# Cell Membrane Engineering for Advancing Drug Delivery Against Infectious Diseases

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**Abstract**

Infectious diseases remain a significant global health challenge, exacerbated by the rise of antimicrobial resistance and the limitations of conventional drug delivery approaches. This chapter examines the potential of cell membrane engineering to enhance drug delivery strategies for combating infectious diseases. By harnessing the natural characteristics of cell membranes, researchers have developed innovative cell membrane-based nanocarriers, such as cell membrane-coated nanoparticles (CMC-NPs). These biomimetic therapeutic nanoplatforms offer enhanced biocompatibility, stability, targeted delivery, immune evasion, and treatment effectiveness, addressing critical challenges in treating infectious

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Z. Hussain, R. Pei (eds.), *Cell Membrane Engineering for Advancing Cell-Based and Nanotechnology-Based Therapies*, Biomaterials, Bioengineering and Sustainability 6, https://doi.org/10.1007/978-3-031-93425-4_15

diseases. The chapter explores the design and fabrication of CMC-NPs, including membrane extraction and coating techniques, and classifies them into two main types: singular-sourced and hybrid CMC-NPs. It provides a detailed discussion of the drug delivery mechanisms and highlights their potential applications in treating bacterial, viral, fungal, and parasitic infections. Furthermore, this chapter discusses the challenges of scalability, heterogeneity, and immune responses while outlining future directions for optimizing drug loading, release, and clinical translation. By integrating cutting-edge nanotechnology with biological principles, cell membrane-engineered nanoplatforms hold promises to transform the treatment of infectious diseases and improve global health outcomes.

**Keywords**

Cell membrane types · Membrane-coated nanoparticles · Drug delivery systems · Infectious diseases therapy · Nanomedicine · Biomimetic nanocarriers

## 15.1 Introduction

Infectious diseases remain one of the most critical global health challenges, contributing significantly to morbidity and mortality worldwide. Recent studies highlight that these diseases account for a substantial proportion of global deaths, particularly in developing nations where healthcare infrastructure and resources are often inadequate (World Health Organization (WHO) 2023). Diseases such as tuberculosis, malaria, and lower respiratory infections continue to be leading causes of death, with their impact exacerbated by factors like antimicrobial resistance, climate change, and population displacement. Furthermore, the zoonotic origin of many emerging infectious diseases complicates prevention and control efforts, underscoring the urgent need for integrated, multidisciplinary approaches to mitigate their impact (Bloom and Cadarette 2019). Addressing the burden of these diseases and implementing effective strategies are essential for reducing their toll on global health and achieving sustainable development goals (Ellwanger et al. 2021).

The alarming rise of antimicrobial resistance is compounding this challenge, rendering many common infections progressively harder to treat (Dadgostar 2019). Over 2.8 million cases of antimicrobial-resistant infections are reported annually in the United States alone, resulting in more than 35,000 deaths. Globally, antimicrobial resistance contributed to at least 1.27 million direct deaths and nearly 5 million associated fatalities in 2019. The COVID-19 pandemic has further exacerbated this crisis by increasing antibiotic use and disrupting healthcare systems (Klein et al. 2018; Farrell et al. 2021). Without urgent action, antimicrobial resistance deaths could exceed 10 million annually by 2050, underscoring the need for innovative solutions for infectious diseases management (Naghavi et al. 2024).

Infectious diseases arise from a diverse array of pathogens, encompassing bacterial infections (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA),

tuberculosis), viral infections (e.g., human immunodeficiency virus (HIV), hepatitis, COVID-19), fungal infections (e.g., *Candida albicans*, cryptococcal meningitis), and parasitic infections (e.g., malaria, leishmaniasis) (McArthur 2019). Each class presents distinct challenges in diagnosis, treatment, and prevention. Bacterial infections are becoming increasingly resistant to conventional antibiotics, viral infections demand complex antiviral regimens, fungal infections remain difficult to manage due to the limited availability of antifungal agents, and parasitic infections persist as endemic threats in resource-constrained settings. Furthermore, emerging infectious diseases, including those caused by novel viruses and multidrug-resistant strains, pose a critical challenge as no fully effective treatments or vaccines currently exist. These pressing concerns highlight the urgent need for innovative therapeutic strategies capable of addressing the dynamic and evolving landscape of infectious diseases (Strasfeld and Chou 2010; Bloom and Cadarette 2019; Hossain et al. 2023; Ikuta et al. 2024).

In response to these challenges, the proliferation of pharmaceutical science and the continuous development of new therapeutic agents have significantly transformed modern medical practices. A key focus in combating infectious diseases is delivering medications effectively to targeted tissues, ensuring optimal drug release at the infection site to maximize therapeutic efficacy and minimize side effects. As a result, contemporary pharmaceutical research is increasingly directed toward designing advanced drug delivery systems capable of selectively transporting therapeutics to precise disease locations (Mitragotri et al. 2014).

Recent advancements in material science and nanotechnology have paved the way for developing innovative nanoscale formulations, including micelles, liposomes, and nanoparticles (Muzammil et al. 2018). Many of these cutting-edge delivery systems are either already in clinical use or nearing clinical application, particularly in infectious diseases, where timely and effective treatment is paramount (Farokhzad and Langer 2009). Among these, liposomes have emerged as a promising drug carrier, with over ten categories of liposomal formulations having received regulatory approval and commercialization (Omolo et al. 2019). However, despite their success, traditional delivery systems like liposomes face limitations, including stability issues and challenges in replicating the complexity of natural cell membranes (Lian and Ho 2001).

A new frontier in drug delivery has emerged, leveraging a range of biomimetic platforms, including cell membrane-coated nanoparticles (CMC-NPs), extracellular vesicles, bacterial membrane vesicles, and whole-cell-based delivery systems (Liu and Huang 2022). At the core of these systems lies the fundamental role of cell membranes, which provide structural and functional advantages. Their intricate composition and diverse molecular landscape endow them with biocompatibility, immune evasion, and precise biological interactions, making them ideal candidates for targeted drug delivery. Recent advancements in cell membrane engineering, such as genetic modifications, click chemistry, hydrophobic insertion, and membrane fusion, have further refined these platforms to optimize their therapeutic potential (Zhai et al. 2017; Huang et al. 2024). Among these, CMC-NPs have garnered significant attention for their potential to integrate nanotechnology with the

biomimetic properties of natural cell membranes, offering superior biocompatibility, immune evasion, and targeting precision. By closely mimicking their source membranes, CMC-NPs effectively target drug-resistant pathogens while minimizing systemic toxicity. Their capacity to mimic natural cell-pathogen interactions positions them as a groundbreaking innovation in nanomedicine (Liu et al. 2023a, b).

This chapter will explore the foundational principles and recent advancements in cell membrane engineering for drug delivery against infectious diseases. We will examine various production techniques, unique characteristics, and applications of CMC-NPs, focusing on their role in infectious disease therapy. Additionally, we will highlight emerging opportunities and potential future developments in this field. By advancing cellular and biological membrane-based drug delivery methods, we anticipate significant improvements in treatment protocols for infectious diseases, ultimately enhancing patient outcomes and contributing to global public health.

Central to these advancements is the rise of biomimetic nanotechnology, which has revolutionized drug delivery by enabling the engineering of CMC-NPs. These innovative nanocarriers merge the distinctive attributes of NPs with the inherent characteristics of cellular membranes, including their biocompatibility, bioactivity, selective permeability, and ability to interact specifically with target cellular environments—thereby improving the stability and targeting efficiency of encapsulated therapeutics (Liu et al. 2023a, b; Zhang et al. 2024b). Integrating engineered cell membranes into NP designs has become a sophisticated strategy to enhance therapeutic efficacy, minimize systemic toxicity, and reduce immunogenic responses associated with conventional drug delivery systems (Yang et al. 2021; Imran et al. 2022). As a result, this approach has led to more efficient treatment options for various diseases, including infectious diseases (Li et al. 2023b).

## 15.2 Design and Fabrication of CMC-NPs

The design and fabrication of CMC-NPs are intricate, requiring a thorough understanding of cellular biology and nanotechnology applications (Li et al. 2024). Every stage of this procedure is vital so, that the resulting product delivers therapeutic payloads while retaining the beneficial features of source cell membranes. Various approaches have been used to prepare CMC-NPs. The classic preparation of CMC-NPs involves a top-down approach, which can be divided into three main steps: cell membrane extraction, inner core nanocarrier fabrication, and cell membrane coating, each key to the resulting NP functionalization (Liu et al. 2019; Liu et al. 2023a, b).

