the translation of biomimetic cell membrane-coated nanoparticles from laboratory research to clinical applications remains challenging. Important issues include reproducible membrane isolation and coating, preservation of membrane proteins and biological functions, batch-to-batch variability, manufacturing scalability, physicochemical characterization, long-term stability, safety, immunogenicity and regulatory requirements. The complexity of these biological nanocarriers can also make large-scale manufacturing and quality control more difficult than for conventional synthetic nanoparticles [12,13]. Therefore, systematic evaluation of their therapeutic benefits, limitations and translational potential is essential. In this context, the present review focuses on “Biomimetic Cell Membrane-Coated Nanoparticles for Precision Cancer Therapy: Recent Advances and Clinical Translation.” The review discusses the fundamental concept of biomimetic cell membrane-coated nanoparticles, different sources of cell membranes, preparation and coating strategies, physicochemical characterization, mechanisms of tumor targeting and their applications in cancer therapy. [14] Overall, understanding the integration of natural cell-membrane functions with engineered nanoparticle systems may provide a promising pathway toward more selective, personalized and effective cancer therapy.[15]

2. Concept and Design Principles of Cell Membrane-Coated Nanoparticles (CMNPs)

2.1. Definition and Basic Concept

Cell membrane-coated nanoparticles (CMNPs) are biomimetic nanocarrier systems in which a synthetic or inorganic nanoparticle is surrounded by a naturally derived cell membrane. The resulting structure combines the physicochemical properties of the nanoparticle core with the biological functions of the cell membrane.

Traditional nanoparticles can efficiently encapsulate drugs and provide controlled drug release, but they may undergo rapid clearance by the mononuclear phagocyte system, show nonspecific interactions with biological components, and have limited ability to recognize particular tumor cells. Cell membrane coating is designed to overcome some of these limitations by transferring naturally occurring membrane proteins, lipids, glycans and other surface components onto the nanoparticle surface.

Thus, CMNPs can be considered a hybrid biological–synthetic delivery system:

Synthetic nanoparticle + Natural cell membrane = Biomimetic CMNP

The membrane acts as a biological “camouflage” around the nanoparticle. Depending on the source of the membrane, the resulting CMNP can acquire properties such as immune evasion, prolonged circulation, self-recognition, homotypic targeting and specific interactions with receptors on tumor cells.

- Different cell types can be used as membrane sources, including:
- Red blood cells (RBCs) – mainly useful for prolonged circulation and immune evasion.
- Cancer cells – useful for homotypic tumor targeting.
- Platelets – can interact with components associated with tumors and metastasis.
- Macrophages/neutrophils – can provide tumor/inflammation-homing properties.
- T cells and other immune cells – can provide specific biological interactions.
- Stem cells – investigated for tumor-homing properties.

The biological properties obtained depend strongly on the membrane source and the preservation of functional membrane proteins during membrane isolation and coating.[16,17]

2.2. Architecture: nanoparticle core, cell membrane shell and therapeutic cargo

The basic architecture of a CMNP can be represented as:

Therapeutic cargo → Nanoparticle core → Cell membrane shell → Biological targeting

A CMNP generally contains three major components:

A. Nanoparticle core

The nanoparticle core forms the inner structural component of CMNPs. It provides the physicochemical properties required for drug loading, protection and controlled release.

Possible core materials include:

- Polymeric nanoparticles
- Liposomes
- Mesoporous silica nanoparticles
- Gold nanoparticles
- Magnetic nanoparticles
- Other inorganic nanoparticles
- Biodegradable nanomaterials
- The choice of core depends on the intended application. For example, polymeric cores may be useful for controlled drug release, while magnetic or gold nanoparticles can provide additional imaging or photothermal functions.
- The core can therefore be designed according to the therapeutic requirement rather than relying only on the natural properties of the cell membrane.

B. Cell membrane shell

The cell membrane forms the outer shell of the nanoparticle.

The cell membrane is primarily composed of a phospholipid bilayer containing membrane proteins, glycoproteins, glycolipids and other biomolecules. When this membrane is transferred onto the nanoparticle surface, many of its functional surface components can remain associated with the nanoparticle.

Therefore, the membrane shell acts as a biological interface between the synthetic nanoparticle and the surrounding biological environment.

This shell can provide:

1. Biocompatibility

Because the external surface resembles a naturally occurring biological membrane, interaction with biological systems can be improved.

2. Immune evasion

Certain membrane-associated “self” markers can reduce recognition and uptake by phagocytic cells.

3. Prolonged circulation

Reduced rapid clearance can allow nanoparticles to remain in circulation for longer periods.

4. Target recognition

Membrane proteins and glycans can mediate interactions with specific cells or tissues.

5. Homotypic targeting

Cancer-cell-derived membranes can promote interactions with tumor cells originating from the same or similar cancer type.

C. Therapeutic cargo

The therapeutic cargo is the active component carried by the CMNP.

Depending on the treatment strategy, CMNPs can carry:

- Chemotherapeutic drugs
- Small-molecule anticancer agents
- siRNA
- miRNA
- DNA
- Proteins
- Peptides
- Immunotherapeutic agents
- Photothermal/photodynamic therapeutic agents
- Combination therapeutic agents

For your review topic, doxorubicin can be used as a representative anticancer drug example. A nanoparticle core can be engineered to carry doxorubicin, while the cell membrane coating provides biological camouflage and targeting properties.

Conceptually:

Doxorubicin → loaded into nanoparticle core → cell membrane coating → circulation → tumor recognition → cellular uptake → drug release → anticancer action

CMNPs have been investigated for delivery of chemotherapeutic drugs, nucleic acids and immunotherapeutic agents in preclinical cancer models.[18,19]

2.3 Biomimetic mechanisms: self-recognition, immune evasion, homotypic targeting and receptor–ligand interactions

A. Biomimetic Mechanisms of Cell Membrane-Coated Nanoparticles

Cell membrane-coated nanoparticles (CMNPs) are designed to mimic the biological properties of their source cells by transferring naturally occurring membrane proteins, lipids, and surface carbohydrates onto the nanoparticle surface. This biomimetic coating provides nanoparticles with biological identity and enables functions such as self-recognition, immune evasion, homotypic targeting, and receptor–ligand-mediated interactions. Consequently,

CMNPs can achieve prolonged circulation, selective tumor accumulation, and improved therapeutic delivery compared with many conventional nanoparticle systems.[18,19]

B. Self-recognition

Self-recognition is an important biological characteristic imparted by cell membrane coating. Membrane proteins and surface markers retained on the nanoparticle surface can enable the coated nanoparticles to interact preferentially with cells or biological components originating from the same or compatible cell type. For example, nanoparticles coated with cancer-cell membranes can display tumor-associated membrane antigens and adhesion molecules, allowing them to recognize and interact with tumor cells. This biological identity can improve tumor localization while reducing nonspecific interactions.[19]

C. Immune evasion

The immune system can rapidly recognize and eliminate conventional nanoparticles, particularly through opsonization and uptake by macrophages of the mononuclear phagocyte system (MPS). Cell membranes can provide nanoparticles with natural “self” signals that reduce recognition by immune cells. In particular, proteins such as CD47 present on red blood cell membranes can interact with signal regulatory protein alpha (SIRP α) on macrophages and transmit a “don’t eat me” signal, thereby decreasing phagocytic clearance. This mechanism can prolong nanoparticle circulation and increase the probability of reaching tumor tissue.[18]

D. Homotypic targeting

Homotypic targeting refers to the preferential interaction of nanoparticles coated with a particular cancer-cell membrane with tumor cells of the same or closely related origin. Cancer-cell membranes retain membrane proteins, adhesion molecules and tumor-associated antigens involved in cell–cell recognition. Nanoparticles coated with membranes derived from a particular tumor type may therefore preferentially bind to homologous tumor cells through homophilic interactions. This approach is attractive for enhancing tumor accumulation and reducing nonspecific drug distribution.[19]

