

# Cell Membrane-Coated Nanoparticles: Advanced Drug Delivery Systems for Chronic Wound Healing Therapy

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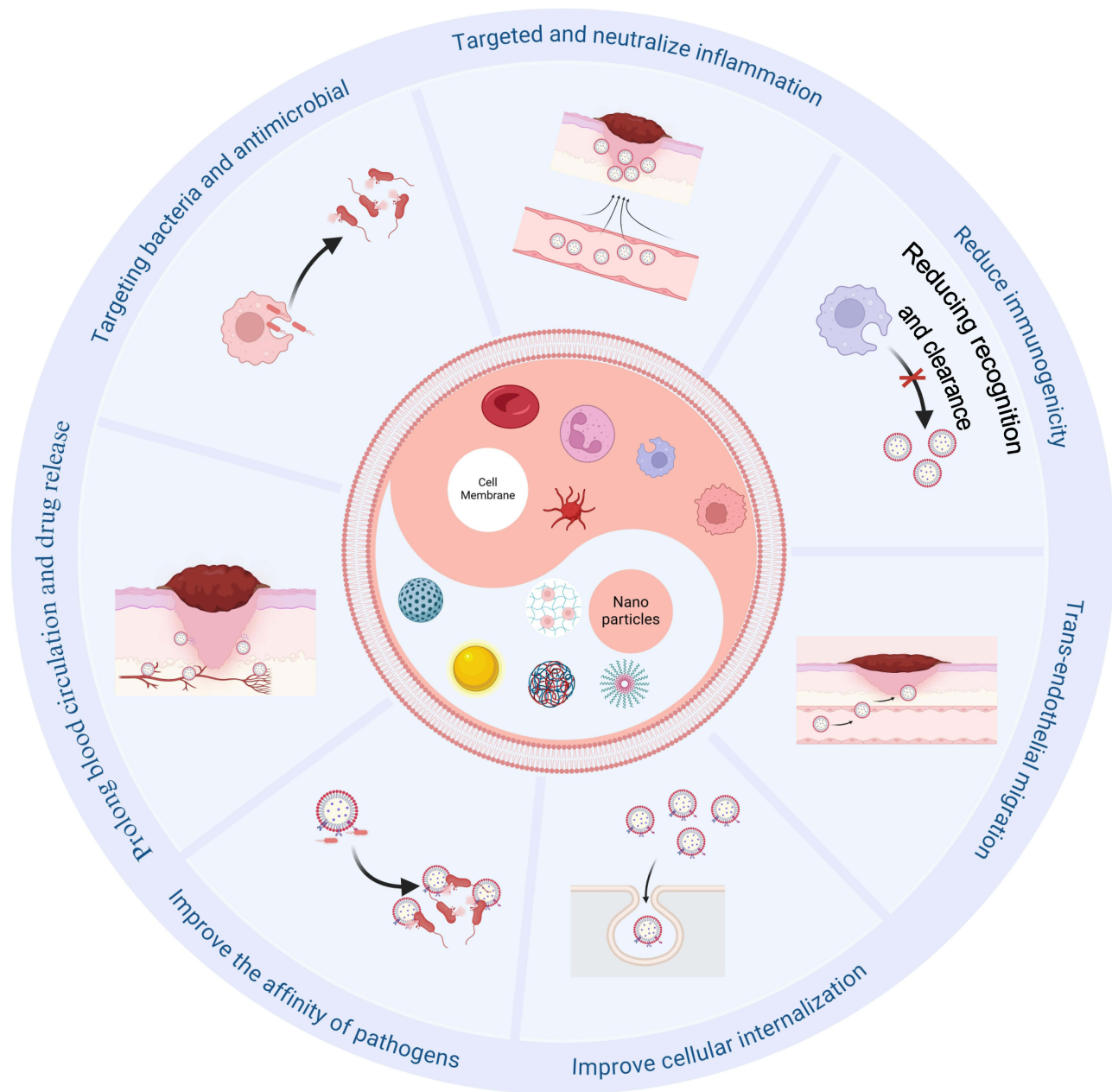
**Abstract:** Cell membrane-coated nanoparticles (CMNPs) have emerged as a promising platform for targeted drug delivery and therapeutic applications due to their unique properties, such as improved biocompatibility, prolonged circulation time, and ability to mimic natural cell functions. The preparation of CMNPs involves three critical stages: extraction of the cell membrane, preparation of the nanoparticle core, and membrane coating. The cell membrane is isolated through various methods, including hypotonic lysis, freeze-thaw cycles, and centrifugation, with careful attention paid to preserving its integrity and functionality. Nanoparticle cores, which can be organic (eg, PLGA, liposomes) or inorganic (eg, metal-based cores), offer distinct advantages in terms of drug loading capacity, stability, and therapeutic potential. The fusion of the core and the membrane is typically achieved through techniques such as membrane extrusion, sonication, and electroporation. These methods enable the efficient formation of core-shell nanostructures, which can be utilized for a range of biomedical applications, particularly in drug delivery, cancer therapy, and tissue regeneration. This review discusses the key aspects of CMNP preparation, including membrane extraction and purification techniques, core selection, and fusion methods, as well as the current trends and future directions in the development of CMNPs for therapeutic purposes.

**Keywords:** cell membrane-coated nanoparticles, drug delivery, wound healing, nanoparticles, chronic wound healing

## Introduction

Chronic non-healing wounds (CRWs) are defined as wounds that fail to achieve complete structural and functional repair within the expected timeframe, despite receiving standard systemic treatments. Due to their complex pathogenesis, prolonged course, and poor prognosis, CRWs present one of the most challenging clinical problems.<sup>1,2</sup> Based on their complicated mechanisms of pathogenesis, chronic wounds are often categorized into seven subtypes: diabetic foot ulcers, pressure ulcers, burns, surgical incisions, neuropathic ulcers, arterial ulcers, and venous ulcers. Among these, non-healing pressure ulcers (NHPUs), venous ulcers (VUs), and diabetic foot ulcers (DFUs) are the most common.<sup>3,4</sup> In recent years, the prevalence of chronic wound patients has surged, primarily due to the increasing numbers of individuals with conditions such as diabetes and obesity, in addition to external physical injuries.<sup>5,6</sup> In the United States, chronic wounds affect approximately 10.5 million Medicare beneficiaries (an increase of 2.3 million compared to 2014), with annual treatment costs exceeding \$25 billion.<sup>7,8</sup> Despite this, there are still numerous challenges in rapidly and efficiently promoting the healing of skin wounds.

Graphical Abstract



At present, the clinical treatment of chronic wounds mainly relies on traditional methods such as debridement, dressing coverage, negative pressure drainage, and hyperbaric oxygen therapy, as well as emerging biological therapies such as growth factor and stem cell therapy. However, all these strategies have obvious limitations:<sup>9-15</sup> traditional debridement and dressing replacement can only provide a basic physical barrier and passive healing environment, and are unable to actively regulate the microenvironment of the wound surface. Systemic antibiotic administration is difficult to achieve an effective concentration at the infection site and is prone to drug resistance. Exogenous growth factors and stem cells, however, are confronted with bottlenecks such as poor stability *in vivo*, low survival rates, and insufficient targeting.