The design and preparation of CMC-NPs begin with the careful selection of a cell type for membrane isolation, which can include red blood cells, platelets, immune cells, cancer cells, or stem cells, each offering unique advantages based on their biological properties (Yaman et al. 2020). Once the cell type is chosen, the cell membranes are extracted and isolated using techniques that preserve their membrane contents and architecture (Liu et al. 2023a, b). Standard methods for

membrane isolation include hypotonic lysis, freeze-thaw cycles, ultrasonic disruption, and homogenization, each followed by centrifugation or ultrafiltration to separate membranes from intracellular contents (Spanjers and Städler 2020; Chugh et al. 2021; Javed et al. 2021). Hypotonic lysis, which relies on osmotic swelling to rupture cells, is simple and widely used but is primarily effective for red blood cells and less effective for other cell types (Xia et al. 2019; Le et al. 2021; Zhang et al. 2022). Freeze-thaw cycles, involving repeated freezing and thawing, are effective for isolating platelet membranes but risk damaging membrane integrity and protein activity if not carefully controlled (Wei et al. 2016). Ultrasonic disruption uses shock waves to rupture cells but is limited to small-scale applications due to heat generation, which can alter cell structures (Liu et al. 2022; Shen et al. 2023). Membrane isolation via homogenization, another mechanical process, is versatile and applicable for lysing a wide range of cell types, such as neutrophils and carcinoma cells (Kang et al. 2017; Oroojalian et al. 2021), but is energy-intensive and unsuitable for highly viscous samples (Liu et al. 2023a, b). Combining these methods can improve membrane quality and obtain satisfactory results (Shu 2024). Subsequent purification steps, such as differential or density gradient centrifugation, are employed to isolate membrane fragments from contaminants (Jiménez-Jiménez et al. 2020). These processes ensure the production of high-quality cell membranes for coating NPs, which is critical for their biomedical applications.

CMC-NPs utilize diverse NP templates, each offering unique properties that influence permeability, functionality, and therapeutic potential. Polymeric NPs, such as those made from poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), are highly versatile and biocompatible, enabling sustained drug release and tailored therapeutic applications (Qureshi et al. 2024). Liposomes, with their lipid bilayer structure, excel in encapsulating both water- and fat-soluble drugs, providing a dual-release system that enhances bioavailability and facilitates direct delivery to target cells (Liu et al. 2023a, b; Qureshi et al. 2024). Inorganic NPs, including gold, silver, and silica, are valued for their optical and electronic properties and ability to be functionalized for targeted delivery (Zou et al. 2020). Metal-organic frameworks (MOFs) are gaining attention for their high surface area and tunable pores, which improve drug loading and release. At the same time, cell membrane coating enhances targeting and reduces toxicity (Jiménez-Jiménez et al. 2020). Carbon-based NPs, such as carbon nanotubes and graphene oxide, offer high mechanical strength and large surface areas, making them ideal for drug delivery and imaging, especially when surface-modified for better biocompatibility (Liu et al. 2023a, b). Hybrid NPs combine different materials like polymers and inorganic components and capitalize on the strengths of each element to optimize performance. These NPs optimize stability, drug delivery efficiency, and customization for specific therapeutic needs (Liu et al. 2019; Liu et al. 2023a, b).

The production of NP cores involves techniques like solvent evaporation, coacervation, or electrospinning, followed by characterization using methods such as dynamic light scattering and scanning electron microscopy to ensure they meet application-specific requirements (Mahmood et al. 2017). Selecting the appropriate NP template is crucial for optimizing CMC-NPs, as each variant offers distinct

advantages that can be leveraged to enhance drug delivery systems (Alimohammadvand et al. 2024). This versatility is key to advancing nanomedicine and improving therapeutic outcomes across various medical fields.

Various methods have been developed to merge cell membrane vesicles with core NPs, each with distinct advantages and limitations. Membrane extrusion, a widely used technique, involves passing a mixture of NPs and membrane fragments through a porous membrane to achieve uniform coating, followed by centrifugation to separate unencapsulated vesicles. This method is scalable and produces NPs of consistent size but requires precise parameter control, which can be challenging for sensitive NPs (Liu et al. 2019; Ozsoy et al. 2024). Sonication uses ultrasonic waves to rapidly combine NPs with membrane fragments, making it versatile for different NP types (Fernández-Borbolla et al. 2024). However, it may generate heat, potentially damaging membrane proteins or NPs, and does not always ensure uniform NP size, necessitating careful optimization of parameters like duration, frequency, and intensity (Shi et al. 2022; Ozsoy et al. 2024). Microfluidic electroporation, a newer technique, employs high-voltage electric pulses to create temporary openings in cell membranes, allowing NPs to enter vesicles (Rao et al. 2017; Fang et al. 2018). This method preserves membrane integrity and surface proteins while offering scalability and storage potential, although it lacks standardized specifications for industrial production (Rao et al. 2017; Zou et al. 2020). Additionally, an innovative *in situ* encapsulation approach involves exposing live cells to NP cores, such as iron-oxide NPs, gold NPs, or quantum dots, which then release vesicles containing the NPs when cultured in serum-free media (Andriola Silva et al. 2013; Guan et al. 2024b). Each technique offers unique advantages and limitations, tailored to the specific application and characteristics of CMC-NPs. Key factors such as membrane coverage, size distribution, uniformity, and protein retention must be considered to optimize production efficiency and ensure high-quality outcomes (Liu et al. 2023a, b).

## 15.3 Major Types of CMC-NPs and Their Potential Scope

Several cell membrane types, such as erythrocytes/red blood cells (RBCs), platelet cells, cancer cells, neutrophil, and macrophage cells, stem cells, bacterial outer membranes, and hybrid cell membranes, can be used to create CMC-NPs (Baig et al. 2024). Each cell membrane vesicle offers unique advantages based on its biological functions, facilitating targeted drug delivery and enhanced efficacy.

### 15.3.1 Singular-Sourced Membrane-Coated NPs

#### 15.3.1.1 Erythrocyte Membrane-Coated Nanoparticles

NPs coated with erythrocyte membranes (EMC-NPs) represent a groundbreaking advancement in drug delivery, harnessing the unique biological properties of RBCs membranes to enhance therapeutic and diagnostic applications. These EMC-NPs encapsulate therapeutic agents within RBCs-derived membranes, significantly

improving biocompatibility, circulation time, and targeted delivery. The inherent biocompatibility of erythrocyte membranes, abundant in the human body, minimizes immune recognition, allowing EMC-NPs to evade the mononuclear phagocyte system and extend their presence in the bloodstream (Zhang et al. 2021a; Guan et al. 2024a). This immune evasion is further supported by surface proteins like CD47, which act as a "don't eat me" signal to macrophages, reducing clearance and enhancing drug bioavailability (Zhang et al. 2021a). Additionally, the lipid bilayer of erythrocyte membranes functions as a diffusion barrier, enabling controlled and sustained drug release, which is particularly beneficial for therapies requiring long-lasting therapeutic effects and reduced dosing frequency (Hu et al. 2011). EMC-NPs can also be conjugated with targeting ligands to improve precision, such as binding to receptors overexpressed on cancer cells, thereby enhancing therapeutic efficacy while minimizing off-target effects (Chen et al. 2018, 2021). Furthermore, the natural composition of erythrocyte membranes stabilizes the NPs, preventing aggregation and ensuring uniform dispersion in biological fluids, which is critical for maintaining therapeutic effectiveness during intravenous administration (Guo et al. 2023). By fusing the versatility of NP technology with the biocompatibility, stability, and targeting capabilities of erythrocyte membranes, EMC-NPs offer a promising platform for advancing drug delivery systems, with potential applications in improving clinical outcomes across various medical fields.

#### 15.3.1.2 Platelet Membrane-Coated NPs

Platelet membrane-coated NPs (PMC-NPs) represent a significant breakthrough in drug delivery systems, leveraging the natural biological functions of platelets to enhance therapeutic precision and efficacy. These NPs mimic platelets' inherent ability to target damaged blood vessels, inflamed tissues, and pathogens, making them particularly valuable in cancer therapy and infectious disease treatment (Han et al. 2022). The platelet membrane coating provides PMC-NPs with improved targeting capabilities, enhanced biocompatibility, and the ability to evade immune detection, which is critical for effective drug delivery (Wang et al. 2020b). For instance, their surface proteins enable specific interactions with subendothelial tissues and pathogens, allowing PMC-NPs to deliver therapeutic agents like siRNA to vascular damage sites with high precision, minimizing off-target effects (Wang et al. 2019; Zhuang et al. 2020). Additionally, surface markers such as CD47 help PMC-NPs avoid phagocytosis by macrophages, extending their circulation time and improving therapeutic outcomes (Wei et al. 2018a, 2019). The platelet membrane's lipid bilayer also facilitates controlled and sustained drug release, which is especially beneficial in cancer treatment, where maintaining therapeutic drug levels while reducing systemic toxicity is crucial (Zhou et al. 2021). PMC-NPs can be engineered to carry multiple therapeutic agents, such as chemotherapeutics, antibiotics, or anti-inflammatory drugs, enhancing their versatility in personalized medicine (Geng et al. 2023). Furthermore, their stability, high drug-loading capacity, and ability to incorporate additional targeting molecules make PMC-NPs a promising platform for addressing complex medical conditions, including atherosclerosis and cancer (Park et al. 2021; Feng and Zheng 2023; Fernández-Borbolla et al. 2024). By

combining the natural targeting and biocompatibility of platelet membranes with the versatility of NP technology, PMC-NPs offer a transformative approach to improving drug delivery systems and clinical outcomes.