E. Receptor–ligand interactions

Cell membrane coatings retain various receptors, ligands and adhesion molecules that can participate in specific molecular interactions with cells in the tumor microenvironment. These receptor–ligand interactions can promote nanoparticle adhesion, cellular uptake and intracellular drug delivery. Membrane-associated targeting molecules can recognize receptors overexpressed on cancer cells, while tumor-associated endothelial cells and stromal components may provide additional binding sites. Thus, CMNPs can exploit naturally occurring molecular recognition mechanisms rather than relying exclusively on artificially attached targeting ligands.[19]

2.4 Advantages of CMNPs Over Conventional Nanoparticles

Compared with conventional synthetic nanoparticles, cell membrane-coated nanoparticles offer several biologically relevant advantages, including improved biomimicry, immune evasion, prolonged circulation, homotypic targeting, receptor-mediated interactions, and multifunctional biological interfaces.[20,21]

Feature	Conventional nanoparticles	Cell membrane-coated nanoparticles
Biological identity	Usually absent or artificially engineered	Naturally derived from source-cell membrane
Immune evasion	May undergo rapid opsonization and MPS clearance	Membrane proteins can reduce immune recognition
Targeting	Often requires antibodies, peptides or ligands	Can exploit naturally occurring membrane molecules
Self-recognition	Limited	Can exhibit biological self-recognition
Homotypic targeting	Generally weak/absent	Possible through tumor-cell membrane components
Circulation	Depends on composition and surface modification	Can be prolonged by appropriate membrane coating
Biocompatibility	Depends on synthetic material	Biological membrane can improve biomimicry
Tumor specificity	Often depends on passive/active targeting	Can combine passive accumulation with biomimetic targeting
Multifunctionality	May require additional engineering	Multiple membrane components can provide simultaneous functions

Key Advantages for Precision Cancer Therapy

1. **Enhanced immune escape:** Natural membrane components can decrease premature clearance by immune cells.
2. **Improved tumor targeting:** Cancer-cell membranes can provide homotypic recognition, while specific membrane receptors can facilitate receptor-mediated targeting.
3. **Prolonged systemic circulation:** Reduced recognition and phagocytic uptake may increase circulation time and potentially improve tumor exposure.
4. **Reduced off-target toxicity:** Improved localization of therapeutic cargo may reduce exposure of healthy tissues, depending on nanoparticle design.
5. **Multifunctional biological interface:** A single membrane coating can present multiple proteins and biomolecules simultaneously, providing targeting, immune modulation and cell-interaction functions.
6. **Better biomimicry:** CMNPs reproduce aspects of natural cellular interfaces, making them attractive for precision drug delivery.

Important Limitation for Review

CMNPs are not automatically superior to conventional nanoparticles. Their performance depends on the source cell, membrane isolation method, coating integrity, nanoparticle core, membrane-to-core ratio, tumor type and manufacturing process. Membrane heterogeneity, scalability, storage stability, reproducibility and regulatory standardization remain major barriers to clinical translation.[21]

3. Types of Cell Membranes Used for Cell Membrane-Coated Nanoparticles

3.1 Red Blood Cell (RBC) Membrane

RBC or erythrocyte membrane is one of the earliest and most extensively investigated membranes for nanoparticle coating. RBCs are abundant and relatively easy to obtain. After removal of intracellular contents, the RBC membrane can be processed into membrane vesicles and fused around nanoparticles.

Key characteristics: The membrane retains proteins and glycans involved in self-recognition and prolonged circulation. CD47 is particularly important because it interacts with signal-regulatory proteins on phagocytic cells and contributes to a “self” signal.

Mechanism: Synthetic nanoparticle → RBC membrane coating → self-like biological identity → reduced macrophage uptake → prolonged circulation → increased opportunity for tumor accumulation.

Advantages: prolonged blood circulation, reduced mononuclear phagocyte-system uptake, good biocompatibility, reduced immune recognition and preservation of membrane proteins.

Cancer relevance: explored for chemotherapy, phototherapy, hypoxia modulation and immunotherapy.

Limitation: RBC membrane primarily provides immune evasion and long circulation; it does not inherently provide strong tumor-specific recognition, so additional targeting strategies may be required.[23]

3.2 Cancer Cell Membrane

Cancer-cell membrane is isolated from tumor cells and retains tumor-associated membrane proteins, antigens and adhesion molecules.

Key principle: homotypic targeting, in which nanoparticles coated with a membrane derived from a particular cancer type can preferentially interact with cells sharing similar molecular characteristics.

Mechanism: cancer-cell membrane → self-recognition/homotypic adhesion → tumor-cell interaction → enhanced tumor targeting.

Advantages: homotypic tumor targeting, tumor/metastasis recognition, preservation of tumor-associated antigens, potential for cancer vaccination, chemotherapy and phototherapy.

Cancer relevance: investigated for chemotherapy, tumor imaging, photothermal/photodynamic therapy, cancer vaccination and immunotherapy.

Limitation: tumor heterogeneity may reduce universal targeting. Source-cell variability, safety, membrane preparation and reproducibility are important translational concerns.[23]

3.3 Platelet Membrane

Platelets are anucleate cellular fragments involved in hemostasis, vascular repair and interactions with damaged vasculature. Their membrane contains adhesion and immune-interactive proteins.

Important functions: CD47 contributes to immune evasion, while P-selectin and glycoprotein receptors contribute to interactions with tumor cells and vascular structures.

Mechanism: platelet membrane → immune evasion + vascular/tumor adhesion → tumor accumulation → enhanced nanoparticle delivery.

Advantages: immune evasion, prolonged circulation, tumor/vascular targeting, interaction with circulating tumor cells and metastatic sites.

Cancer relevance: chemotherapy, photothermal therapy, combination therapy, anti-metastatic strategies and targeting of circulating tumor cells.

Limitation: preservation and control of platelet membrane functionality, source variability, membrane integrity and manufacturing reproducibility are important issues.[23]

3.4 Macrophage Membrane

Macrophages participate in phagocytosis, inflammation, antigen presentation and tissue remodeling. Their membranes contain receptors and adhesion molecules that can interact with inflammatory and tumor microenvironments.

Mechanism: macrophage membrane → immune-cell-like surface → interaction with tumor microenvironment → tumor homing → nanoparticle accumulation.

Advantages: tumor homing, immune evasion, prolonged circulation, molecular recognition and interaction with inflammatory microenvironments.

Cancer relevance: tumor-targeted chemotherapy, photothermal therapy, immunotherapy and tumor-microenvironment targeting.

Limitation: macrophages are nucleated cells, making membrane isolation and purification more complex than for RBCs or platelets. Membrane integrity and reproducibility also require careful control.

3.5 Neutrophil Membrane

Neutrophils are abundant innate immune cells that rapidly migrate toward sites of infection, inflammation and tissue injury. Their natural inflammatory homing makes their membranes attractive for tumor and inflammatory-site targeting.

Mechanism: inflammatory/tumor signals → neutrophil recruitment → neutrophil membrane-coated nanoparticle follows related molecular interactions → accumulation at target site

Advantages: inflammatory-site homing, tumor tropism, immune evasion, reduced nonspecific clearance and potential tumor-microenvironment targeting.

Cancer relevance: chemotherapy, photothermal therapy and photodynamic therapy.

Limitation: isolation of intact neutrophil membranes is technically challenging because neutrophils are fragile nucleated cells; maintaining membrane proteins and orientation is important[23].

3.6 Stem-Cell Membrane

Mesenchymal stem cell (MSC) membranes are particularly investigated because MSCs possess intrinsic tissue-homing properties and can migrate toward sites of inflammation, injury and tumors.

Mechanism: stem-cell membrane → tissue/tumor homing properties → interaction with tumor microenvironment → enhanced tumor accumulation

Advantages: tumor homing, tissue-specific targeting, reduced immune clearance, prolonged circulation and enhanced accumulation at pathological sites.

Cancer relevance: targeted chemotherapy, tumor imaging, combination therapy and delivery to the tumor microenvironment.

Limitation: stem-cell source, passage number, differentiation state and membrane composition can influence performance. Large-scale manufacturing and reproducibility remain challenges.[23]

3.7 Exosome Membrane

Exosome membrane is not exactly the same as a whole-cell plasma membrane. Exosomes are naturally produced extracellular vesicles with a lipid bilayer and biological components derived from their parent cells.