In response to these challenges, researchers have proposed many new therapeutic methods in wound healing studies, aiming to develop effective treatments for various stages of wound healing, or even for the entire process. Since wounds

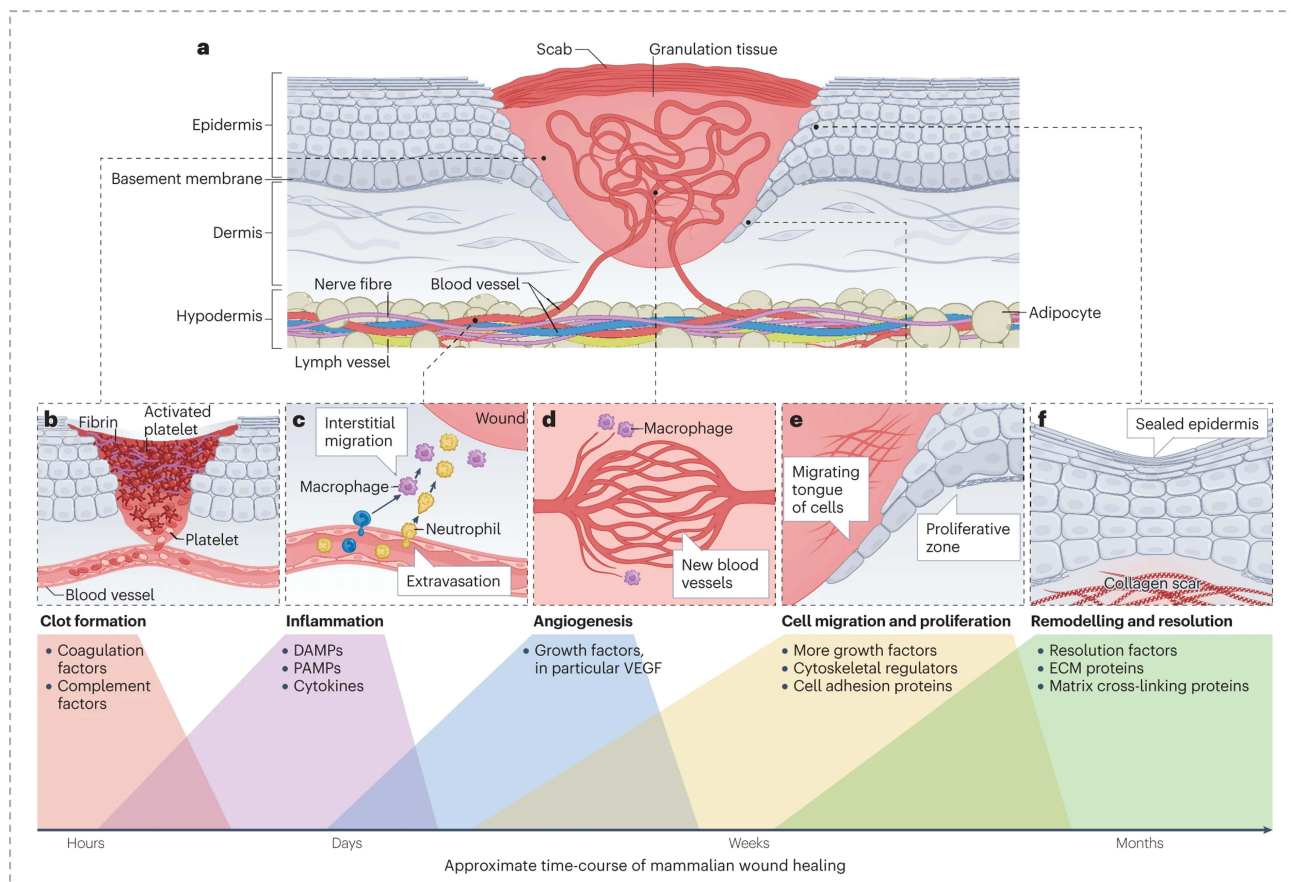
exhibit differences in molecular and cellular mechanisms, the treatment strategies for these injuries are diverse.<sup>16</sup> The emergence of nanoparticle (NPs) technology has provided a new approach to overcoming the aforementioned limitations. In recent years, localized drug delivery strategies using nanoparticles (NPs), stem cells, bioprinting, extracellular matrix (ECM), platelet-rich plasma, cold atmospheric plasma, and microRNAs have been increasingly applied in the treatment of CRWs. These strategies can be used to initiate and maintain cellular functions, activate collagen synthesis, promote angiogenesis, regulate cytokines, activate growth factors (GFs), and provide antimicrobial effects, among other functions.<sup>17</sup> Among these, various types of nanoparticles have been widely used in wound healing therapy due to their unique properties.<sup>18</sup> NPs, with its nanoscale size effect, can effectively penetrate the biofilm barrier, protect the active ingredients of drugs from degradation, and accumulate locally in the wound through the enhanced penetration and retention effect (EPR).<sup>19,20</sup> These nanoparticles can also load various drugs, enhancing the stability and solubility of the encapsulated agents, facilitating transmembrane transport, prolonging circulation time, and improving safety and efficacy.<sup>21,22</sup> For example, mesoporous silica nanoparticles (MSNs), with their unique mesoporous structure, large surface area, high loading capacity, stable pore volume, controllable particle size, ease of surface functionalization, and excellent biocompatibility and biodegradability, make them excellent substrates for constructing various nanocomposite drug delivery systems.<sup>23</sup> Through special design, MSNs have significantly accelerated the healing process of diabetic wounds (DWs) and infectious wounds.<sup>24–26</sup> Common engineered precision nanoparticles for drug delivery include polymeric nanoparticles, inorganic nanoparticles, and lipid nanoparticles, each of which has multiple subtypes with distinct advantages and disadvantages in drug loading, delivery efficiency, and patient response.<sup>27</sup>

However, most nanoparticle platforms are synthetically engineered, and their foreign nature may lead to recognition by the immune system once they enter the body, resulting in their rapid clearance, which limits their biostability and targeting ability.<sup>28,29</sup> This limitation reveals a key scientific question: How can we retain the excellent drug loading capacity of synthetic nanoparticles while endowing them with the biological intelligence for seamless interaction with biological systems? Cell membrane-coated nanoparticles (CNP) technology is precisely a revolutionary strategy to address this challenge, ingeniously integrating the high loading capacity of synthetic nanomaterials with the biocompatibility of natural cell membranes.<sup>28–31</sup> To enable nanoparticles to achieve immune escape, cell membrane-coated nanoparticles (CNNPs) emerged. In recent years, CNNPs have shown promising prospects for disease diagnosis, treatment and prevention.<sup>30,31</sup> Compared with traditional nanoparticles, CNPs demonstrate unique advantages in the treatment of chronic wounds: their natural membrane structure can precisely identify and target the lesion site, effectively evade immune clearance, and prolong the duration of drug action.<sup>32,33</sup> At the same time, it can actively interact with the wound microenvironment through the receptor proteins retained on the membrane surface, achieving multiple functions such as inflammation regulation, targeted bacterial clearance, and promotion of angiogenesis.<sup>34</sup> By coating the core of synthetic nanoparticles with natural cell membranes, the resulting CNNPs exhibit a range of surface markers that enable them to replicate natural cellular interactions and be used in various biomedical applications.<sup>35</sup> This bionic strategy endows CNNPs with numerous universal advantages, including excellent biocompatibility, long-cycle characteristics, immune escape ability, and active targeted delivery capability, enabling them to perform exceptionally well in complex physiological environments.<sup>28–31</sup> The core breakthrough of this bionic strategy lies in successfully bridging the gap between the physicochemical advantages of synthetic nanoparticles and the functional complexity of biological systems, providing an innovative approach to addressing the aforementioned scientific gaps. CNNPs have certain advantages. For instance, the cell membrane endows nanoparticles with natural physicochemical properties and biological characteristics, which prevent them from being cleared by the immune system and extend their half-life, and also enhance the safety of nanoparticles in animals. In addition, through cell membrane modification, the functions of nanoparticles can be made more effective, specific and targeted.<sup>32,33</sup> Various cell types have been used as sources for the membranes to coat nanoparticles, and each type can utilize its unique properties to provide functions for the nanoparticle core, with the materials being adaptable according to the required applications.<sup>30</sup>

In this review, we mainly discuss the construction and properties of different types of cell membrane-coated nanoparticles, with a focus on explaining how CNNPs improve wound healing by bridging the functional gap between synthetic materials and biological systems, analyzing their potential mechanisms of action in treatment, and exploring the opportunities and challenges that will be faced in the future.