#### 15.3.1.3 Neutrophil Membrane-Coated Nanoparticles

Neutrophil membrane-coated NPs (NMC-NPs) leverage the unique biological properties of neutrophils to create potent drug delivery systems, particularly for treating inflammatory and malignant conditions (Zhang et al. 2024a). Neutrophils, as key immune cells, possess surface markers and functional traits that enable NMC-NPs to target inflamed or infected tissues precisely (Li et al. 2023a). For instance, NMC-NPs can replicate neutrophils' ability to migrate toward chemokine signals, enhancing their localization at disease sites. This targeting is further facilitated by β2 integrins on neutrophil membranes, which bind to ICAM-1 on inflamed endothelium, improving vascular localization (Kang et al. 2017). NMC-NPs have shown promise in cancer therapy, particularly in combating metastasis, by exploiting neutrophils' natural tendency to navigate toward tumors. Their stability and therapeutic efficacy are bolstered by hydrophobic interactions and electrostatic repulsion between the neutrophil membrane and the NP core, ensuring efficient drug delivery (Kang et al. 2017; Wang et al. 2023). Additionally, NMC-NPs can cross biological barriers, such as the blood-pancreas barrier, making them valuable for treating pancreatic disorders (Xu et al. 2019). Their immunomodulatory properties, derived from neutrophil membrane components, allow them to regulate inflammation and enhance therapeutic outcomes in conditions like sepsis and chronic inflammatory diseases (Gao et al. 2017). Furthermore, the "self" properties of neutrophil membranes help NMC-NPs evade immune detection, extending their circulation time and improving drug delivery efficiency (Zhao et al. 2023). By harnessing innate targeting, immune-modulating capabilities, and prolonged circulation of neutrophils with NP technology, NMC-NPs represent a versatile and potent platform for advancing targeted and personalized therapeutic strategies.

#### 15.3.1.4 Macrophage Membrane-Coated Nanoparticles

Macrophages, key immune cells, play a critical role in inflammation, tissue repair, and pathogen clearance, making their membrane properties ideal for biomimetic NPs. (Zhang et al. 2021c; Hasan et al. 2023). Macrophage membrane-coated NPs (MMC-NPs) represent a notable innovation in targeted drug delivery, leveraging the natural biological functions of macrophages to enhance therapeutic precision and efficacy (Wu et al. 2022). MMC-NPs benefit from the innate ability of macrophages to migrate to inflamed or tumorous tissues, enabling targeted drug delivery to disease sites (Li et al. 2022; Sha et al. 2022). Surface proteins like CD47 on macrophage membranes help MMC-NPs evade immune detection, prolonging their circulation time and reducing clearance by the reticuloendothelial system (Tang et al. 2021; Wang et al. 2024). This immune evasion is crucial for achieving sustained therapeutic effects. Additionally, MMC-NPs exhibit enhanced biocompatibility, as the natural cell membrane coating improves integration with biological systems, minimizing adverse reactions and toxicity (Wu et al. 2022). Their stability

also protects encapsulated drugs from degradation, ensuring controlled release at target locations (Tang et al. 2021; Wang et al. 2024). Recent engineering advancements, such as genetic modifications and the incorporation of functional peptides, have further improved the targeting and therapeutic capabilities of MMC-NPs (Li et al. 2019; Duan et al. 2023). For instance, using M2 macrophage membranes, known for their anti-inflammatory properties, has shown promise in treating atherosclerosis and cancer (Wang et al. 2021b; Zou et al. 2024). Moreover, stimuli-responsive MMC-NPs, designed to release drugs in response to environmental cues like pH or temperature changes, offer precise control over drug delivery, reducing off-target effects (Liang et al. 2021; Feng and Zheng 2023). Thanks to the diverse spectrum of potential applications, engineering progress, and combination therapies, MMC-NPs hold immense potential for treating many diseases, including cancer, infections, and autoimmune disorders.

#### 15.3.1.5 Cancer Cell Membrane-Coated Nanoparticles

A cutting-edge approach in drug delivery systems, cancer cell membrane-coated NPs (CCM-NPs) harnesses the distinctive biological features of cancer cell membranes to boost therapeutic compounds' targeting, effectiveness, and safety. These NPs leverage tumor-specific surface markers and receptors, enabling precise homing to cancer cells and facilitating receptor-mediated endocytosis for efficient drug release (Hisato and Saya 2022; Guo et al. 2024). By mimicking cancer cells, CCM-NPs exhibit reduced immunogenicity, allowing them to evade the immune system and prolong their circulation time. This is critical for ensuring therapeutic agents reach their targets effectively (Harris et al. 2019; Zhang et al. 2024b). Additionally, CCM-NPs can co-deliver multiple therapeutic agents, such as chemotherapeutics and siRNAs, addressing various pathways involved in cancer growth and resistance, thereby overcoming the limitations of single-drug therapies (Zhang et al. 2020). Their ability to respond to tumor microenvironment stimuli, such as pH or enzyme activity, further enhances targeted drug release, minimizing off-target effects and improving therapeutic outcomes (Zeng et al. 2023). Moreover, using patient-derived cancer cell membranes enhances biocompatibility, reducing the risk of immune rejection and improving overall treatment acceptance (Li et al. 2023b).

#### 15.3.1.6 Stem Cell Membrane-Coated Nanoparticles

NPs coated with stem cell membranes (SCM-NPs) represent a transformative approach in drug delivery, leveraging the unique biological properties of stem cells to enhance therapeutic precision and efficacy. Stem cells' inherent ability to self-renew and migrate toward injured or diseased tissues, such as tumors, enables SCM-NPs to navigate complex biological environments effectively (Jiménez-Jiménez et al. 2020; Zhang et al. 2021c). This natural tropism, driven by chemokines and inflammatory signals, allows SCM-NPs to target tumor microenvironments with high specificity, improving cellular uptake and therapeutic outcomes (Wang and Wu 2022). The stem cell membrane coating reduces immunogenicity, enabling SCM-NPs to evade immune detection and extend their circulation time, which is critical for sustained drug delivery (Ma et al. 2019). The biocompatibility of

SCM-NPs, derived from natural stem cell membranes, minimizes the risk of adverse immune reactions, enhancing patient safety (Mei et al. 2024). These nanomaterials can encapsulate diverse therapeutic agents, including proteins, nucleic acids, and small molecules, enabling combination therapies that target multiple disease pathways simultaneously (Bose et al. 2018; Zou et al. 2023). In regenerative medicine, SCM-NPs offer a safer alternative to live stem cells by reducing tumorigenicity and immunogenicity while retaining therapeutic interactions with damaged tissues. For instance, SCM-NPs engineered to express CXCR4 have demonstrated improved targeting of ischemic tissues, showcasing their potential for precise and effective treatment (Bose et al. 2018).

### 15.3.2 Hybrid Cell Membrane-Coated Nanoparticles

Despite the potential of singular-sourced membrane-coated NPs, they often face limitations such as restricted functionalities, batch-to-batch variability, and limited capacity for multi-targeting, which can hinder their effectiveness in biomedical applications (Kroll et al. 2017). These limitations highlight the importance of developing hybrid cell membrane-coated NPs (HCM-NPs), which combine membranes from different cell types to enhance functionality. These hybrid platforms offer significant advantages over their counterparts by presenting a broader array of membrane ligands and receptors, improving biocompatibility, targeted delivery, and immune evasion (Yu et al. 2024). HCM-NPs expand upon the groundwork laid by CMC-NPs, which have shown significant promise in diverse biomedical applications. Scientists can develop NPs that replicate cells' inherent properties while augmenting their functional abilities by incorporating membranes from multiple cell types. For example, combining cancer cell membranes, which exhibit tumor-targeting characteristics, with erythrocyte membranes, renowned for their extended circulation periods, can produce NPs that successfully avoid immune system detection while concurrently targeting tumor locations (Dehaini et al. 2017; Zhao et al. 2021). This twofold functionality plays a vital role in enhancing the therapeutic efficacy of encapsulated drugs by reducing systemic toxicity and optimizing drug concentration at the target site.