Mechanism: parent cell → exosome → natural membrane proteins → recognition/communication with recipient cells → membrane-coated nanoparticle targeting.

Advantages: natural cell-to-cell communication properties, potential tissue/cell targeting, reduced immune recognition and potential for tumor-specific targeting when tumor-derived exosomes are used.

Cancer relevance: tumor targeting, drug delivery, imaging, gene/RNA delivery and theranostics

Limitation: source-cell variability, isolation and purification, heterogeneous composition, batch-to-batch variation, characterization, scalability and regulatory standardization are major concerns.[23]

3.8 Hybrid Cell Membranes

Hybrid cell membranes are produced by combining or fusing membranes obtained from two or more cell types before coating the nanoparticle core. This strategy attempts to combine the advantages of individual membranes.

Example: RBC + platelet membrane can combine prolonged circulation/immune evasion with platelet-associated vascular and tumor interactions.

Mechanism: membrane A function + membrane B function → multifunctional biological corona → improved targeting and/or circulation.

Advantages: multifunctionality, combination of targeting mechanisms, immune evasion plus tumor targeting, design flexibility and suitability for combination therapy/theranostics.

Limitations: membrane fusion efficiency, preservation and orientation of proteins, membrane composition ratio, reproducibility, scalability, stability and regulatory characterization are more complex than for single-membrane systems.[24]

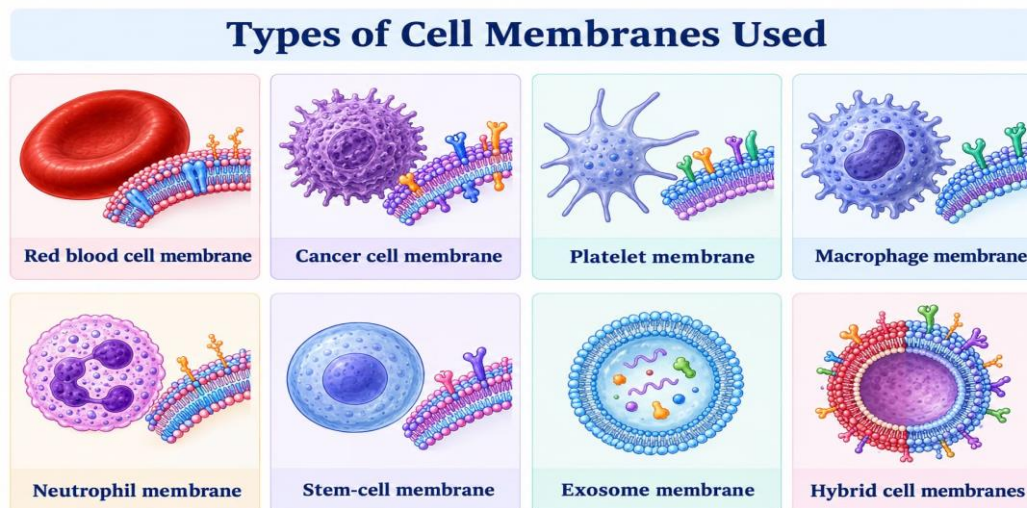


Figure1. Types of cell membranes used for biomimetic cell membrane-coated nanoparticles and their major functional roles in targeted drug delivery.[23,24]

4. Nanoparticle Cores

Cell membrane-coated nanoparticles (CMNPs) consist of a functional nanoparticle core surrounded by a biologically derived cell membrane. The core primarily determines drug loading, controlled release and physicochemical or therapeutic properties, whereas the membrane provides biomimetic functions such as immune evasion and cell-specific targeting. Different core materials have therefore been investigated according to the intended therapeutic application.[25]

4.1 Lipid Nanoparticles

Lipid nanoparticles, particularly liposomes, are spherical vesicular systems composed mainly of phospholipid bilayers. They offer good biocompatibility and can encapsulate both hydrophilic and hydrophobic therapeutic agents. Their surfaces can also be readily modified or coated with cell membranes. However, relatively limited physical stability can be a concern.[25]

Role in CMNPs: Drug delivery, chemotherapy and combination therapy.

4.2 Polymeric Nanoparticles

Polymeric nanoparticles are prepared from biodegradable or biocompatible polymers and provide good structural stability, controlled drug release and flexibility in formulation design. Common polymeric materials include PLGA, PCL and other biodegradable polymers. Their physicochemical properties can be adjusted according to the desired drug-delivery profile.[25]

Role in CMNPs: Controlled/sustained drug delivery and co-delivery of therapeutic agents.

4.3 PLGA Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) is one of the most extensively used nanoparticle cores for cell-membrane coating. It is biodegradable and biocompatible, and its degradation rate can be modified by changing the lactic acid:glycolic acid ratio. PLGA can efficiently encapsulate different therapeutic molecules and provide sustained drug release. It has also been widely investigated for membrane-coated cancer nanomedicine.[25]

Role in CMNPs: Chemotherapy, gene delivery, immunotherapy and sustained drug release.

4.4 Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) possess well-defined pores, high surface area and tunable pore sizes. These characteristics allow relatively high drug loading and controlled release of therapeutic molecules. Pore size can be adjusted according to the size of the intended cargo, making MSNs versatile drug-delivery cores.[25]

Role in CMNPs: Drug delivery, controlled release, imaging and combination cancer therapy.

4.5 Gold Nanoparticles

Gold nanoparticles (AuNPs) possess unique optical properties, particularly localized surface plasmon resonance (LSPR). They can convert absorbed light into heat, making them useful for photothermal therapy (PTT). Gold nanocages and nanoshells have also been explored as membrane-coated cores because their structures can enhance photothermal effects.[25]

Role in CMNPs: Photothermal therapy, imaging and light-triggered drug delivery.

4.6 Iron Oxide Nanoparticles

Iron oxide nanoparticles, particularly Fe₃O₄, possess magnetic properties that enable magnetic guidance, separation and imaging applications. They can also generate heat under an alternating magnetic field, providing opportunities for magnetic hyperthermia. Cell-membrane-coated magnetic nanoparticles have consequently been investigated for targeted cancer therapy and imaging.[26]

Role in CMNPs: Magnetic targeting, MRI-related applications and magnetic hyperthermia.

4.7 Inorganic and Hybrid Nanoparticles

Other inorganic and hybrid cores include metal-organic frameworks (MOFs), upconversion nanoparticles, carbon-based materials and combinations such as Fe₃O₄@Au or silica-magnetic systems. These platforms can combine drug delivery with imaging, photothermal, photodynamic or magnetic functions. Hybrid cores are particularly useful when multiple therapeutic or diagnostic functions are required in a single nanoplatform.[26]

Role in CMNPs: Multimodal imaging, phototherapy, drug delivery and theranostics.

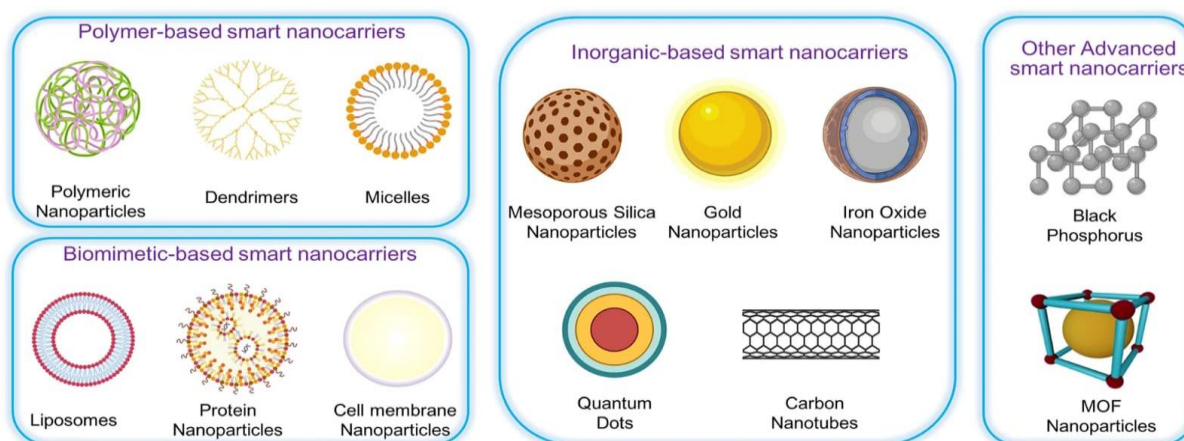


Figure 2. Schematic representation of major nanoparticle cores used in cell membrane-coated nanoplatforms for cancer therapy, including lipid, polymeric, PLGA, mesoporous silica, gold, iron oxide and hybrid/inorganic nanoparticles.[25,26]