## Pathophysiology of Chronic Wound Healing

Skin is an important organ that covers the surface of the human body and directly interacts with the external environment, serving functions such as immunity, sensation, and protection.<sup>36,37</sup> When factors such as trauma, burns, and physiological/medical conditions cause damage or disruption to the skin's structure and function, the anatomical integrity of the skin is compromised, leading to the loss of its physiological functions.<sup>38,39</sup> After injury, the damaged skin initiates a complex repair process involving interactions between various cell types, cytokines, and biological mediators. Typically, this repair process progresses through several stages: clot formation, inflammation, new tissue formation (including re-epithelialization and granulation tissue formation), and finally, tissue remodeling and contraction<sup>40</sup> (Figure 1). Following tissue injury, both endogenous and exogenous coagulation pathways are rapidly activated within the body to form a clot that temporarily seals the wound gap. At the same time, local vascular smooth muscle contraction limits blood flow to reduce blood loss.<sup>41,42</sup> The hemostatic fibrin clot, composed of platelets and coagulation cascade factors, not only prevents hemorrhage but also forms a temporary scaffold for cell adhesion and migration.<sup>43–45</sup> Subsequently, platelets are activated by thrombin and release various growth factors. These growth factors act as biological signals, recruiting neutrophils, monocytes, leukocytes, and macrophages to the wound site, mediating the inflammatory response, protecting the skin from infection, and secreting more growth factors to accelerate wound healing.<sup>46–48</sup> The wound then enters the proliferative phase, characterized by cellular proliferation and migration.<sup>48</sup> In the wound area, pro-angiogenic factors released by platelets and inflammatory cells promote

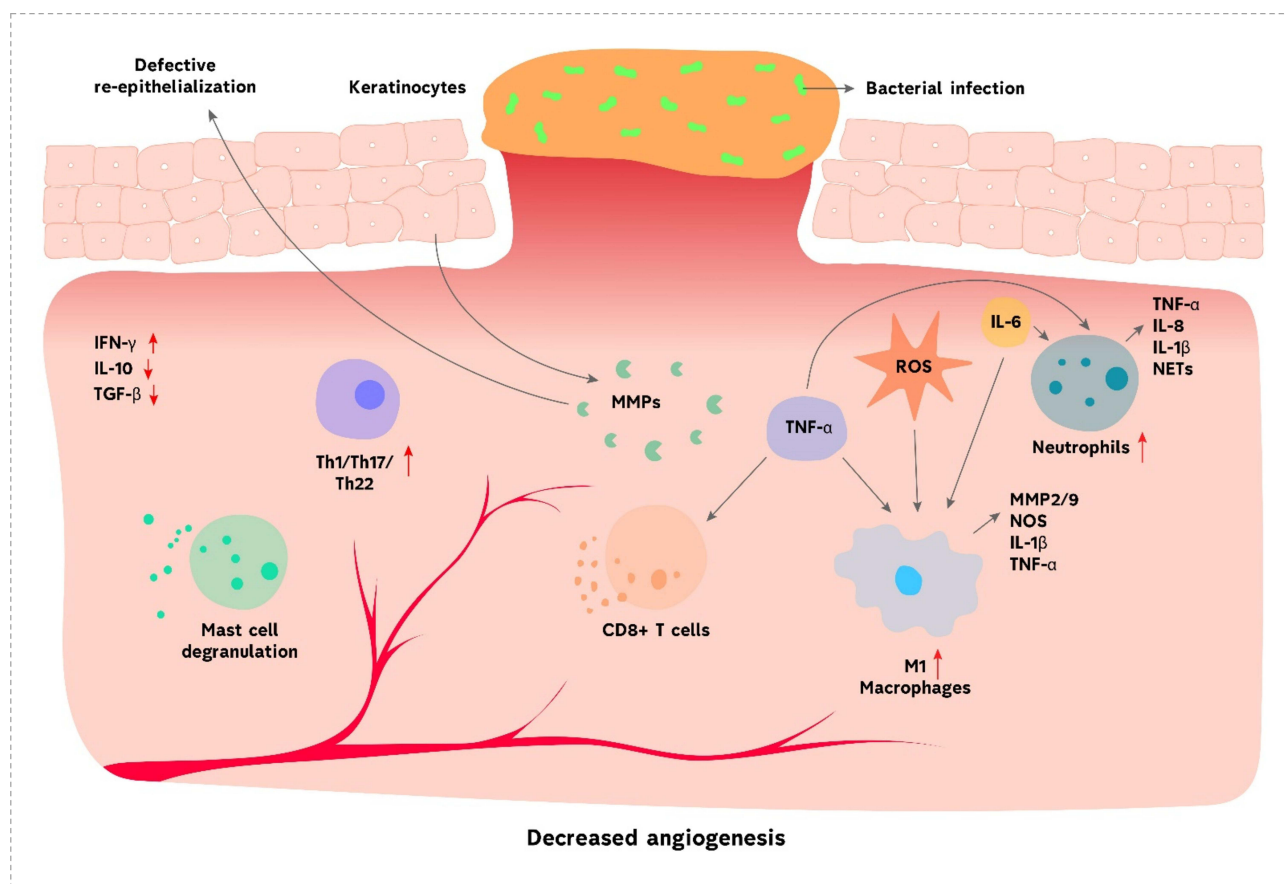


**Figure 1** Phases of wound healing (a) Schematic of a skin wound as it closes to illustrate the various phases and contributing cell players. (b) Immediately upon tissue damage, a clot forms to temporarily plug the wound gap. (c) Soon after this, the wound inflammatory response kicks in, with innate immune cells, neutrophils and macrophages drawn from local resident populations and through recruitment by extravasation from nearby vessels before migrating into the wound. (d) These inflammatory cells, particularly macrophages, orchestrate the formation of granulation tissue to replace the missing connective tissue, which entails wound angiogenesis, fibroblast migration and deposition of a new collagen matrix. (e) As the granulation tissue is being laid down, resurfacing is driven by re-epithelialization, which involves both epidermal migration and cell division to restore barrier integrity. (f) Finally, these episodes cease as the wound edges confront one another and the wound has healed; however, the various cells and tissues have not resolved and remodelled, which they now do to varying degrees, generally leaving a wound scar.