The primary benefit of HCM-NPs is their capacity to provide NPs with a "self" signature, enabling them to bypass immune detection and extend their blood circulation time (Liao et al. 2020). For instance, coatings derived from RBCs membranes significantly reduce elimination by the mononuclear phagocyte system (Lu et al. 2023a), and when combined with other membrane types, they can introduce certain functions. Furthermore, merging various cell membranes can improve targeting accuracy. HCM-NPs, for instance, can achieve high-precision targeting by incorporating membrane proteins from cancer cells or immune cells (Han et al. 2024). Coatings derived from cancer cell membranes facilitate homotypic targeting, where the NPs preferentially attach to cancer cells of the same kind (Harris et al. 2019). Components from immune cell membranes can target inflamed or infected tissues precisely (Oroojalian et al. 2021).

The development of HCM-NPs creates opportunities for multifunctional applications by combining the characteristics of their source membranes. For instance, NPs coated with hybrid membranes from platelets (which target vascular injuries) and tumor cells (home to malignant growths) can simultaneously tackle thrombosis and cancer metastasis. Furthermore, the adaptability and inherent bioactivity of HCM-NPs are applied to various complex therapeutic approaches, such as gene therapy, immunotherapy, and targeted anti-inflammatory drug administration (Fang et al. 2018; Bahmani et al. 2021; Zeng et al. 2022). Consequently, HCM-NPs represent a groundbreaking strategy in drug delivery, merging the benefits of various biomimetic cell membranes with the flexibility of synthetic NP cores. Their exceptional abilities to avoid immune system detection, target specific cells, improve drug stability, and adapt to a range of therapeutic applications position HCM-NPs as top contenders for upcoming advancements in biomedicine.

## 15.4 Mechanisms of Drug Delivery Using CMC-NPs

CMC-NPs employ various mechanisms for drug delivery, which can be classified into several primary processes. These include targeted delivery methods (passive, active, and homotypic targeting), immune evasion and prolonged circulation, cellular uptake, and controlled release. Cell-specific targeting is a highly desirable characteristic that reduces unintended side effects when utilizing CMC-NPs for treating diseases. Passive targeting takes advantage of the enhanced permeability and retention effect, which enables NPs to accumulate in inflamed areas due to their porous blood vessels (Hao et al. 2021; Feng and Zheng 2023). On the other hand, active targeting involves modifying NPs with specific ligands or antibodies that bind to overexpressed receptors on target cells, such as integrins found on tumor blood vessels or ICAM-1 in inflamed tissues. This strategy significantly improves the precision of drug delivery and reduces off-target effects (Zeng and Pu 2020; Zhang et al. 2021b).

CMC-NPs also offer a unique approach to drug targeting by utilizing the natural adhesion properties of their source cells as an alternative to active targeting methods (Gao and Zhang 2015). This homotypic targeting plays a crucial role in biological processes. For instance, cancer cell-derived membranes express surface antigens that demonstrate homophilic adhesion, enabling CMC-NPs to target tumors of the exact origin (Gao and Zhang 2015). Similarly, NPs coated with platelet membranes can locate damaged blood vessels or inflammation sites due to platelets' innate attraction to injury areas (Qindeel et al. 2021). In systemic drug delivery, NPs with extended circulation times offer improved tissue targeting. Therefore, proper surface coatings are necessary to prevent the early uptake of NPs by reticuloendothelial system, prolong circulation, and effectively deliver NPs to the target tissues. CMC-NPs exploit the biomimetic features of cell membranes to evade immune detection. A critical protein on RBCs membranes, CD47, for example, interacts with macrophages' signal regulatory protein alpha to send a "don't eat me" signal (Russ et al. 2018). Furthermore, natural cell membranes delay bloodstream clearance, resulting

in more extended circulation than uncoated nanocarriers. Adding PEG or specific ligands to CMC-NPs can further extend circulation by reducing protein corona formation (Suk et al. 2016; Gao et al. 2021b).

Cellular uptake is another advantageous mechanism for drug delivery using CMC-NPs. These engineered nanocarriers have the potential to deliver their therapeutic payloads by exploiting several cellular uptake and release mechanisms, including receptor-mediated endocytosis, in which surface ligands on the NPs attach to specific receptors on target cells, triggering endocytosis and internalizing the nanocarrier into the cell (Yaman et al. 2020). Sometimes, the NP coating fuses directly with the target cell membrane, evading endocytosis and delivering drugs directly into the cytoplasm. This mechanism works exceptionally well for administering medications prone to endosomal degradation (Ju et al. 2020). The controlled release mechanisms of CMC-NPs are also a significant feature. Scientists can engineer NPs to respond to specific triggers, such as changes in pH or temperature, allowing for targeted drug delivery at the intended site. For instance, NPs sensitive to pH can discharge their therapeutic contents in the acidic environment surrounding tumors or infection sites, optimizing drug availability where it is most effective (Yang et al. 2018; Chai et al. 2019). This approach enhances treatment outcomes while reducing the systemic toxicity typically associated with traditional drug delivery methods. These pathways facilitate precise drug administration and improve therapeutic results by ensuring the payload effectively reaches its cellular target.

## 15.5 Applications of CMC-NPs in Infectious Disease Therapy

CMC-NPs have shown great potential for functioning effectively within the body due to their exceptional ability to mimic biological systems. This makes them an ideal foundation for various therapeutic applications, especially in the fight against infectious diseases (Narain et al. 2017a). CMC-NPs offer crucial advantages in targeted and sustained antimicrobial drug delivery, primarily through enhanced circulation time and improved biodistribution (Liu et al. 2023a, b). Various CMC-NPs have recently been utilized to combat pathogen infections, leveraging the intimate interactions between pathogens and cellular membranes (Li et al. 2023b). Researchers are developing these biomimetic nanocarriers to enhance the effectiveness of diverse antimicrobial substances in combating bacteria, viruses, and other disease-causing microorganisms. The next section explores the therapeutic applications of CMC-NPs in treating bacterial, viral, fungal, and parasitic infections. Table 15.1 summarizes reported CMC-NPs, detailing membrane sources, payloads, fabrication methods, and applications.

### 15.5.1 CMC-NPs for Bacterial Infections

Persistent pathogenic bacteria engage with their infectious microenvironment, shaping the development of cell membrane-coating strategies for enhanced

**Table 15.1** Summary of various CMC-NPs and their applications in combating infectious diseases

| Cell membrane source | Incorporated payloads | Fabrication techniques | Applications | References |
|---|---|---|---|---|
| *Bacterial infections* | | | | |
| Erythrocyte | Vancomycin-loaded nanogel | Membrane vesicle templated *in situ* | MRSA infections | Zhang et al. (2017) |
| | Tedizolid phosphate -PLGA NPs | Ultrasound method | MSSA and MRSA wound infection | Wu et al. (2021) |
| | Gold/polydopamine NPs | Extrusion | NIR photothermal therapy against MRSA infections | Bai et al. (2024) |
| Neutrophil | Sparfloxacin-loaded PCL-PEG NPs | Sonication method | MRSA pneumonia | Wang et al. (2020a) |
| | Antimicrobial peptide KLA-NPs | Ultrasound method | *K. Pneumoniae* lung infections | Liu et al. (2023a) |
| | Resolvin D1/ceftazidime | Extrusion | *P. aeruginosa* pneumonia | Gao et al. (2021a) |
| | Indocyanine green/rifampicin-loaded PLGA NPs | Co-extrusion | Photothermal-responsive therapy against *P. aeruginosa* infections | Li et al. (2023a) |
| | Fucoidan-loaded PLGA NPs | Sonication method | MRSA wound infection | Li et al. (2023c) |
| Macrophage | Silver-gold nanocage | Extrusion | Bone infection | Wang et al. (2018) |
| | $Ca_3(PO_4)_2/TiO_2$ magnetic nano-composite | Electroporation | | Shi et al. (2021) |
| | Triclosan/ciprofloxacin antimicrobial NPs | Homogenization | Intracellular *S. aureus* infections | Li et al. (2020) |
| | D-alanine-functionalized gold NPs | Extrusion | Cascade targeting photothermal therapy against intracellular *S. aureus* infections | Xiong et al. (2024) |
| | Antimicrobial peptide NPs | Co-extrusion | Bacterial sepsis | Meng et al. (2023) |
| | Silk fibroin NPs | Physical extrusion | Periodontitis | Deng et al. (2023) |
| Platelets | PLGA NPs | Sonication | Systemic *S. aureus* infections | Kim et al. (2021) |
| | Vancomycin-loaded Ag-MOFs | Ultrasound | MRSA infections | Huang et al. (2021) |
| | Fe/Zn-MOFs nanozyme | NA | *S. aureus* and *E. coli* wound infections | Shi et al. (2024) |
| Stem cells | FZ/MER-Ag-MOFs | Ultrasonic extrusion | Bacterial sepsis | Lu et al. (2023b) |