5.Preparation and Fabrication Strategies of Cell Membrane-Coated Nanoparticles (CMNPs)

Cell membrane-coated nanoparticles (CMNPs) are generally fabricated through a top-down biomimetic approach in which a synthetic nanoparticle core is surrounded by a biologically derived cell membrane. The overall fabrication process can be divided into three major stages: (1) cell membrane isolation

and purification, (2) nanoparticle core preparation, and (3) membrane–nanoparticle assembly/coating. Further membrane engineering can be performed to introduce additional targeting or therapeutic functions.[27]

5.1 Cell Membrane Isolation and Purification

The first step in CMNP fabrication is obtaining a relatively pure and functionally intact membrane from the selected source cell, such as red blood cells, cancer cells, platelets, macrophages, neutrophils or stem cells. The cells are initially harvested and washed to remove plasma, serum proteins and other extracellular contaminants. The cells are then subjected to hypotonic lysis, mechanical homogenization or repeated freeze–thaw cycles to disrupt the plasma membrane and release intracellular components. For nucleated cells, the resulting membrane fraction must be separated from nuclei, mitochondria and cytoplasmic components. Differential centrifugation and/or density-gradient centrifugation are commonly used for purification. RBCs are relatively simple because they lack nuclei and most intracellular organelles. The purified membrane fragments can subsequently be processed by extrusion or other methods to generate nanosized membrane vesicles. An important objective during isolation is to preserve the native lipid composition, membrane proteins, glycoproteins and their orientation, because these components are responsible for immune evasion, cellular recognition and tissue-specific interactions. Excessive mechanical or ultrasonic stress may damage membrane proteins and compromise biological functionality.[27]

5.2 Nanoparticle Core Preparation

The second stage involves preparation of the nanoparticle core, which acts as the therapeutic or diagnostic payload carrier. The choice of core depends on the intended application, drug properties, desired release profile and imaging or therapeutic function. Commonly investigated cores include PLGA, liposomes, mesoporous silica nanoparticles, gold nanoparticles, iron oxide nanoparticles, upconversion nanoparticles, metal–organic frameworks, nanogels and other polymeric or inorganic nanoparticles. PLGA has been widely used because of its biocompatibility, biodegradability and ability to provide controlled drug release. The core can be prepared using techniques such as nanoprecipitation, emulsion/solvent evaporation, self-assembly, ionic gelation, desolvation or other material-specific synthesis methods. After preparation, the core nanoparticles are characterized for particle size, polydispersity index (PDI), zeta potential, morphology, drug-loading efficiency and stability. The surface characteristics of the core are important because they influence membrane wrapping. Appropriate surface charge and hydrophilicity can facilitate interaction with membrane vesicles and formation of a stable core–shell structure.[28]

5.3 Membrane Coating/Fabrication Methods

After membrane isolation and nanoparticle–core preparation, the membrane and nanoparticle are brought together to produce the final core–shell CMNP structure. Major techniques include extrusion, sonication, co-incubation, membrane–nanoparticle fusion, microfluidic electroporation and self-assembly.[28]

A. Extrusion

Extrusion is one of the most widely used techniques for preparing CMNPs. Purified cell membrane fragments or membrane-derived vesicles are mixed with nanoparticle cores and repeatedly passed through porous polycarbonate membranes. During passage through the pores, mechanical deformation promotes membrane rearrangement around the nanoparticle surface, resulting in formation of a membrane-coated core. Different pore sizes can be used sequentially to obtain relatively uniform particles.

Advantages: relatively simple and reproducible; good control over particle size; effective membrane wrapping; can preserve many membrane proteins and their biological functions.

Limitations: repeated extrusion can be laborious; mechanical stress may affect membrane integrity; large-scale production can be challenging.[27,28]

B. Sonication

In the sonication method, purified membrane vesicles and nanoparticle cores are mixed and exposed to ultrasonic energy. The acoustic energy temporarily disrupts or deforms membrane vesicles and promotes their fusion or reorganization around the nanoparticle surface. Sonication is generally faster than repeated extrusion and can facilitate efficient membrane coating. However, excessive sonication may cause membrane protein damage, membrane fragmentation or changes in nanoparticle properties; therefore, sonication conditions require optimization.

Advantages: rapid processing, simple operation and effective membrane fusion.

Limitation: excessive ultrasonic energy may compromise membrane integrity and biological functionality.[28]

C. Co-incubation

In the co-incubation approach, nanoparticle cores are incubated with isolated membrane vesicles. Appropriate incubation conditions allow interaction between the nanoparticle and membrane components. This can promote spontaneous membrane association and, depending on the system, membrane fusion around the nanoparticle. Co-incubation is comparatively mild but may provide less precise control over coating efficiency and uniformity than optimized extrusion or microfluidic methods.[28]

D. Membrane–Nanoparticle

Fusion Membrane–nanoparticle fusion represents the fundamental assembly event in CMNP fabrication. Purified membrane vesicles interact with nanoparticle cores through hydrophobic, van der Waals, electrostatic and membrane-fusion interactions, depending on the physicochemical properties of the two components. The membrane rearranges around the nanoparticle surface, producing a biological membrane shell surrounding a synthetic core. The resulting structure combines the physicochemical properties of the nanoparticle with biological recognition properties derived from the source cell membrane. Fusion can be facilitated by extrusion, sonication or microfluidic electroporation. Proper control is necessary to maintain membrane orientation and preserve functional surface proteins.[28]

E. Microfluidic Electroporation

Microfluidic electroporation is an advanced fabrication technique that provides controlled interaction between membrane vesicles and nanoparticles. Membrane vesicles and nanoparticle cores are introduced into a microfluidic device and exposed to controlled electrical pulses. The electrical field temporarily increases membrane permeability and facilitates nanoparticle entry into or fusion with membrane vesicles, leading to formation of membrane-coated nanoparticles. This method provides precise control of flow conditions and electrical parameters and has been demonstrated for RBC membrane-coated magnetic nanoparticles.

Advantages: precise process control; potentially improved coating efficiency; good reproducibility; promising for continuous or controlled fabrication.

Limitation: specialized equipment and optimization are required, which may complicate scale-up.[27,28]

F. Self-Assembly

Self-assembly is a spontaneous or assisted process in which membrane components and nanoparticle cores organize into a stable core–shell structure through non-covalent interactions. The driving forces may include hydrophobic interactions, electrostatic attraction, van der Waals forces, membrane curvature effects and interfacial-energy minimization. Self-assembly can reduce the need for extensive mechanical processing and may help preserve natural membrane architecture. Important challenges include uniform coating, membrane orientation and batch-to-batch reproducibility.[28]

5.4 Membrane Engineering

Although naturally derived membranes already provide biological functions, membrane engineering can introduce additional targeting, therapeutic or imaging capabilities. Three important strategies are chemical modification, genetic engineering and ligand/antibody/peptide functionalization.[29]

A. Chemical Modification

Chemical modification involves introducing functional molecules onto the membrane surface without completely replacing native membrane components. One approach is lipid insertion, where a functional ligand is conjugated to a lipid–linker molecule. The lipid portion inserts into the membrane bilayer while the functional ligand remains exposed on the external surface. Other approaches use suitable chemical groups present on membrane proteins or lipids for conjugation. The objective is to add targeting or therapeutic functionality while preserving natural membrane properties.

Examples: targeting ligands, fluorescent molecules, peptides, therapeutic molecules and imaging agents.