**Abbreviations:** DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; PAMPs, pathogen-associated molecular patterns; VEGF, vascular endothelial growth factor.<sup>40</sup>

the gradual formation of new blood vessels and capillaries.<sup>49</sup> Among them, hypoxia-inducible factor-1  $\alpha$  (HIF-1 $\alpha$ ), as a key regulatory factor for cells to respond to hypoxic environments, promotes the transcription of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) during normal healing and is crucial for the formation of new blood vessels.<sup>50,51</sup> Meanwhile, fibroblasts continue to migrate and form granulation tissue.<sup>52,53</sup> The transforming growth factor - $\beta$  (TGF- $\beta$ ) signaling pathway plays a core role in this process, regulating the differentiation of fibroblasts into myofibroblasts and extracellular matrix synthesis.<sup>54,55</sup> As fibroblasts accumulate and proliferate, extracellular matrix (ECM) components such as collagen, proteoglycans, and elastin are continuously produced. Additionally, some fibroblasts differentiate into myofibroblasts, which help close the wound through their contractile function.<sup>54</sup> Subsequently, activated keratinocytes at the wound margins migrate into the injured area, completing the re-epithelialization process.<sup>56</sup> Finally, in the remodeling phase, type III collagen in granulation tissue gradually transitions to type I collagen, while collagen fibers rearrange, cross-link, and align, thereby strengthening and contracting the ECM, ultimately forming a mature scar. This process is characterized by structural remodeling and cellular attrition.<sup>57,58</sup>

Wound repair is a highly organized and complex pathological process. However, when the wound fails to progress through this organized process, healing is delayed, ultimately leading to chronic wounds.<sup>59,60</sup> Despite differences in etiology, chronic wounds share certain common features, including prolonged inflammatory exudation, persistent infection, bacterial biofilm formation, and elevated levels of proteases and reactive oxygen species (ROS)<sup>4,61</sup> (Figure 2). These factors contribute to tissue necrosis, epithelial regeneration defects, and reduced angiogenesis, ultimately resulting in delayed or non-healing wounds<sup>62,63</sup> The inflammatory response is crucial for wound healing. In chronic wounds, the nuclear factor - $\kappa$ B (NF- $\kappa$ B) signaling



**Figure 2** Immune system in chronic wound healing. Common features of chronic wounds are recurrent bacterial infections, decreased angiogenesis, impaired tissue epithelialization and overabundance of ROS. The prolonged presence of neutrophils and M1 macrophages leads to a highly inflammatory profile in the wound. The process is enhanced by mast cells and CD8+ T cells' activity. The level of other inflammatory T cell subtypes, such as Th1, Th17 and Th22, is also increased. Various MMPs, secreted by keratinocytes, contribute to defective re-epithelialization. Together, all those pathological processes promote inflammation, tissue fibrosis and poor vascularization.<sup>61</sup> Upward arrows indicate upregulation, while downward arrows indicate downregulation.

pathway is continuously activated, leading to the overexpression of pro-inflammatory cytokines (such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6), which further recruit and activate neutrophils and macrophages, forming a vicious cycle and hindering the transition of the wound from the inflammatory stage to the proliferating stage.<sup>64–66</sup> However, when systemic defects (such as hyperglycemia in diabetes) and local insults (such as infection and hypoxia) are present, the inflammatory phase is prolonged, leading to delayed wound healing.<sup>67,68</sup> In such cases, there is extensive infiltration of neutrophils and macrophages, and the wound microenvironment is characterized by an increase in pro-inflammatory cytokines and unchecked protease activity.<sup>64,65</sup> For example, studies have shown that diabetic wounds are closely associated with heightened pro-inflammatory features caused by the overexpression of inflammatory cytokines (such as TNF- $\alpha$ ).<sup>66</sup> Additionally, large amounts of ROS are released into the wound environment, placing chronic wounds in a highly pro-oxidative state, which damages cell membranes and the extracellular matrix.<sup>69</sup> Due to the imbalance in the inflammatory response, the proliferation and function of endothelial cells and fibroblasts are severely inhibited.<sup>70</sup> Moreover, the imbalance between pro-angiogenic and anti-angiogenic mediators leads to impaired angiogenesis in chronic wounds. For instance, hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) is considered a key angiogenic mediator, and its expression is reduced due to metabolic disturbances (such as hyperglycemia).<sup>50</sup> The decreased expression of HIF-1 $\alpha$  significantly inhibits the transcription of pro-angiogenic factors such as VEGF and impairs neovascularization.<sup>51</sup> Furthermore, due to limited HIF-1 $\alpha$  levels and fibroblast dysfunction, the expression levels and activities of pro-angiogenic growth factors, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), are significantly suppressed. The result is poor angiogenesis, leading to insufficient nutrient supply, further delaying tissue remodeling and wound healing.<sup>51</sup>

In the wound microenvironment, infection, tissue hypoxia, local ischemia, and excessive protease activity collectively contribute to keratinocyte dysfunction. Dysfunctional keratinocytes exhibit excessive proliferation at the edges of chronic wounds but fail to migrate and close the wound, resulting in incomplete or excessive keratinization.<sup>71</sup> Additionally, dermal and/or epidermal cells in chronic wounds fail to respond to repair stimuli. These cells exhibit abnormal phenotypes, such as lower expression of growth factor (GF) receptors and reduced mitotic potential, preventing them from responding to external environmental signals.<sup>72</sup> Moreover, various pro-epithelialization factors, such as vitronectin and tenascin-C, are inactivated and degraded by proteolytic cleavage.<sup>38</sup> ECM remodeling is the final stage of wound healing. During ECM remodeling, collagen undergoes repeated synthesis and degradation to replace the matrix rich in fibronectin with a stronger collagenous matrix. During this process, various cytokines and enzymes play key roles, such as transforming growth factor- $\beta$ 1, transglutaminase, and lysyl oxidase. However, in chronic wounds, these cytokines and enzymes are inhibited and degraded by overactive proteases.<sup>55</sup> In particular, impaired function of the TGF- $\beta$  signaling pathway will directly affect the differentiation of myofibroblasts and collagen deposition, leading to tissue remodeling disorders.<sup>54,55</sup> Additionally, enzymes from the matrix metalloproteinase (MMP) family control the conversion of type III collagen to type I collagen. Dysfunction of these enzymes also leads to ECM remodeling failure and delayed wound healing.<sup>73</sup>