(continued)

**Table 15.1** (continued)

| Cell membrane source | Incorporated payloads | Fabrication techniques | Applications | References |
|---|---|---|---|---|
| Macrophage/ OMVs | Gold NPs | Extrusion | Nanovaccines against *P. aeruginosa* infections | Peng et al. (2024) |
| Macrophage/ RBCs | Black phosphorous QDs | Co-extrusion | Photothermal therapy | Liu et al. (2024a, b) |
| Platelets/RBCs | Fe3O4/ cinnamaldehyde-loaded sodium alginate NPs | Ultrasound | MRSA pneumonia | Hu et al. (2023) |
| *Viral infections* | | | | |
| T-cells | PLGA NPs | Sonication | HIV infections | Wei et al. (2018b) |
| Mosquito cell line | Gelatin NPs | Cell membrane cloaking | Zika virus | Rao et al. (2019) |
| RBCs Hepatocytes | CRISPR/Cas9 nanodrug | Extrusion | Hepatitis B infections | Wu et al. (2024) |
| Hybrid (393 T/ ACE-II cells/ human myeloid TPH1 cells | – | Sonication/ extrusion | COVID-19 | Rao et al. (2020) |
| ACE-II-rich cells | – | Extrusion | | Wang et al. (2021a, b, c) |
| | Quercetin-loaded PLGA NPs | Sonication | | Fang et al. (2024) |
| Macrophage | Lopinavir-loaded PLGA NPs | Sonication | | Tan et al. (2021) |
| Pulmonary alveolar epithelial cells | PLGA NPs | Extrusion | | Chen et al. (2024) |
| Alveolar macrophage | PLGA NPs | Sonication | | Li et al. (2021a, b) |
| *Fungal and parasitic infections* | | | | |
| *Streptococcus salivarius* K12 membranes | Triclosan-loaded PLGA NPs | Extrusion | Oral candidiasis | Ye et al. (2023) |
| Vaginal epithelial cells | $O_2$-dissolved perfluorocarbon | Ultrasonication | *Candida albicans* | Lin et al. (2023) |
| Macrophage | Natamycin-loaded PLGA NPs | Extrusion | Fungal keratitis | Liu et al. (2024a, b) |
| Brain microvascular epithelial cells | Dihydroartemisinin-loaded MSNs | – | Cerebral malaria | Wei et al. (2022) |
| Parasite membrane | PLGA NPs | Sonication | *Giardia lamblia* | Zhou et al. (2022) |

Abbreviations: *NPs* nanoparticles, *CMC-NPs* cell membrane-coated nanoparticles, *RBCs* red blood cells, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-sensitive *S. aureus*, *PLGA* poly(lactic-co-glycolic acid), *PCL-PEG* polycaprolactone-polyethylene glycol, *MOFs* metal-organic frameworks, *Ag* silver, *Fe* iron, *QDs* quantum dots, *NIR* near-infrared, *OMVs* outer membrane vesicles, *HIV* human immunodeficiency virus, *ACE-II* angiotensin-converting enzyme II, *MSNs* mesoporous silica nanoparticles

antimicrobial therapy. CMC-NPs effectively combat bacterial infections by evading immune detection, targeting pathogens, neutralizing toxins, enabling toxoid vaccine delivery, and ensuring prolonged circulation (Li et al. 2023b). This strategy positions CMC-NPs as promising candidates for targeted and sustained antibacterial therapies (Ai et al. 2018; Elhassan et al. 2022). Researchers investigated NPs enveloped in membranes extracted from various cellular sources within this domain. These membrane sources encompass erythrocytes, neutrophils, macrophages, platelets, stem cells, and hybrid cells. The potential applications of these diverse CMC-NPs in addressing bacterial infections are discussed.

Various nanosystems have been modified by applying erythrocyte membrane coatings to enhance antibiotic delivery. This approach reduces immune system clearance and extends blood circulation time, thereby improving the pharmacokinetic properties of antibiotic nanocarriers. Extensive research has been conducted to tackle the significant challenge of *S. aureus* and methicillin-resistant *S. aureus* (MRSA) infections. For example, researchers developed an RBC membrane-coated nanogel system (RBC-nanogel) to combat MRSA-associated toxins while facilitating targeted vancomycin delivery, thus enhancing treatment efficacy against this persistent pathogen. The RBC-nanogel acts as a decoy for MRSA-produced pore-forming toxins, boosting the immune response by encouraging bacterial uptake by immune cells and aiding in bacterial elimination (Zhang et al. 2017). In a similar vein, promising outcomes were demonstrated using a straightforward ultrasound technique to create RBC membrane-coated tedizolid phosphate (TR-701)-loaded PLGA NPs (TR-701-PLGA@RBC NPs) for addressing methicillin-sensitive *S. aureus* and MRSA wound infections (Wu et al. 2021). RBC membranes were recently extracted and coated onto gold/polydopamine NPs containing aptamer (Au/PDA@RBCM-aptamer) through extrusion for targeted near-infrared II photothermal therapy against *S. aureus* infections (Fig. 15.1). The encapsulation of Au/PDA@RBCM-aptamer with RBC membrane yielded the highest and most selective photothermal conversion capability and maximized localized therapeutic effect (Bai

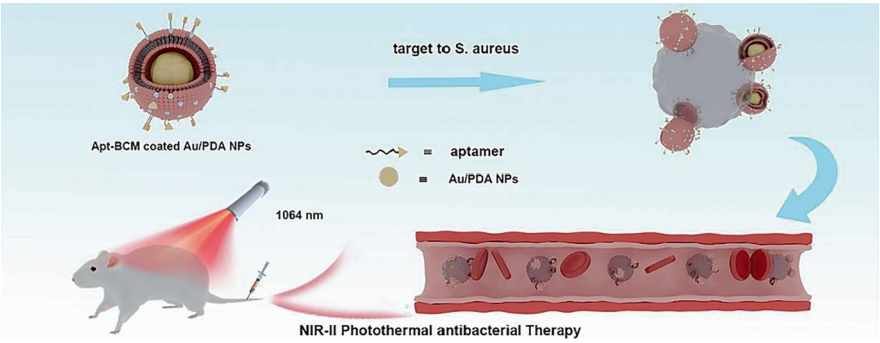


**Fig. 15.1** The scheme illustrates the design of RBC membrane-coated gold/polydopamine NPs for targeted near-infrared II (NIR-II) photothermal therapy against *S. aureus* infections. (Reproduced with permission from Bai et al. 2024, copyright 2024, Elsevier B.V.)

et al. 2024). While various strategies were implemented in these investigations, all engineered NPs demonstrated enhanced biocompatibility, controlled antibiotic release, improved antibacterial effectiveness, decreased immunogenicity, and substantial toxin-neutralization capabilities. These groundbreaking studies present promising approaches to combat susceptible and resistant *S. aureus* infections by developing biomimetic erythrocyte membrane-coated NPs.