A major consideration is avoiding excessive chemical modification because alteration of membrane proteins can interfere with their natural biological functions[29]

B. Genetic Engineering

Genetic engineering modifies the source cells before membrane isolation so that desired proteins or targeting molecules are expressed on the cell surface. The engineered membrane is subsequently isolated and coated onto nanoparticle cores. This strategy is useful when a specific protein ligand, receptor-binding domain or immunomodulatory molecule is required. Unlike post-isolation chemical conjugation, genetic engineering allows the desired membrane protein to be produced as part of the natural membrane architecture.

Advantages: precise biological presentation and preservation of membrane-associated functionality.

Limitations: requires cell engineering, optimization of protein expression and additional biosafety/manufacturing considerations.[28,29]

C. Ligand Functionalization

Targeting ligands can be incorporated onto CMNP surfaces to increase recognition of specific receptors on target cells. Examples include folic acid for folate-receptor-mediated targeting, hyaluronic acid for CD44-mediated targeting, peptides for receptor-specific cellular targeting, aptamers for nucleic-acid-based molecular recognition, and antibodies or antibody fragments for antigen–receptor recognition. Ligands can be introduced through lipid insertion, chemical conjugation or genetically engineered membrane expression.[29]

D. Antibody Functionalization

Antibodies or antibody fragments can be attached to the engineered membrane surface to provide specific recognition of tumor-associated or tissue-specific antigens. Because antibodies possess high molecular recognition specificity, they can facilitate receptor-mediated binding and cellular uptake.

Antibody conjugation requires careful control of orientation, surface density and conjugation chemistry because random attachment may reduce antigen-binding activity.[29]

E. Peptide Functionalization

Short targeting peptides can be incorporated into cell membranes to provide receptor-specific recognition. Peptides are attractive because they are generally smaller than antibodies and can be synthesized and modified relatively easily.

Examples include peptides designed to recognize integrins, tumor-associated receptors or other overexpressed cellular markers. Peptide functionalization can improve cellular binding and internalization while maintaining the biomimetic properties of the underlying membrane.[29,30]

6.Characterization and Quality Assessment of Cell Membrane-Coated Nanoparticles (CMNPs)

6.1 Particle Size, PDI, Zeta Potential and Morphology

Particle size: Dynamic light scattering (DLS) determines hydrodynamic diameter and size distribution. Successful membrane coating generally increases particle diameter compared with the uncoated nanoparticle core. Size influences colloidal stability, cellular uptake, biodistribution, circulation and tumour penetration.

Polydispersity index (PDI): PDI indicates the width of the size distribution. Lower PDI generally indicates a more homogeneous nanoparticle population, whereas high PDI indicates greater heterogeneity. It is useful for formulation optimization and storage stability assessment.

Zeta potential: Zeta potential reflects surface electrostatic characteristics and colloidal stability. After membrane coating, the zeta potential commonly shifts toward that of the source cell membrane, supporting successful coating.

Morphology: TEM and SEM can examine particle morphology. TEM is particularly useful for demonstrating the core-shell architecture. Confocal microscopy can be used with differently labelled membrane and nanoparticle components.[31]

6.2 Membrane Integrity and Protein/Lipid Retention

Protein retention:

SDS-PAGE and Western blotting compare protein profiles of the original membrane, membrane vesicles and final CMNPs. Mass spectrometry can provide more comprehensive membrane-proteome information.

Lipid retention: Lipidomics or mass spectrometry can assess lipid composition. Preserved membrane lipids contribute to membrane structure, fluidity, stability and biological recognition.

Membrane integrity: Fluorescent membrane labelling with confocal microscopy and TEM can help confirm membrane coverage and core-shell architecture. Functional assays can verify retention of biological activity.

Quality consideration: Protein presence alone is insufficient; functional preservation and appropriate orientation are important for targeting and immune evasion.[31]

6.3 Drug Loading, Encapsulation Efficiency and Release Kinetics

Drug loading (DL): $DL (\%) = (\text{Amount of drug in nanoparticles} / \text{Total weight of nanoparticles}) \times 100$.

Encapsulation efficiency (EE):

$EE (\%) = (\text{Amount of encapsulated drug} / \text{Total amount of drug initially added}) \times 100$.

Drug quantification: UV-visible spectroscopy, HPLC or another validated analytical method can be used according to the therapeutic agent.

In-vitro release: Dialysis or diffusion-based systems can be used under physiologically relevant conditions. Release profiles may be fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas models.[31]

6.4 Cellular Uptake and Targeting Efficiency

Cellular uptake determines whether CMNPs are efficiently internalized by target cells. Fluorescently labelled nanoparticles can be evaluated by flow cytometry, confocal laser scanning microscopy or fluorescence microscopy. Targeting efficiency can be assessed by comparing target and non-target cells, or membrane-coated and uncoated nanoparticles. Cell membrane coating can improve disease-relevant targeting and biointerfacing.[31]

A.Immune Evasion

CMNPs can mimic the biological identity of their source cells, potentially reducing rapid recognition and clearance by the mononuclear phagocyte/reticuloendothelial system.

RBC-derived membranes containing CD47 can contribute to self-recognition and reduced phagocytic clearance. Macrophage uptake, complement activation and blood-circulation studies can assess immune-evasion performance.[31]

B.Cytotoxicity

Cytotoxicity determines safety and therapeutic selectivity. Common assays include MTT, Alamar Blue, CCK-8, LDH release and live/dead staining. For anticancer CMNPs, compare free drug, uncoated nanoparticle, membrane-coated nanoparticle and blank membrane-coated nanoparticle to determine therapeutic enhancement and nonspecific toxicity.[31]

C.Hemocompatibility

For systems intended for intravenous administration, blood interactions should be evaluated. Important tests include hemolysis, platelet interaction/activation, complement activation and, where appropriate, plasma-protein interaction studies. Good hemocompatibility is important for reducing blood-related toxicity and improving systemic safety.[31]

6.5 In-vitro Evaluation

In-vitro evaluation can include particle size/PDI, zeta potential, TEM/SEM, SDS-PAGE/Western blot, drug loading and encapsulation efficiency, drug release, cellular uptake, targeting, cytotoxicity, hemolysis and macrophage-uptake studies.[31]

6.6 In-vivo Evaluation

Pharmacokinetics: Determine C_{max}, T_{max}, AUC, circulation half-life and clearance using serial blood sampling.

Biodistribution: Fluorescent, radioactive or other suitable labels can assess accumulation in liver, spleen, kidney, lung and tumour tissue.

Tumour targeting: Tumour accumulation can be evaluated using fluorescence imaging, ex-vivo organ imaging, histology or suitable imaging methods.

Therapeutic efficacy: Assess tumour volume, tumour-growth inhibition, tumour weight, survival and histopathological markers.

In-vivo safety: Monitor body weight, haematological parameters, serum biochemical markers, major-organ histopathology and inflammatory/immune markers.[31]

7.Mechanisms of Precision Tumor Targeting

7.1 Passive Targeting and the Enhanced Permeability and Retention (EPR) Effect

Passive tumor targeting exploits abnormalities in tumor vasculature and lymphatic drainage. Rapid angiogenesis produces vessels that may be structurally irregular and more permeable than normal tissue, while impaired lymphatic clearance can favor retention of appropriately sized macromolecules and nanoparticles. This phenomenon is commonly described as the EPR effect. Nanocarriers that remain in circulation long enough can extravasate into some solid tumors and accumulate within the tumor interstitium. However, EPR is highly heterogeneous across tumor types, patients, tumor stages and experimental models; therefore, it should not be considered a universal mechanism for tumor accumulation. Recent work also emphasizes active transport and retention (ATR) and pharmacokinetic determinants of tumor delivery.[32]

7.2 Active Targeting and Receptor–Ligand Interactions

Active targeting adds molecular recognition to a nanocarrier surface by displaying ligands such as antibodies or antibody fragments, peptides, proteins, aptamers or other receptor-binding molecules. These ligands recognize receptors or antigens that are overexpressed on tumor cells, tumor endothelium or selected stromal cells. Binding can increase cellular association and, when the receptor undergoes internalization, promote receptor-mediated endocytosis and intracellular delivery. Examples of commonly investigated targets include folate receptor, transferrin receptor, EGFR, HER2 and integrins. Active targeting does not eliminate the need for systemic delivery and tumor access; ligand–receptor recognition is most useful after the carrier reaches the relevant vascular or tissue compartment.[32]