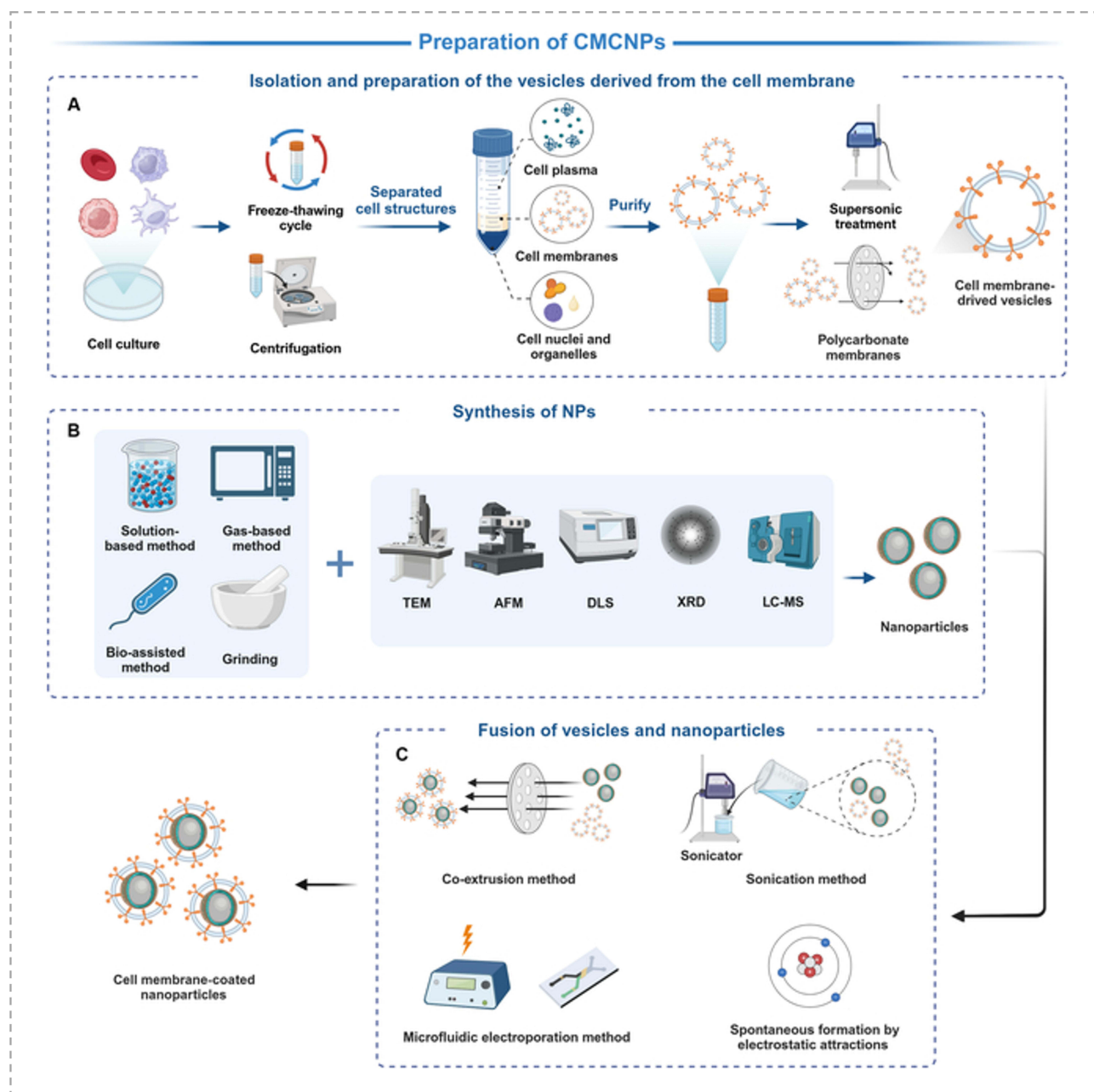
## Preparation and Classification of Cell Membrane-Coated Nanoparticles

### Preparation of Cell Membrane-Coated Nanoparticles (CMNPs)

The preparation of Cell Membrane-Coated Nanoparticles (CMNPs) involves three major steps: extraction of the cell membrane, preparation of the nanoparticle core, and coating the core with the cell membrane. Each step is crucial in the design of CMNPs and plays an important role in ensuring the efficacy and functionality of the final product<sup>74</sup> (Figure 3).

#### Cell Membrane Extraction

The extraction of the cell membrane involves isolating and purifying the membrane, which consists of phospholipids embedded with specific surface proteins.<sup>75</sup> These membranes play a central role in various biological functions, such as material transport and signal recognition.<sup>28</sup> The extraction process needs to be carried out under mild conditions to preserve the purity and integrity of the membrane. This ensures that the cell membrane can replicate its functional properties on the surface of the nanoparticle core and minimize adverse effects.<sup>76,77</sup> Common membrane separation methods include hypotonic lysis, freeze-thaw cycles, sonication, and homogenization,<sup>78–81</sup> while purification methods include differential centrifugation, density gradient centrifugation, and ultrafiltration.<sup>82–84</sup> In practice, the extraction method is selected based on the type of cells used. For nucleated cells, such as leukocytes, cancer cells, and stem cells, the process is more complex. First, the target cells



**Figure 3** The fabrication of CMCNPs. (A) Acquisition of cell membrane vesicles from cell culture. (B) Manufacture techniques of NPs. (C) Fusion techniques of vesicles and NPs.<sup>74</sup> The original figure contained a spelling error “drived”, corrected here as “derived”.

**Abbreviations:** AFM, atomic force microscopy; DLS, dynamic light scattering; LC-MS, liquid chromatography–mass spectrometry; TEM, transmission electron microscopy; XRD, x-ray diffraction.

need to be isolated from tissue or blood, followed by cell culture.<sup>85–88</sup> Afterward, the cell membranes are extracted using methods like hypotonic lysis, mechanical disruption, and discontinuous sucrose gradient centrifugation to remove the cell nucleus and cytoplasm. The membranes are then cleaned with plasma buffer and further purified by ultrasonication and extrusion through a porous polycarbonate membrane.<sup>89</sup> For non-nucleated cells, such as mature red blood cells and platelets, the extraction process is relatively simple. Cells are separated from whole blood, then subjected to hypotonic lysis or repeated freeze-thaw cycles to mechanically disrupt the membrane. Differential centrifugation removes soluble proteins, and the membrane is then extruded into nanoparticles.<sup>79,90</sup>

## Nanoparticle Core

The nanoparticle core serves as an effective carrier for delivering cargo to the target tissue. Different types of cores confer different properties and functions to the CMNPs. The core can be either organic or inorganic, each offering distinct advantages. Organic cores are generally safer, with better loading capacity and biocompatibility, while inorganic cores have unique functionalities in areas like photodynamic therapy, fluorescence imaging, and magnetic resonance imaging (MRI).<sup>76,77,91</sup> Organic cores have better biocompatibility and biodegradability.<sup>92,93</sup> For example, the FDA has approved materials like gelatin, liposomes, and poly(lactic-co-glycolic acid) (PLGA) for clinical applications. Among these, PLGA is the most commonly used material for fabricating membrane-biomimetic carriers and has significant clinical application potential. Membranes can be modified on PLGA particles to prevent aggregation and achieve better delivery efficiency.<sup>76,77,94</sup> A widely used inorganic core is the liposome, which is similar to the cell membrane.<sup>95,96</sup> Liposomes are biodegradable colloids capable of carrying both hydrophobic and hydrophilic drugs.<sup>97,98</sup> Moreover, they are flexible, which allows them to penetrate in vivo barriers.<sup>97</sup> Cell membrane coating enhances the stability of the phospholipid membrane, providing longer circulation times without compromising the drug-loading capacity.<sup>99</sup> Compared to organic cores, inorganic cores have superior stability and resistance to enzymatic degradation. They are also cost-effective, easy to synthesize, and can be coated with appropriate membrane vesicles. Furthermore, by manipulating the form, size, composition, and surface properties of inorganic nanoparticles, their inherent electrical, optical, and magnetic properties can be enhanced to fully utilize their therapeutic potential.<sup>76,77,100</sup> Therefore, the selection of the core material should be based on the specific delivery needs of the cargo.