Drawing inspiration from neutrophils' natural ability to target inflamed tissues, scientists have developed NPs coated with neutrophil membranes for targeted therapy of inflammation and bacterial infections. Studies have explored the application of NMC-NPs in treating lung infections. For example, one study examined NMC-NPs as an innovative targeted drug delivery system for addressing inflammation, particularly in pneumonia and other acute lung injuries. A straightforward sonication method was employed to coat polycaprolactone-polyethylene glycol NPs loaded with sparfloxacin using neutrophil membranes (SPX/PCL-PEG@NMC-NPs). The resulting NMC-NPs exhibited preserved functional integrity of neutrophil membranes, favorable biocompatibility, controlled drug release characteristics, enhanced antibacterial activity against MRSA, and notable interaction with pulmonary inflammation sites (Wang et al. 2020a). Also, through targeted therapy, scientists critically evaluated NMC-NPs' effectiveness in treating antibiotic-resistant *Klebsiella pneumoniae* (*K. pneumoniae*) lung infections. The study involved the creation of KLA-neutrophil NPs (KLA-NMC-NPs), which integrate the antimicrobial peptide KLA with neutrophil membranes to form a targeted delivery mechanism capable of efficiently infiltrating infected cells. The engineered KLA-NMC-NPs could bypass immune system detection, achieve highly efficient targeted accumulation at infection sites, and successfully impede the progression of pneumonia caused by *K. pneumoniae* (Liu et al. 2023a). Furthermore, NMC-NPs were utilized to concurrently deliver multiple drugs to target inflammatory pathways and disease-causing bacteria. One example is using nanovesicles derived from human neutrophil membranes to simultaneously deliver Resolvin D1, a potent anti-inflammatory agent, and ceftazidime antibiotic. This approach has been introduced for enhanced antibacterial treatment of pneumonia caused by *Pseudomonas aeruginosa* (*P. aeruginosa*). (Gao et al. 2021a). Moreover, an innovative neutrophil-inspired PLGA-NP (PLGA@NM NP) was successfully engineered to simultaneously carry the photothermal agent indocyanine green and the antibiotic rifampicin. This technology combines targeted photothermal therapy, stimulus-triggered antibiotic delivery, and *P. aeruginosa* endotoxin neutralization (Li et al. 2023a). NMC-NPs loaded with fucoidan were investigated to treat MRSA wound infections. The researchers sought to combine fucoidan's anti-inflammatory qualities with neutrophil membranes' targeted delivery capabilities to enhance fucoidan accumulation at infection sites, boost therapeutic effectiveness, and reduce systemic toxicity. (Li et al. 2023c). In summary, these studies highlight the promise of NMC-NPs in combating infamous multidrug-resistant bacterial infections. By harnessing neutrophils' natural targeting abilities and integrating cutting-edge drug delivery methods, this strategy offers a prospective remedy for the escalating issue of antibiotic resistance and related inflammatory complications in infectious diseases.

The plasma membranes of macrophages are equipped with various functional proteins, including toll-like receptors and pattern recognition receptors, which play a vital role in identifying and attaching to pathogens (Li and Wu 2021). Encapsulating NPs in membranes derived from macrophages allows the coated particles to seek out inflammatory areas, identify pathogens, and adhere to infectious agents such as bacteria (Khatoon et al. 2022). The use of macrophage membrane-coated NPs (MMC-NPs) in fighting infectious diseases is diverse. These biomimetic particles excel at locating infection sites due to their natural tendency to accumulate in inflamed areas, similar to macrophages. This property can be utilized to deliver antibiotics directly to infected regions, enhancing drug effectiveness while reducing unintended effects and overall toxicity in the body (Wang et al. 2024). Leveraging these advantages, numerous studies have employed macrophage membranes to create effective nano drug delivery systems for complex diseases involving both microbial infections and immune dysregulation. To illustrate, researchers have utilized macrophage membranes to encapsulate a photothermal silver-gold nanocage (SGNC@MM) and calcium phosphate/titanium dioxide magnetic nanocomposite ($Ca_3(PO_4)_2/TiO_2$@MM-NPs), substantially improving their antibacterial effectiveness in combating bone infections. These engineered nanocarriers demonstrated remarkable biocompatibility, extended blood circulation times, enhanced bacterial adhesion, superior anti-inflammatory characteristics, and improved tissue penetration capabilities (Wang et al. 2018; Shi et al. 2021). Advancements have also been made in using MMC-NPs to treat infections caused by intracellular bacteria, particularly *S. aureus*. One example is developing a macrophage-based antimicrobial system that responds to pH changes. This system, which combines triclosan and ciprofloxacin, is taken up by macrophages harboring intracellular staphylococci and shows improved antibacterial efficacy in the acidic phagosomal environment (Li et al. 2020). Another approach involves creating a novel macrophage-based system using D-alanine-functionalized gold NPs (DAu-NPs@MM). This innovative method employs cascade-targeting photothermal therapy to target and eliminate intracellular pathogens. The DAu-NPs@MM system demonstrated strong photothermal effects and exhibited exceptional cascade-targeting capabilities, allowing for precise and localized antibacterial action (Xiong et al. 2024). Furthermore, antimicrobial peptide NPs coated with macrophage membranes (AMP-NPs@MM) have shown promise in combating bacterial sepsis. These NPs exhibited improved stability, longer circulation time within macrophages, superior antibacterial and antibiofilm properties, and decreased cytokine levels, leading to improved therapeutic outcomes (Meng et al. 2023). Recently, genetically engineered macrophage membranes functionalized with TLR4 ligands have been employed to coat silk fibroin NPs to address antibacterial treatment and immune regulation in periodontitis. These macrophage-coated nanosystems effectively targeted harmful bacteria and reduced inflammation, thereby promoting healing in periodontal tissues affected by the disease (Deng et al. 2023). These findings demonstrate the encouraging potential of MMC-NPs as a revolutionary strategy for treating numerous bacterial infections, which may pave the way for further clinical applications.

PMC-NPs have shown significant potential in combating bacterial infections. These particles perform two crucial functions: neutralize toxins produced by bacteria and improve the delivery of antibacterial substances. For example, PMC-NPs effectively attach to and neutralize virulence factors, including toxins released by *S. aureus*, a significant contributor to invasive infections. This neutralization process safeguards immune cells, such as macrophages and neutrophils, maintaining their bacteria-killing abilities while decreasing inflammation (Kim et al. 2021). Furthermore, the distinctive characteristics of platelet membranes facilitate the creation of "decoy" NPs. These decoys intercept bacterial toxins before they can harm host cells, thereby reducing systemic toxicity and enhancing survival rates in severe infections such as bacteremia. Research has demonstrated that PMC-NPs effectively neutralize MRSA toxins, decrease bacterial populations in the bloodstream, and boost host survival in experimental models (Huang et al. 2021). PMC-NPs also enhance the targeted delivery of antibiotics, addressing a significant challenge in treating infected wounds. The platelet membrane coating improves the interaction between NPs and the wound environment, advancing bacterial-targeted therapy with potent antibacterial effects against common wound-causing pathogens. A recent investigation showcased the improved delivery of metal organic framework (MOF)-based nanozyme using a platelet membrane coating approach to combat wound infections caused by *Escherichia coli* and *S. aureus*. The developed PMC-nanozymes exhibited enhanced biodegradability, favorable metabolism, non-toxic accumulation, and significant antibacterial and antibiofilm activities. They also reduced inflammatory cytokine levels, improving targeting capabilities and accelerating wound healing (Shi et al. 2024). In conclusion, the capacity of PMC-NPs to neutralize toxins and precisely deliver antibiotics positions them as a crucial component in future therapeutic approaches against drug-resistant pathogens.

Stem cell membrane-coated NPs (SCM-NPs) show great promise in combating bacterial infections, including antibiotic-resistant ones. These particles employ a two-pronged strategy: precisely delivering antimicrobial agents and influencing the host's immune response (Ramos et al. 2024). Additionally, SCMs can boost antibiotic effectiveness, creating a combined effect that enhances bacterial elimination (Song et al. 2023). The stem cell membrane coating provides several benefits to the encapsulated NPs in treating bacterial infections. Firstly, the membrane's inherent characteristics enable the NPs to evade opsonization and clearance by phagocytes, resulting in extended circulation in the bloodstream and improved accumulation at infection sites. Secondly, the membranes possess adhesion molecules that enable direct interaction with bacteria or biofilms, allowing for specific targeting of pathogens (Wang et al. 2021a). Moreover, stem cell membranes, especially those from mesenchymal stem cells, exhibit anti-inflammatory and immunomodulatory properties vital in combating infections. These membranes can reduce the excessive inflammatory reactions typically seen in bacterial infections, thus lessening tissue harm and facilitating recovery (Johnson et al. 2017). Mesenchymal SCM-NPs have demonstrated increased accumulation at bacterial infection sites in preclinical studies, enhancing drug delivery and treatment effectiveness (Wang et al. 2021a). Similarly, researchers have created bone marrow-derived mesenchymal SCM-NPs

that combine anti-inflammatory and antimicrobial qualities to treat bacterial sepsis. These bioengineered NPs showed improved antibacterial action against MRSA and considerable anti-inflammatory effects through the modulation of inflammatory responses (Lu et al. 2023b).