7.3 Homotypic Tumor Targeting

Homotypic targeting uses tumor-cell-derived membranes, cancer-cell-mimicking surfaces or tumor-associated biological recognition mechanisms to improve preferential interaction with tumors. Cancer-cell membrane-coated nanoparticles can retain membrane proteins that participate in homotypic adhesion and recognition, potentially increasing accumulation at tumors derived from the same or related cell populations. This approach can combine biomimetic camouflage with tumor affinity and may reduce nonspecific interactions. Important limitations include tumor heterogeneity, variation of membrane markers, manufacturing complexity and the need to establish reproducible safety and quality attributes.[33]

7.4 Immune-Cell-Mediated Targeting

Immune cells can act as biological carriers or targeting intermediates because they naturally traffic toward tumors and inflammatory tissues. Macrophages, neutrophils, monocytes, dendritic cells and other immune-cell populations have therefore been investigated as carriers, cell-hitchhiking platforms or targets of nanomedicines. Tumor-associated macrophages (TAMs), in particular, are abundant in many tumors and can internalize nanoparticles. Depending on the therapeutic objective, immune-cell-mediated delivery may either exploit these cells for transport or modulate them to reduce immunosuppression. The major challenge is controlling biodistribution and biological function without producing unwanted systemic immune effects.[32,33]

7.5 Tumor Microenvironment Targeting

The tumor microenvironment (TME) contains vascular, stromal, metabolic and immune barriers that can restrict nanoparticle extravasation, penetration and therapeutic activity. Precision delivery can therefore target TME features rather than cancer cells alone.[34]

7.6 Immune Evasion and Prolonged Circulation

After systemic administration, nanoparticles interact with plasma proteins and can acquire a protein corona. Opsonization may promote recognition and clearance by the mononuclear phagocyte system, reducing the fraction reaching tumors. Hydrophilic surface coatings such as PEG and other stealth materials can reduce nonspecific protein adsorption and delay immune clearance, thereby extending circulation time and increasing the opportunity for tumor delivery. However, stealth is not absolute: anti-PEG antibodies and other immune mechanisms can contribute to accelerated blood clearance or altered biodistribution. Emerging strategies include cleavable or stimulus-responsive coatings, zwitterionic polymers, biomimetic membranes and other adaptive surfaces. Thus, prolonged circulation should be viewed as a pharmacokinetic component of precision targeting rather than a guarantee of tumor specificity.[34,35]

8. Therapeutic Applications in Cancer

8.1 Chemotherapy

Nanocarriers can encapsulate or conjugate cytotoxic drugs and modify their pharmacokinetics, biodistribution and release. Liposomes, polymeric nanoparticles and micelles can improve apparent solubility, protect drugs from premature degradation, prolong circulation and increase tumor exposure. Controlled or stimulus-responsive release may reduce premature drug leakage and improve the therapeutic index. Nanocarriers may also help address multidrug resistance through improved intracellular delivery or co-delivery of therapeutic combinations.[36]

8.2 Gene Therapy: siRNA, miRNA, mRNA, DNA and CRISPR-related Delivery

Nanotechnology provides non-viral systems for nucleic acids that otherwise suffer from degradation, poor membrane permeability and inefficient intracellular trafficking. siRNA can silence selected oncogenic or resistance-associated genes; miRNA systems can modulate dysregulated microRNA pathways; DNA can deliver tumor-suppressor or immune-stimulatory genes; and mRNA can transiently express therapeutic proteins or tumor antigens. CRISPR-related systems require coordinated delivery of guide RNA with Cas proteins or nucleic acids encoding the editing machinery. Lipid and polymeric nanoparticles can protect nucleic acids, facilitate uptake and support endosomal escape. Important translational issues include tissue-specific delivery, immune activation, off-target effects, editing control and manufacturing.[36,37]

8.3 Photothermal Therapy (PTT)

Photothermal therapy uses agents that absorb light, commonly in the near-infrared region, and convert it into localized heat. The resulting thermal stress can damage tumor cells. Gold nanostructures, carbon-based materials and other photothermal platforms can concentrate activity at tumor sites. Targeting ligands and stimulus-responsive designs may improve localization and activation. Limitations include light penetration, heterogeneous heat distribution and possible injury to adjacent tissues.[37]

8.4 Photodynamic Therapy (PDT)

PDT combines a photosensitizer, suitable light and molecular oxygen to generate reactive oxygen species, producing oxidative damage and tumor-cell death. Nanocarriers can improve photosensitizer solubility, stability, tumor localization and cellular uptake. PDT can also promote immunogenic cell death. A major limitation is dependence on light delivery and oxygen availability; hypoxic regions can reduce ROS generation. Smart nanoplatforms are therefore being developed to improve photosensitizer delivery and address hypoxia.[37]

8.5 Chemo-Photothermal Combination Therapy

Combining chemotherapy with PTT provides complementary mechanisms: the chemotherapeutic agent produces cytotoxic effects while localized heating produces thermal stress and can enhance drug release or cellular susceptibility. Nanocarriers can co-deliver both components and coordinate their pharmacokinetics. Such platforms may improve tumor control compared with either modality alone, although treatment sequence, dose ratio, heat distribution and systemic safety require optimization.[37,38]

8.6 Radiotherapy Enhancement

Nanoparticles can function as radiosensitizers or radiation-response enhancers. High-atomic-number materials, including gold-based nanoparticles, can increase local radiation interactions and potentially amplify tumor damage. Nanocarriers can also co-deliver radiosensitizing agents or oxygen-modulating components. The aim is to increase tumor response while limiting normal-tissue exposure. Translation requires careful assessment of biodistribution, radiation dose, tumor penetration, clearance and long-term safety.[38]

8.7 Cancer Immunotherapy and Immune Modulation

Nanomedicine can deliver tumor antigens, adjuvants, immune agonists, checkpoint-modulating agents and nucleic acids to tumors or immune cells. Nanoparticles can enhance antigen presentation, stimulate dendritic cells and promote T-cell responses. They can also modulate immunosuppressive tumor-associated macrophages and other components of the tumor microenvironment. Combining PTT or PDT with immunotherapy may induce immunogenic cell death, releasing tumor antigens and danger signals that strengthen systemic antitumor immunity. Immune activation nevertheless needs spatial and temporal control because nonspecific activation can cause toxicity.[38]

9. CMNPs for Cancer Theranostics

9.1 Concept of Theranostics

Cancer theranostics integrates diagnostic imaging and therapy in one platform or coordinated system. A theranostic nanoparticle can carry an imaging component together with a therapeutic payload, enabling tumor localization, treatment delivery and response assessment. This supports precision oncology by helping identify target-positive lesions, visualize biodistribution and monitor treatment. Cell membrane-camouflaged nanoparticles (CMNPs) are attractive because the nanoparticle core can provide imaging and therapeutic functions while the membrane can contribute biological recognition, immune evasion and prolonged circulation. [39]

9.2 MRI Imaging

Magnetic resonance imaging provides high soft-tissue contrast without ionizing radiation. CMNPs containing magnetic cores, particularly superparamagnetic iron-oxide materials, can alter magnetic relaxation and generate contrast. MRI-visible CMNPs can therefore help visualize tumor localization and nanoparticle distribution while the same platform carries therapy. Limitations include relatively lower molecular sensitivity than nuclear imaging and the need for careful optimization of magnetic properties, dose and safety.[39]

9.3 PET Imaging

Positron emission tomography is a highly sensitive molecular imaging technique using positron-emitting radionuclides. Radiolabeled theranostic nanoparticles can provide whole-body information about biodistribution and target localization. PET can complement CMNP therapy by showing whether the platform reaches the intended tumor and by supporting quantitative assessment. Limitations include ionizing radiation, radiolabel stability and specialized infrastructure. PET can also be combined with fluorescence or MRI for multimodal imaging.[39]