## Fusion of Core and Cell Membrane

Once the nanoparticle core and cell membrane are prepared, the next crucial step is the fusion of the two components. This process is typically achieved using methods like membrane extrusion, sonication, or microfluidic electroporation.<sup>101–103</sup>

### Membrane Extrusion

This is the most commonly used method, also known as the “top-down” approach. It involves subjecting the cells to hypertonic treatment or repeated freeze-thaw cycles to obtain empty membranes devoid of cellular contents. The extracted membranes are then extruded through a porous filter together with other nanostructures to form core-shell structures of cell membrane-derived nanoparticles.<sup>104</sup> Although this method is fast and simple, large-scale production can be challenging.

### Sonication

This method uses ultrasound treatment to mix the purified cell membranes with the nanoparticle core, resulting in the cell membrane coating the surface of the nanoparticle core. The application of ultrasonic energy disrupts both components, promoting the spontaneous formation of the core-shell nanostructures. This method not only yields results similar to membrane extrusion but also reduces material loss.<sup>105,106</sup>

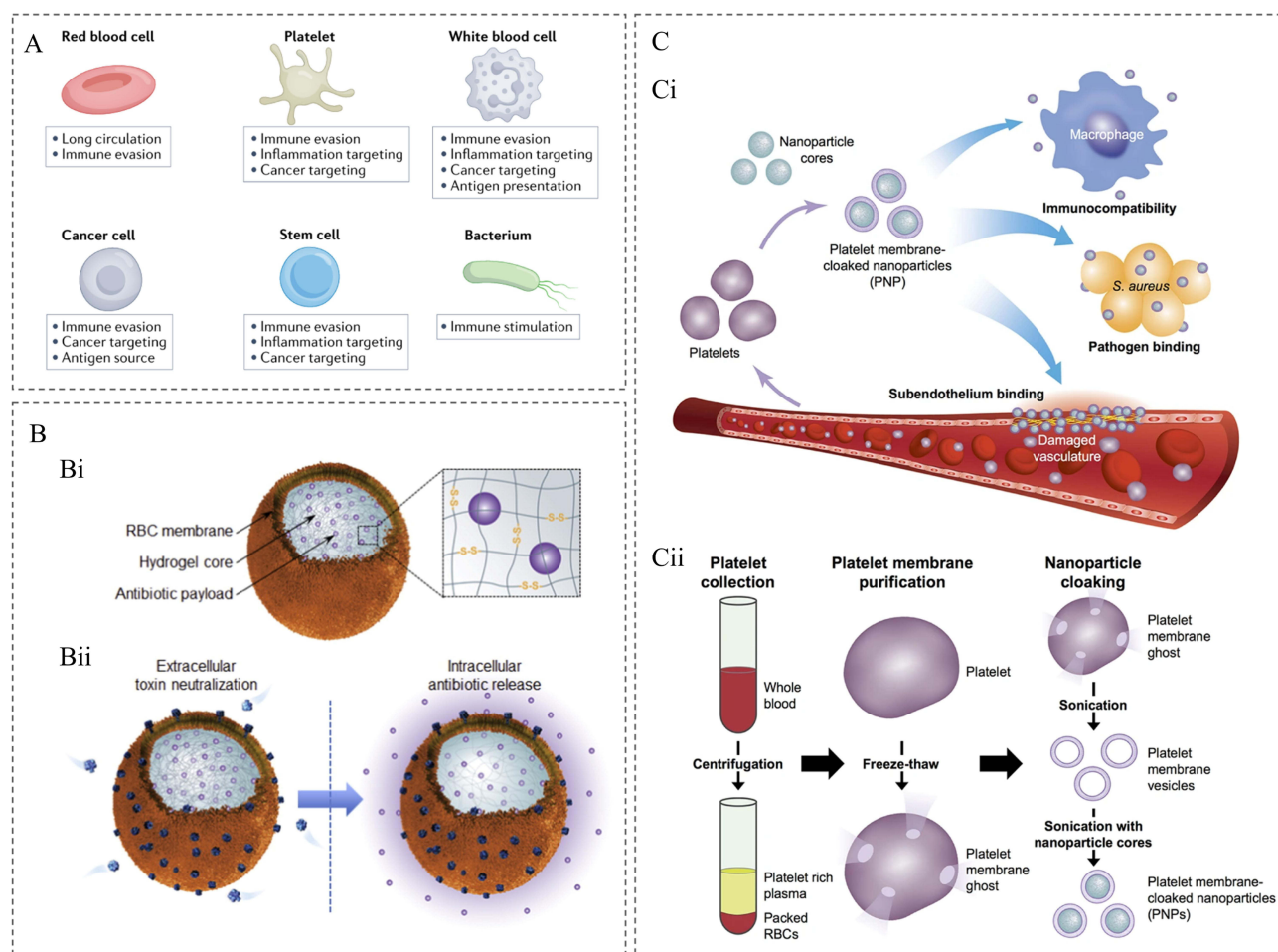
### Electroporation

This method utilizes microfluidic devices to apply electrical pulses, facilitating the entry of the nanoparticle core into the cell membrane. This allows the fusion of the core and the cell membrane to form the desired CMNPs.<sup>30,106</sup>

## Classification of Cell Membrane-Coated Nanoparticles (CNNPs)

The plasma membrane is embedded with various biomolecules, playing a vital role in processes such as recognition and signal transduction. Therefore, theoretically, directly transferring the intact cell membrane onto nanoparticles (NPs) can impart the physiological functions of the membrane, including its significant ability to interface with and interact with the surrounding environment.<sup>28,76,77</sup> Currently, numerous types of cell membranes or hybrid membranes have been explored for constructing biomimetic CNNPs, with each type of membrane coating imparting specific characteristics<sup>31</sup> (Figure 4A).

Red blood cells (RBCs) are responsible for transporting oxygen and nutrients and have a lifespan of about 120 days in circulation. When RBC membranes are used to coat NPs, the resulting particles exhibit surface antigens consistent with the



**Figure 4** (A) Common membrane sources for the fabrication of cell membrane-coated nanoparticles. Cell membrane-coated nanoparticles can be fabricated using cell membrane materials sourced from red blood cells, platelets, immune cells, cancer cells, stem cells or bacteria. Each type of membrane coating confers specific properties that can be leveraged for anticancer applications.<sup>31</sup> (B) Schematic illustrations of a red blood cell (RBC) membrane-coated nanogel (RBC-nanogel) system for combinatorial extracellular toxin neutralization and intracellular redox-responsive antibiotic release. (Bi) The RBC-nanogel is constructed with a natural RBC membrane shell and a hydrogel core containing antibiotic payload. The hydrogel core is cross-linked with disulfide bonds, cleavable in reducing environment. (Bii) In extracellular environment, the RBC-nanogel absorbs and neutralizes pore-forming toxins (PFTs) secreted by bacteria. Such toxin sequestration facilitates the intracellular uptake of the toxin-secreting bacteria and the RBC-nanogel. Once inside the cell, the RBC-nanogel rapidly releases its encapsulated antibiotic payload triggered by a redox reaction.<sup>107</sup> (C) Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are enclosed entirely in plasma membrane derived from human platelets. The resulting particles possess platelet-mimicking properties for immunocompatibility, subendothelium binding, and pathogen adhesion. (Cii) Schematic depicting the process of preparing PNPs.<sup>108</sup>

“self” identity, allowing these particles to circulate for longer periods without being recognized and eliminated by macrophages in the body.<sup>109,110</sup> RBCs possess good biocompatibility and low immunogenicity, making them an ideal material for preparing long-circulating NPs. For instance, Zhang et al constructed an RBC-nanogel system for combined virulence inhibition and reactive antibiotic delivery to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections<sup>107</sup> (Figure 4B). Platelets, which are non-nucleated cell fragments, are involved in many pathophysiological processes, including atherosclerosis, tumor progression, and inflammation. Similar to RBC membranes, platelet membranes also contain various “self” markers. CD47 helps platelets evade phagocytosis by macrophages, while CD55 and CD59 prevent complement system activation; therefore, platelet membranes are also suitable for CNNPs.<sup>111</sup> Zhang et al first demonstrated the preparation of platelet membrane-coated nanoparticles (PNPs). Compared with uncoated NPs, PNPs reduced macrophage-like cell uptake, did not trigger complement activation in human plasma, and exhibited platelet-mimicking characteristics<sup>108</sup> (Figure 4C).