Hybrid cell membranes (HCMs) have become a promising avenue in creating advanced materials for fighting bacterial infections. These membranes serve as multifunctional platforms that combine antibacterial, anti-inflammatory, and detoxification properties, making them essential in combating bacterial infections (Zhao et al. 2021). One example of this approach is the development of an antibacterial nanovaccine, which involves coating gold NPs (Au-NPs) with a hybrid membrane composed of bacterial outer membrane vesicles (OMVs) and macrophage membranes (Fig. 15.2). This system addresses *P. aeruginosa*-related infections by modulating immune responses and delivering effective bactericidal action (Peng et al. 2024). Furthermore, HCM-NPs were enhanced with photothermal agents to improve infection treatment. For instance, NPs that combine macrophage and RBCs membranes with black phosphorus quantum dots exhibit improved targeting of inflamed bacterial sites and enhanced bactericidal effects when exposed to near-infrared

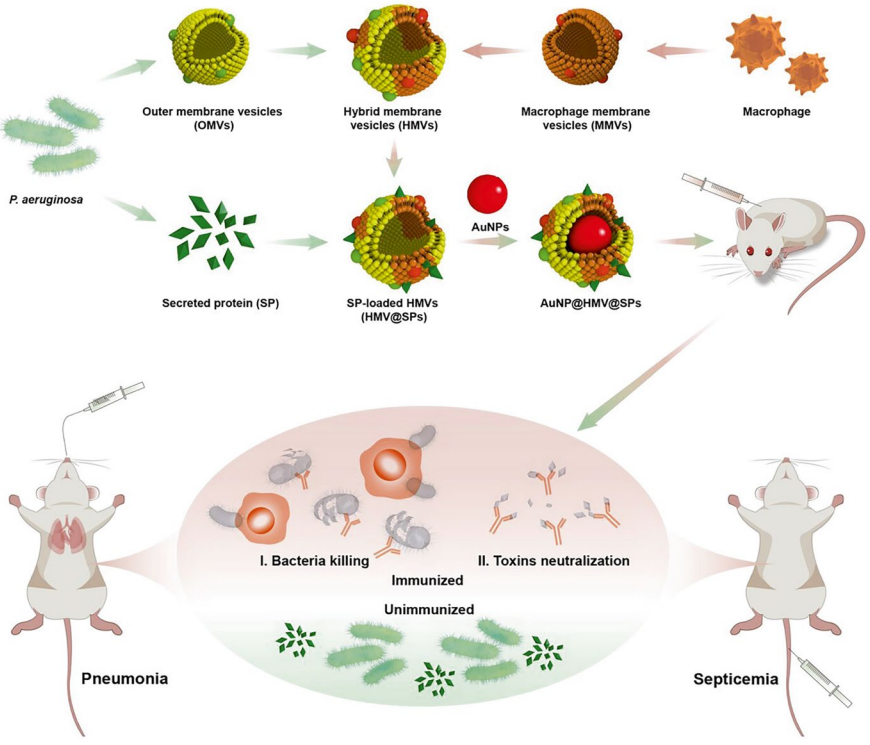


**Fig. 15.2** Schematic illustration of the development and use of multi-antigenic hybrid cell membrane-based Au NPs vaccine against *P. aeruginosa* infection. (Reproduced with permission from Peng et al. 2024, copyright 2024, Wiley-VCH GmbH)

light. These strategies show potential for addressing infections caused by biofilm-forming bacteria (Liu et al. 2024a, b). Additionally, researchers have developed a ferroptosis-inducing agent based on iron oxide ($Fe_3O_4$) by encapsulating $Fe_3O_4$/cinnamaldehyde NPs within a composite membrane derived from RBCs and platelets. This approach was designed to induce ferroptosis in MRSA, disrupt bacterial communication through quorum sensing, and eradicate biofilm, ultimately providing effective treatment for severe MRSA pneumonia (Hu et al. 2023). These biomimetic NPs show potential in fighting MRSA infections by simultaneously targeting several crucial aspects of bacterial pathogenesis, including biofilm development, virulence factors, and survival mechanisms. Cell membrane coatings present a multifaceted and potent strategy for addressing bacterial infections. These systems incorporate diverse biological and chemical elements to improve targeting, counteract toxins, and deliver strong antibacterial and anti-inflammatory effects. As a result, they show great potential for clinical use in managing infections. Ongoing research in this field is expected to transform infection treatment, offering new possibilities for tackling some of the most critical global health challenges.

### 15.5.2 CMC-NPs for Viral Infections

Cell membrane coating technology has shown promise in fighting viral infections by creating decoys that mimic natural cell membranes to neutralize viruses. Research has explored the potential advantages and demonstrated effectiveness in treating conditions such as HIV, Zika virus (ZIKV), and Hepatitis B. In this approach, the pathogen can be tricked into binding with a CMC-NP target instead of its intended host cell. For example, researchers have developed T-cell-mimicking NPs (TNPs) by applying plasma membranes from CD4+ T cells to polymeric cores. These TNPs acquire important surface antigens, including the CD4 receptor and CCR5 or CXCR4 coreceptors, crucial for HIV attachment. By serving as decoys, TNPs can redirect HIV away from its intended targets, effectively neutralizing the virus without exerting intense selective pressure that might lead to resistance (Wei et al. 2018b). Similarly, a biomimetic nano decoy (ND) was proposed as a systemic defense against the ZIKV. This ND, composed of a gelatin NP core wrapped in mosquito medium host cell membranes, shows efficient ZIKV adsorption and inhibition of its replication in susceptible cells. The capture of ZIKV by NDs effectively prevents ZIKV transmission across physiological barriers, thus reducing the incidence of ZIKV-induced fetal microcephaly (Rao et al. 2019). CMC techniques have also shown promise in combating hepatitis B (HBV) infection. For example, CRISPR/Cas9 nanodelivery systems modified with RBC or hepatocyte membranes have demonstrated targeted delivery and significant reduction of HBV DNA in infected hepatic cells, without causing notable toxicity to the liver or kidneys. These membrane modifications enhanced the NPs' biocompatibility and decreased their elimination by the reticuloendothelial system, resulting in extended circulation time in the blood. This novel approach offers a potential therapeutic avenue for advancing HBV treatment (Wu et al. 2024).

The global outbreak of COVID-19, triggered by SARS-CoV-2, has led to unparalleled worldwide initiatives to create effective treatments and preventive measures. In this context, CMC-NPs have emerged as a promising tool for combatting viral infections. These NPs replicate the inherent characteristics of biological membranes, offering an innovative approach to enhance biointerfacing, optimize drug delivery, neutralize viruses, and regulate immune responses. This biomimetic strategy presents unique benefits for targeting SARS-CoV-2 and alleviating the severe manifestations of COVID-19 (Pereira-Silva et al. 2021). For example, CMC-NPs can function as decoys, intercepting and neutralizing SARS-CoV-2 before host cell infection. NPs coated with biological membranes from cells that express the ACE2 receptor can capture the virus, inhibiting its attachment to and entry into human cells (Rao et al. 2020; Li et al. 2021a, b; Wang et al. 2021a, b, c; Fang et al. 2024). These NPs also can absorb inflammatory cytokines, including interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are found in elevated levels during COVID-19 infections (Rao et al. 2020; Tan et al. 2021). This two-fold functionality aids in decreasing inflammation and alleviating immune disorders linked to the disease. Specific formulations, such as those utilizing pulmonary alveolar epithelial cell membranes, display antifouling characteristics that safeguard their neutralization capabilities by preventing protein corona formation in blood circulation, thus preserving their efficacy *in vivo* (Chen et al. 2024). Furthermore, NDs derived from lung spheroid cells have demonstrated the ability to remain in the lungs for extended durations when administered through inhalation, enhancing viral clearance and diminishing lung injury without observable toxicity (Li et al. 2021a, b). An additional approach of using macrophage biomimetic nanocarriers could decrease viral burdens and inflammatory responses in COVID-19 studies. The encapsulation of NPs within macrophage membrane vesicles enables targeted drug delivery to inflamed areas, improving therapeutic outcomes and minimizing systemic adverse effects (Tan et al. 2021). Certain NPs incorporate photothermal materials, allowing them to disrupt viral particles when exposed to near-infrared irradiation (NIR), offering a dual approach to antiviral and anti-inflammatory treatment (Li et al. 2021a, b).

Overall, CMC-NPs offer a multifaceted, cutting-edge solution for addressing viral infections. These nanocarriers exploit their capacity to imitate natural cell surfaces, effectively neutralizing viruses and influencing immune responses. This approach presents a promising direction for both therapeutic and preventive strategies. As scientific investigations continue, these technologies may prove instrumental in addressing present and future viral outbreaks.