9.4 Fluorescence Imaging

Fluorescence imaging uses fluorescent dyes or luminescent nanomaterials to visualize nanoparticles. It offers high temporal resolution and is useful for cellular imaging, tumor-margin visualization and image-guided procedures. Near-infrared and NIR-II fluorescence can reduce autofluorescence and improve tissue penetration compared with visible wavelengths. The major limitation remains attenuation and scattering in deep tissue.[39]

9.5 Photoacoustic Imaging

Photoacoustic imaging combines optical absorption with ultrasound detection. Photoabsorbing nanoparticles convert pulsed light into transient thermoelastic expansion, producing ultrasound signals that can be detected deeper than conventional fluorescence. CMNPs with photoabsorbing or photothermal cores can therefore support tumor imaging while also enabling photothermal therapy. Performance depends on optical absorption, tissue depth, light delivery and nanoparticle properties.[40]

9.6 Simultaneous Diagnosis and Therapy

A major advantage of CMNP theranostics is integration of imaging and treatment in one construct. The core may contain chemotherapy, a gene payload, photosensitizer or photothermal agent together with an MRI, PET, fluorescence or photoacoustic component. The membrane can provide tumor recognition or prolonged circulation. This allows localization of the therapeutic platform before or during treatment and supports individualized treatment decisions.[40]

9.7 Image-Guided Drug Delivery

Image-guided drug delivery uses imaging to determine where a nanocarrier accumulates and, in advanced systems, when drug release occurs. CMNPs can incorporate stimuli-responsive components triggered by pH, enzymes, redox conditions or light. Imaging can visualize accumulation or release, connecting biodistribution with therapeutic delivery and potentially helping optimize treatment timing and localization.[40]

9.8 Real-Time Treatment Monitoring

Theranostic platforms can provide longitudinal information on nanoparticle localization, drug release, tumor response and treatment-associated changes. Imaging signals may change after a therapeutic event, such as activation of a fluorophore or alteration of photoacoustic contrast. This can support response-adaptive treatment. However, imaging biomarkers must be validated against pharmacokinetic, pathological and clinical outcomes before being used as reliable surrogate measures.[40]

9.9 Challenges and Future Perspective

Important challenges include reproducible membrane isolation and coating, preservation of membrane proteins, batch variability, protein-corona formation, long-term biocompatibility, clearance, scale-up and regulatory characterization. Multimodal probes may also become structurally complex. Future CMNP systems are likely to emphasize biodegradable or renal-clearable materials, NIR-II imaging, adaptive surface engineering, multimodal imaging and quantitative response monitoring. Clinical translation requires standardized characterization and rigorous pharmacokinetic, biodistribution, efficacy and safety evaluation.[40]

10.Applications Against Different Cancer Types

The therapeutic value of CMNPs is not restricted to one tumor type because the membrane source can be selected according to the biological barrier that must be overcome. Cancer-cell membranes can provide homotypic recognition and tumor-associated antigen presentation, whereas erythrocyte membranes mainly support prolonged circulation, platelet membranes can exploit tumor-associated vascular interactions, and immune-cell membranes can facilitate inflammatory or tumor-microenvironment targeting. The nanoparticle core can simultaneously provide drug loading, controlled release, photothermal or photodynamic activity, imaging, or gene delivery. This modularity makes CMNPs suitable for heterogeneous solid tumors, although most reported evidence remains preclinical[41,42]

Cancer type	Potential CMNP strategy	Therapeutic rationale
Breast cancer	Macrophage-,platelet-cancer-cell-or RBC-membrane coated NPs;chemo/photothermal combinations.	Tumor and metastasis targeting;prolonged circulation; improved tumor interaction;multimodal therapy
Colorectal cancer	RBC- or tumor-cell membrane-coated systems; starvation/enzyme-responsive cores.	Homotypic targeting and response to altered tumor metabolism/TME may improve local payload release
Hepatocellular carcinoma	Cancer-cell or immune-cell membrane-coated chemo-, gene- or immunotherapeutic systems.	Combines biological recognition with multimodal delivery; liver biodistribution requires careful safety assessment
Melanoma	Cancer-cell membrane-coated NPs with photothermal/photodynamic or immunostimulatory payloads.	Tumor antigens may support homotypic targeting or vaccine-like immune activation
Pancreatic cancer	Engineered CMNPs with TME-responsive release, immune modulation and combination therapy.	Dense stroma, poor penetration and chemotherapy resistance make barrier-aware biomimetic delivery attractive

Cancer type	Potential CMNP strategy	Therapeutic rationale
Glioblastoma	Stem-cell/immune-cell/cancer-cell membrane-coated NPs; receptor-targeted systems.	Designed to improve brain-tumor accumulation and overcome biological barriers; multifunctional imaging/therapy is possible

Glioblastoma and other difficult-to-treat cancers. Tumors with restrictive anatomical barriers, dense extracellular matrix, pronounced hypoxia, heterogeneous receptor expression or strong drug resistance may require multi-stage targeting rather than a single ligand–receptor interaction. CMNPs can combine immune evasion, barrier penetration, tumor-cell recognition and stimulus-responsive release. These systems should be tested in clinically relevant models because tumor accumulation in simplified xenografts may not predict performance in humans[43]

11. Combination and Next-Generation Strategies

The next generation of CMNPs is moving from simple biomimetic camouflage toward multifunctional systems integrating biological targeting with programmable physicochemical responses. Hybrid membranes, engineered membrane proteins and stimuli-responsive cores provide multiple layers of selectivity, which is important because cancer heterogeneity makes single-marker targeting insufficient for many tumors[43]

11.1 Hybrid cell membrane-coated nanoparticles

CMNPs Review Article Hybrid membranes combine complementary properties from two or more cell sources. An erythrocyte component may contribute prolonged circulation while a platelet, immune-cell or cancer-cell component contributes tumor-associated interactions. This can separate circulation and targeting functions within one platform. However, membrane composition, protein orientation and fusion efficiency require careful characterization[43]

11.2 Stimuli-responsive CMNPs

- **pH-responsive:** exploits mildly acidic tumor extracellular or endosomal/lysosomal environments to accelerate release or change surface properties.
- **Enzyme-responsive:** uses tumor-associated enzymes to cleave linkers, expose targeting motifs or destabilize the carrier.
- **ROS-responsive:** uses elevated oxidative stress to trigger bond cleavage, membrane disruption or therapeutic activation.
- **Temperature-responsive:** combines CMNPs with photothermal agents so local heating induces release or enhances cytotoxicity.[43,44]

11.3 Multi-targeted systems and TME targeting

Multi-targeted CMNPs can combine homotypic recognition with ligands, antibodies, peptides or TME-responsive mechanisms. Rather than relying only on tumor-cell binding, systems can address hypoxia, acidic pH, abnormal extracellular matrix, tumor-associated macrophages or immune suppression. Such multi-stage designs may improve penetration and reduce premature release, but they also increase formulation complexity and critical quality attributes.

11.4 AI/ML-assisted nanoparticle design

AI/ML can support optimization of nanoparticle size, composition, surface properties, loading, release, biodistribution and toxicity. For CMNPs, future models could integrate membrane proteomics, lipid composition, core formulation variables and patient/tumor biomarkers. Current limitations include small heterogeneous datasets, poor interoperability, limited interpretability and the need for experimental validation; AI should therefore be treated as decision support rather than a replacement for biological testing.[43]

11.5 Personalized cancer nanomedicine and smart theranostics

Patient-derived tumor membranes may preserve patient-specific tumor antigens and could support personalized targeting or vaccine-like approaches. Smart theranostic CMNPs can integrate imaging with therapy for tumor localization and treatment monitoring. The key limitation is the need for rapid, sterile and validated patient-specific manufacturing with reproducible potency and safety[44]

12. Preclinical Evidence and Clinical Translation

12.1 Biodistribution, tumor accumulation and pharmacokinetics

Biodistribution should quantify both the nanoparticle core and, where possible, the membrane-associated component. Fluorescent labels alone can misrepresent localization if the label dissociates. Complementary radiolabeling, ICP-MS, microscopy and membrane-protein analysis can provide

stronger evidence. PK should address circulation half-life, clearance, organ exposure and payload release; liver and spleen uptake are important because the mononuclear phagocyte system can dominate nanoparticle clearance [45]