Inflammatory cells can adhere to and traverse endothelial cells, specifically migrating to sites of inflammation. Leveraging this property, researchers have designed carrier systems derived from inflammatory cells for precise delivery of anti-inflammatory drugs.<sup>112</sup> These NPs, coated with inflammatory cell membranes, effectively retain various biomarkers such as CD45, CD3Z, lymphocyte function-associated antigen-1 (LFA-1), and various adhesion molecules. These “leukocyte-like”

markers not only help avoid rapid clearance by the mononuclear phagocyte system but also promote NP traversal through endothelial cells, allowing accumulation at inflammation sites.<sup>112</sup> Among these, neutrophil membrane-coated nanoparticles are particularly unique as they not only precisely target inflammation sites but also target circulating tumor cells (CTCs), effectively preventing early tumor metastasis and potentially inhibiting the further development of established metastatic lesions.<sup>85</sup> In recent years, tumor cell membrane-coated functionalized nanoparticles have been increasingly developed.<sup>88,92</sup> Compared to other cell types, tumor cell-derived NPs can not only passively leak from capillaries due to the enhanced permeability and retention effect but also actively bind to tumor cells through homotypic recognition.<sup>113</sup> Studies have shown that the targeting efficiency of tumor cell membrane-coated NPs is 20 times and 40 times greater than that of RBC membrane-coated NPs and bare NPs, respectively.<sup>113</sup> Additionally, mesenchymal stem cells (MSCs) have been used in the construction of CNNPs. Stem cells possess self-renewal and multi-directional differentiation potential, along with low immunogenicity and ease of acquisition. These cells exhibit specific tumor-homing ability through interactions between chemokine receptors and endothelial adhesion molecules, making MSC membrane-coated NPs specifically target tumor lesions, thus reducing the systemic toxicity and side effects of chemotherapy drugs.<sup>114</sup> In addition to these, many other types of cell membranes have been applied to CNP construction, such as bacterial cell membranes,<sup>115</sup> fibroblast membranes,<sup>116</sup> and pancreatic  $\beta$ -cell membranes.<sup>117</sup>

In addition to single cell membranes, recent years have seen researchers combine multiple cell membranes to develop hybrid membranes with enhanced functionality, expanding their application potential.<sup>76,118</sup> For example, hybrid NPs coated with both RBC and platelet membranes can circulate for extended periods, making them an ideal choice for *in vivo* studies.<sup>94</sup> Mixed RBC/platelet membrane-coated polypyrrole NPs (PPyNP) can effectively kill tumor cells upon near-infrared laser irradiation and possess self-targeting and prolonged *in vivo* circulation, showing broad application prospects.<sup>119</sup> Recently, Liu et al used a hybrid membrane of platelet membranes and CCR2-high-expressing cell membranes to coat nanoparticles and loaded them with rapamycin and TPPU, two small molecule drugs, to target pathological regions associated with Alzheimer's disease (AD). These nanoparticles can cross the blood-brain barrier and release drugs at the inflammation sites to enhance autophagy and alleviate neuroinflammation, thereby achieving AD treatment.<sup>20</sup> In summary, by integrating the characteristics of different cell types, hybrid membranes can be created, resulting in NPs with longer *in vivo* circulation half-lives and stronger targeting capabilities, providing new ideas for drug delivery.

Whether single-cell membranes or hybrid cell membrane-coated nanoparticles, the functionality of CNNPs primarily depends on their surface functional proteins. With advancements in material science and medicine, the targeting and monitoring capabilities of cell membrane-based nanoplatfoms are continuously improving. To enhance the properties of membrane-coated CNNPs and achieve more precise targeting for research and treatment, cell membrane modification has become a highly promising new research direction.<sup>120,121</sup> Cell membrane modification can primarily be divided into physical, chemical, and bioengineering types. Physical methods anchor targeting groups on the cell membrane through lipid structure and membrane fluidity. Chemical methods utilize activated chemical bonding sites for covalent attachment. Bioengineering methods involve transfecting or transducing the required proteins or peptides into the cell membrane. These three methods provide diverse possibilities for cell membrane modification.<sup>120</sup> These designs demonstrate the diverse characteristics of cell membrane-coated nanoparticles, as well as the flexible and controllable loading capacities of the nanoparticle core. This makes cell membrane-coated nanoparticles a promising platform for chronic wound healing treatment and highlights their vast potential in targeted drug delivery and immune modulation.

## Various Strategies of Cell Membrane-Coated Nanoparticles in Chronic Wound Treatment

The application of cell membrane-coated nanoparticles (CNNPs) in chronic wound treatment represents a cutting-edge therapeutic strategy, combining the advantages of nanotechnology and biomaterials to offer a novel and effective treatment approach. Chronic wounds are typically difficult to heal due to factors such as infection, inflammation, and poor blood circulation. Cell membrane-coated nanoparticles can accelerate the healing process of chronic wounds and enhance treatment efficacy through several strategies (Table 1).