### 15.5.3 CMC-NPs for Fungal and Parasitic Infections

Drug-resistant fungal infections present a significant obstacle in medical care. Researchers have explored biomimetic strategies, including cell membrane coating technology, to tackle this issue. One such approach involves the development of

biomimetic nanoplatforms designed to target *Candida albicans*, a prevalent fungal pathogen. These platforms employ CMC-NPs to specifically attach to the pathogen, improving the delivery and effectiveness of antifungal medications while shielding healthy cells from harm. In one study, researchers created triclosan-loaded PLGA NPs encased in *Streptococcus salivarius* K12 membranes (K12/TCS@PLGA-NPs) using an extrusion method to combat *Candida albicans* and oral candidiasis (Ye et al. 2023). Another investigation led to the development of an oxygen-dissolved perfluorocarbon disguised by a photosensitizer-loaded vaginal epithelial cell membrane for treating intravaginal *Candida albicans* (Lin et al. 2023). Moreover, CMC-NPs were utilized to treat fungal keratitis (FK), a severe infectious disease of the cornea that is the primary cause of blindness. A recent investigation examined the effectiveness and safety of NPs coated with macrophage membranes for delivering natamycin (NAT) in FK therapy (Liu et al. 2024a, b). All the reported CMC-NPs demonstrated improved concentrations of antimicrobial agents in affected areas while shielding healthy tissues from toxic effects. These approaches boost the antifungal properties of the cargoes and maximize their overall therapeutic efficacy. Despite the promising outcomes of using CMC-NPs in combating fungal infections, limited research has been conducted in this area. Consequently, there is a significant need to address the substantial knowledge gap in this field to enhance the efficacy of cell membrane coating technology against fungal-induced infectious diseases.

Parasitic infections pose a major global health challenge, with conventional treatments often facing issues of drug resistance and reduced effectiveness. In this context, NPs have emerged as a promising alternative, offering innovative approaches to combat parasites. These NPs utilize various mechanisms to target parasites, such as disrupting their plasma membranes, inhibiting protein production, and generating free radicals (Bajwa et al. 2022). These strategies have shown the potential to eliminate parasitic organisms effectively. Researchers have developed specialized biomimetic CMC-NPs to combat parasitic infections. One notable example is an NP formulation designed to treat cerebral malaria, a severe condition caused by *Plasmodium falciparum*. This formulation is coated with membranes from brain microvascular endothelial cells, which enhances its ability to deliver drugs to infected red blood cells (Fig. 15.3). Additionally, it helps protect crucial organs from damage caused by the infection. Studies using experimental models showed that this approach improves survival rates (Wei et al. 2022). Furthermore, vaccines created using NPs coated with native parasite membranes have demonstrated the ability to elicit protective immunity against *Giardia lamblia*, highlighting the potential of this approach in vaccine creation (Zhou et al. 2022). Taken together, the technique of cell membrane coating shows promise for enhancing treatment efficacy and improving patient outcomes in combating parasitic infections. Nevertheless, this field of study is still in its early stages, and additional research is necessary to address the considerable knowledge gap in this area.

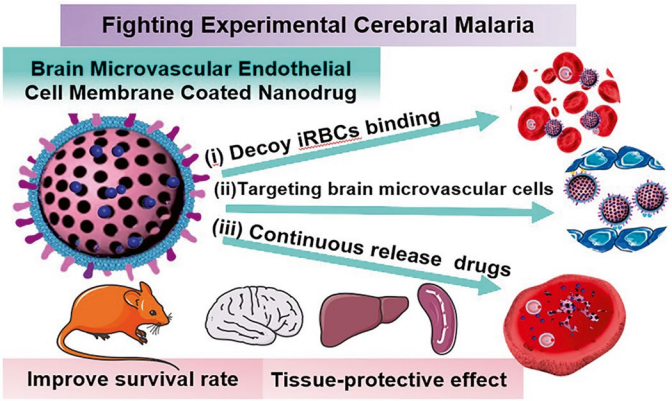


**Fig. 15.3** Scheme illustrating the mechanisms and potential of the CMC-nanodrug in fighting against cerebral malaria. (Reproduced with permission from Wei et al. 2022, copyright 2022, American Chemical Society)

## 15.6 CMC-NPs: Advantages and Limitations

CMC-NPs have emerged as a promising platform in nanomedicine, offering unique advantages in drug delivery, immune evasion, and targeted therapy. However, their translation from laboratory research to clinical applications faces several challenges. This section comprehensively analyzes the advantages, limitations, and future directions for CMC-NPs, focusing on key thematic areas such as manufacturing, targeting, and clinical translation.

### 15.6.1 Manufacturing and Scalability

One of the most significant advantages of CMC-NPs lies in their biomimetic properties, which enable enhanced biocompatibility, immune evasion, and targeted drug delivery. By leveraging the natural properties of cell membranes, CMC-NPs can mimic biological systems, reducing immune system clearance and extending circulation time (Liu et al. 2019; Ai et al. 2020). However, the manufacturing process of CMC-NPs is complex and labor-intensive, involving the extraction of cell membranes and their subsequent coating onto nanoparticle cores. This complexity often leads to inconsistencies between batches, hindering large-scale production and standardization (Kroll et al. 2017; Zhao et al. 2021). Future research should prioritize scalable and reproducible manufacturing to overcome these challenges. Microfluidic technologies and automated systems could offer solutions by ensuring consistency and quality control (Rao et al. 2017; Fang et al. 2018). Additionally, advancements in membrane extraction techniques, such as improved hypotonic lysis and freeze-thaw cycles, could enhance the yield and quality of cell membranes, making the production process more efficient (Spanjers and Städler 2020; Chugh et al. 2021; Javed et al. 2021).

### 15.6.2 Targeting Efficiency and Specificity

CMC-NPs exhibit inherent targeting capabilities due to their membrane composition, which allows them to interact with specific cellular environments. This targeting precision is crucial for applications such as drug delivery, where it minimizes off-target effects and enhances therapeutic efficacy (Rao et al. 2017; Zou et al. 2020). However, achieving precise delivery to diseased tissues remains a challenge. For instance, while NMC-NPs can target inflamed tissues, they may struggle to differentiate between various types of inflammation, such as infection versus autoimmune responses (Zhang et al. 2024b). Future research should explore strategies to enhance targeting specificity by incorporating additional ligands or stimuli-responsive elements that bind selectively to disease-specific markers. Genetic engineering and synthetic biology could enable the design of membranes with improved targeting properties, allowing for more precise delivery of therapeutic agents (Yang et al. 2021; Imran et al. 2022). Furthermore, developing HCM-NPs, which combine membranes from different cell types, could offer multifunctional platforms with enhanced targeting capabilities (Yu et al. 2024).

### 15.6.3 Clinical Translation and Biocompatibility

Several factors, including potential immune responses, biological stability, and regulatory challenges, complicate the clinical translation of CMC-NPs. Although CMC-NPs are designed to evade immune detection, there remains a risk of triggering immune responses, especially when using membranes from heterologous sources (Kroll et al. 2017). Long-term biocompatibility studies are essential to ensure the safety of these systems in clinical applications (Zhang et al. 2024b). Regulatory and ethical considerations also pose significant hurdles. Using human-derived cell membranes raises concerns about donor consent, safety, and potential contamination with pathogens or oncogenic factors (Narain et al. 2017a, b). Future efforts should involve close collaboration with regulatory agencies to establish clear guidelines for the development and clinical testing of CMC-NPs. Ethical considerations, such as the sourcing of cells and the potential for misuse, must also be addressed to ensure responsible innovation (Zhai et al. 2017; Huang et al. 2024).

## 15.7 Conclusion and Future Outlook

CMC-NPs represent a transformative approach to drug delivery, leveraging the natural properties of cell membranes to achieve enhanced biocompatibility, immune evasion, and targeted therapy. Their ability to neutralize bacterial toxins, prolong circulation time, and precisely deliver drugs to infection sites underscores their potential in combating infectious diseases. Despite these advantages, challenges remain in scalability, immune compatibility, and clinical translation—hurdles that must be addressed to realize the promise of CMC-NPs fully. Looking ahead, the

future of CMC-NPs is bright, provided research focuses on optimizing fabrication techniques (e.g., membrane isolation and coating methods) to ensure batch-to-batch consistency and therapeutic efficacy. Integrating emerging technologies, such as artificial intelligence for design optimization and advanced imaging for real-time tracking, could enhance their precision and performance. Beyond infectious diseases, expanding applications to cancer, autoimmune disorders, and regenerative medicine may unlock groundbreaking therapeutic avenues (Yu et al. 2024; Guo et al. 2024). Future studies should also explore CMC-NPs for fungal, viral, and parasitic infections, broadening their impact on global health challenges like antimicrobial resistance. Ultimately, interdisciplinary collaboration and sustained innovation will be pivotal in bridging the gap between preclinical development and clinical implementation. As CMC-NP technology evolves, it holds immense potential to revolutionize nanomedicine, offering targeted, efficient, and adaptable solutions for various diseases. By refining their design and expanding their scope, CMC-NPs could emerge as a cornerstone of next-generation drug delivery systems, reshaping the landscape of modern therapeutics.

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