12.2 Toxicology and biosafety

Safety assessment should include acute and repeated-dose toxicity, hematology, serum chemistry, histopathology, immunotoxicity, complement activation where relevant, hemolysis, coagulation and other product-specific risks. Cancer-cell-derived membranes raise additional concerns regarding residual nucleic acids, intracellular components and potentially oncogenic proteins; rigorous purification and characterization are therefore essential [44,45]

12.3 Manufacturing, scale-up and GMP compatibility

Clinical translation requires a reproducible manufacturing process producing membrane material and nanoparticles with predefined critical quality attributes. Membrane isolation, vesicle formation, nanoparticle coating, purification and sterile processing should be scalable. Microfluidics, membrane extrusion, microfluidization and tangential-flow filtration are potential scale-up tools. FDA guidance emphasizes linking nanomaterial properties, manufacturing changes, characterization, stability and controls to quality, safety and efficacy [45]

12.4 Batch-to-batch consistency, stability and storage

Membrane protein abundance/orientation, lipid composition, particle size distribution, aggregation, drug content and release can vary between batches. Stability programs should monitor membrane integrity, protein degradation, leakage, potency, aggregation and sterility. Cryopreservation or lyophilization may improve storage feasibility for selected systems but must be validated for preservation of membrane function [45]

12.5 Regulatory considerations and bench-to-bedside pathway

Regulatory assessment is product-specific because CMNPs combine a nanomaterial with a biologically derived membrane. Documentation should cover raw materials, cell/donor source, membrane isolation and purification, nanoparticle synthesis, coating, analytical characterization, release specifications, stability, sterility, toxicology and clinical benefit-risk. Current FDA nanomaterial guidance provides a useful framework, while CMNP-specific standards continue to evolve

The practical pathway is design → reproducible manufacture → characterization → GLP toxicology → regulatory submission → early clinical testing → dose optimization → efficacy trials[45,46]

13. Challenges and Limitations

CMNPs are more complex than conventional synthetic nanoparticles because the product contains a biologically derived membrane whose composition can vary with cell source, culture conditions, isolation method and processing. Major challenges are summarized below[47]

Challenge	Why it matters	Potential direction
Membrane isolation and purity	Residual cytosolic proteins, nucleic acids, organelles, endotoxin or other contaminants may alter safety and function.	Validated isolation, purification and orthogonal purity assays.
Batch variability	Membrane proteins/lipids determine targeting and immune behavior.	Defined sources, controlled culture, proteomic/lipidomic profiling and potency assays.
Protein preservation/orientation	Loss or inversion of functional membrane proteins may eliminate targeting or immune-evasion activity.	Gentle processing plus identity, abundance and orientation assays.
Aggregation/storage	Aggregation changes PK, biodistribution, injectability and safety.	Stabilization and validated storage/freezing-thaw or lyophilization.
Cost/scalability	Multi-step biological processing may be labor-intensive and difficult to standardize.	Automation, microfluidics, continuous processing and tangential-flow filtration.
Immunogenicity/long-term toxicity	Membrane components may activate complement, coagulation or immune pathways; repeat dosing may change responses.	Source selection, immune profiling and repeated-dose/long-term studies.

Challenge	Why it matters	Potential direction
Biodistribution uncertainty	Tumor accumulation varies with tumor type, vascularity, burden and host factors.	Quantitative biodistribution and clinically relevant models.
Tumor heterogeneity	Antigen/receptor expression varies between and within tumors.	Multi-targeting, patient stratification and personalized membranes.
Reproducibility/regulation	Complex biological products need well-defined CQAs and validated assays.	Consensus protocols, reference materials and product-specific regulatory strategies.

Key limitation: improved tumor targeting in animal models should not automatically be interpreted as clinical efficacy. Human tumor heterogeneity, immune status, prior therapy and membrane-source compatibility can substantially change CMNP performance. Translational studies should therefore include rigorous controls against uncoated nanoparticles, free drug, conventional targeted nanoparticles and membrane-only controls[47,48]

14. Future Perspectives

Future CMNP research should move from proof-of-concept formulations toward standardized, data-driven and clinically manufacturable platforms. The goal is not simply to increase tumor accumulation, but to create predictable therapeutic products whose identity, potency, safety and performance can be measured before administration.

14.1 AI/ML-assisted design

AI/ML may optimize membrane source, nanoparticle composition, size, surface properties, drug loading and release kinetics. Integration of omics datasets with formulation and in-vivo outcomes could support patient-specific design. Explainable models, standardized datasets and prospective validation will be necessary before AI-guided decisions can influence regulated development[47,48]

14.2 Patient-derived membranes and personalized therapy

Patient-derived tumor membranes offer individualized antigen matching and potentially personalized targeted carriers or vaccines. This is attractive for highly heterogeneous tumors, but rapid, sterile and validated manufacturing with consistent potency and safety will be essential [46,48]

14.3 Multi-membrane hybrid systems

Hybrid membranes can combine long circulation, tumor homing, immune-cell interaction and TME recognition. Rational membrane engineering may ultimately permit modular selection of membrane functions according to tumor phenotype, provided composition and functional contribution are quantitatively characterized[48]

14.4 Smart stimuli-responsive and theranostic systems

pH-, enzyme-, ROS- and temperature-responsive modules can reduce premature release and increase local specificity. Imaging probes can provide tumor localization and treatment monitoring. The benefit of theranostics must be balanced against added manufacturing and regulatory complexity.[47,48]

14.5 Combination with immunotherapy and TME modulation

Combining CMNPs with immune checkpoint blockade, immunostimulatory agents, tumor vaccines or macrophage/TME modulation may address tumor killing and immune suppression simultaneously. This strategy may be valuable for immunologically cold tumors, but immune activation must be balanced against systemic inflammatory toxicity[47,48]

14.6 GMP-compatible manufacturing and standardized characterization

Future protocols should define membrane identity, purity, protein retention/orientation, lipid composition, coating efficiency, particle size/PDI, drug loading, release, sterility, endotoxin, potency and stability. Reference materials and orthogonal assays would improve comparability and regulatory review.[48]

15. Conclusion

Cell membrane-coated nanoparticles represent a promising biomimetic approach for precision cancer nanomedicine because they combine the tunable physicochemical properties of nanoparticles with biological functions inherited from natural cell membranes. Depending on the membrane source, CMNPs can provide prolonged circulation, immune evasion, homotypic tumor recognition, vascular or immune-cell interactions and opportunities for

tumor-microenvironment targeting. These features can be integrated with chemotherapy, gene delivery, photothermal/photodynamic therapy, immunotherapy and imaging to create multifunctional therapeutic systems .[48]

Across breast, lung, colorectal, hepatocellular, melanoma, pancreatic and brain cancers, preclinical studies indicate that CMNPs can improve localization or therapeutic performance in selected experimental settings. Their diagnostic and theranostic potential is also important because membrane-associated targeting can be combined with imaging probes and stimulus-responsive release. Nevertheless, the evidence base remains dominated by laboratory and animal studies, and tumor heterogeneity means that no single CMNP design is likely to be universally optimal .[49]

The major barriers to clinical application are membrane isolation and purity, preservation of membrane proteins, batch-to-batch variability, aggregation and storage stability, manufacturing cost, scalability, immunogenicity, long-term toxicity, uncertain biodistribution and regulatory complexity. Development should therefore progress toward a quality-by-design framework in which critical material attributes and process parameters are linked to safety and therapeutic performance. FDA nanomaterial guidance supports rigorous characterization, control of manufacturing changes and stability assessment for nanomaterial-containing drug products.[48,49]

Future progress will depend on standardized membrane characterization, GMP-compatible manufacturing, clinically relevant tumor models, patient stratification, AI/ML-assisted formulation, personalized membranes, hybrid membrane systems and smart theranostic architectures. If these scientific and regulatory priorities are addressed, CMNPs could evolve from an experimentally powerful biomimetic concept into clinically useful precision nanomedicines. At present, their therapeutic promise should be interpreted as strong preclinical potential rather than established clinical efficacy.[50,51]

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