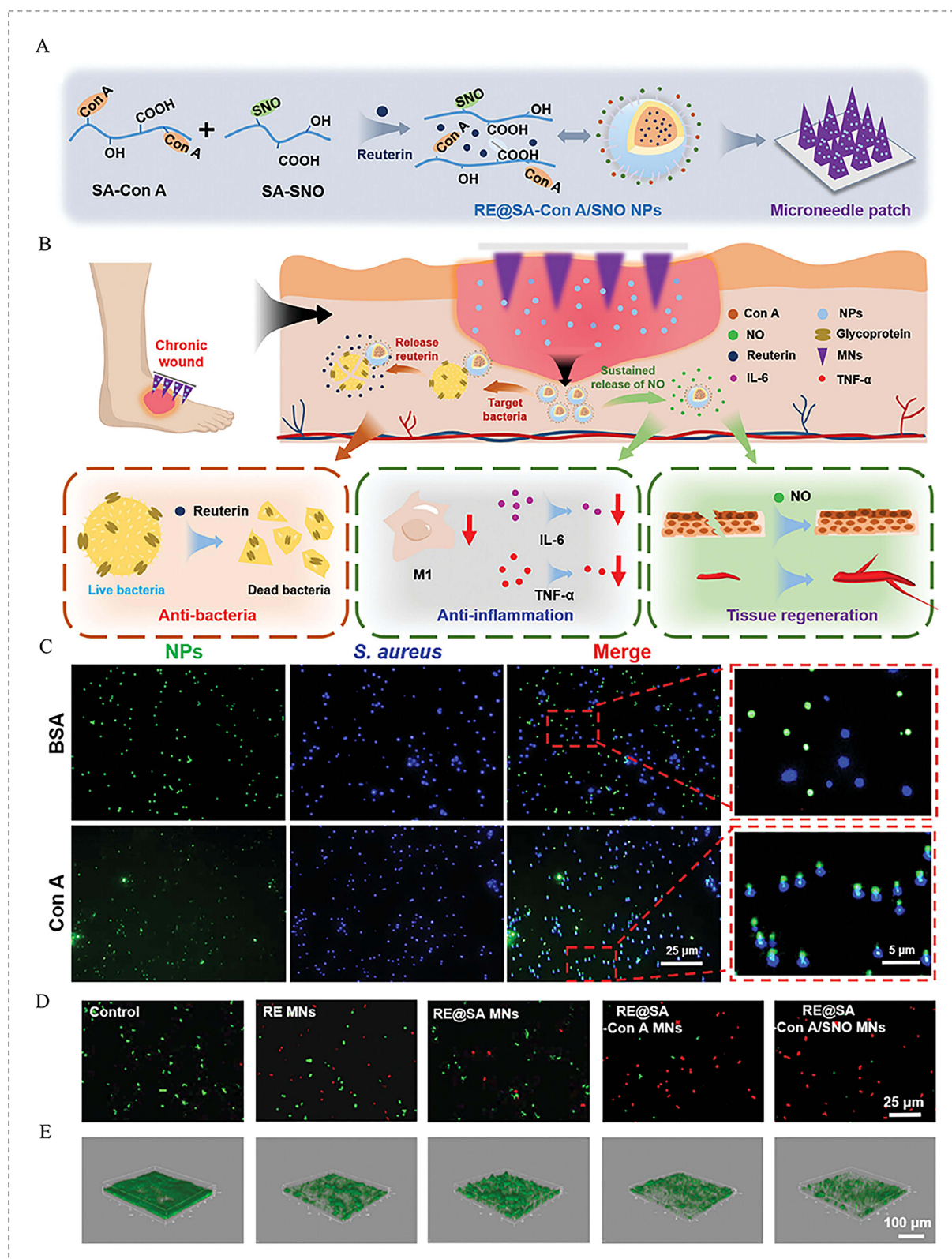
**Table 1** Strategies and Representative Cases of Cell Membrane-Coated Nanoparticles (CNNPs) in Chronic Wound Treatment

Nanoparticle System	Mechanism	Target/Effect	Application Model	Key Outcome	Ref.
HER2-CAR T cell-coated polymer NPs	Membrane receptors mediate active targeting	Tumor/ inflammatory sites	Tumor model	Precise drug delivery, improved accumulation	[122]
Platelet membrane-coated nanogels with DOX	Platelet adhesion molecules	Tumor/injury site	Tumor model	Targeted drug delivery, reduced systemic toxicity	[19]
Macrophage-like nanoparticles	PRRs recognize PAMPs; neutralize TNF- $\alpha$ , IL-6	Bacteria & inflammatory mediators	Sepsis/chronic wounds	Targeted pathogen elimination, inflammation modulation	[123]
RE@SA-ConA/SNO NPs	ConA binds bacterial polysaccharides; NO + reuterin	<i>S. aureus</i> biofilms	Chronic wound infection	Biofilm clearance 78%, antibacterial	[124]
NK cell membrane + photosensitizer NPs	Targeting cancer cells; PDT-induced M1 polarization	Tumor cells	Tumor model	Enhanced antitumor immune response	[125]
BPQDs + AM-loaded AB@LRM	RBC + macrophage membranes for retention; PTT/PDT + AM	Inflammation site/ bacteria	<i>P. aeruginosa</i> wounds	Faster closure, reduced inflammation, improved angiogenesis	[126]
MoS <sub>2</sub> -CeO <sub>2</sub> nanocomposites	Photothermal antibacterial + antioxidant	Bacteria & ROS	Diabetic ulcer wounds	Antibacterial, antioxidant, promotes healing	[127]
MMP-9-responsive Exo@MRH	Stimulus-responsive exosome release	Macrophage M1 $\rightarrow$ M2; TNF- $\alpha$ $\downarrow$ IL-10 $\uparrow$	Diabetic wounds	Organized epidermis, uniform collagen, inflammation resolution	[128]
Cu-NP-PVA@SEW hydrogel	pH/NIR dual-responsive; macrophage recruitment	Bacteria & inflammatory sites	Bacteria-infected skin wounds	Enhanced tissue regeneration, angiogenesis, collagen deposition	[129]
Septic arthritis microenvironment-responsive CNNPs	Stimulus-responsive	Macrophages & inflammatory cytokines	Septic arthritis model	Controlled drug release, inflammation modulation	[130]

## Targeted Drug Delivery for Therapeutic Treatment

CNNPs leverage the characteristics of cell membranes to enhance biocompatibility, extend circulation time, and potentially confer targeting capabilities. In drug delivery, nanoparticles can protect drugs from degradation, increase accumulation at the site of injury, and reduce systemic side effects. For example, HER2-based chimeric antigen receptor (CAR) engineered T cell-coated polymer nanoparticles,<sup>122</sup> and platelet membrane-coated nanogels loaded with doxorubicin,<sup>19</sup> utilize specific receptors or adhesion molecules on the cell membrane, enabling active targeting and tumor accumulation, thus achieving precise drug delivery. The microenvironment of chronic wounds is characterized by persistent inflammation, and cell membrane-coated nanoparticles can target inflammatory or infected areas to enhance local drug accumulation. For instance, macrophage-like nanoparticles possess the same antigenic exterior as macrophages, thereby inheriting their ability to bind to endotoxins and pro-inflammatory cytokines. Specifically, pattern recognition receptors (PRRs) on the macrophage cell membrane, such as Toll-like receptors (TLRs), can recognize pathogen-associated molecular patterns (PAMPs). Thereby mediating the targeting and elimination of pathogens such as bacteria; Meanwhile, these membrane structures can bind to and neutralize inflammatory mediators, such as tumor necrosis factor - $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6). It provides a brand-new perspective for the treatment of sepsis.<sup>123</sup>

In rheumatoid arthritis (RA), the fibroblast-like synoviocytes (FLS) “regulatory” phenotype (FLSreg) is defective, while FLS in RA instead act as a “pro-inflammatory” phenotype, mediating prolonged inflammation. Liu et al encapsulated IFN- $\gamma$  and rapamycin-induced FLSreg cell membranes on nanoparticles, demonstrating significant therapeutic effects, stability, and inflammation-targeting capabilities in an RA model.<sup>131</sup> In chronic wound treatment, nanoparticles loaded with drugs for targeted delivery have shown positive effects. For example, Jin et al developed a microneedle patch with nanoparticles (RE@SA-Con A/SNO NP) (Figure 5A), where the nanoparticles are composed of sodium alginate



**Figure 5** (A) Schematic illustration of the synthesis of RE@SA-Con A/SNO NPs and subsequent encapsulation in a MN patch. (B) Schematic illustration of the application of a MN patch loaded with RE@SA-Con A/SNO NPs for targeted and synergistic therapy of chronic wounds. (C) Representative fluorescence-field microscopy images of RE@SA-Con A/SNO-FITC NPs targeting bacteria. (D) Live/dead assay of *S. aureus* after incubation with different MNs for 24 h. (E) Confocal laser scanning microscopy of *S. aureus* with different treatments. Green: live bacteria.<sup>124</sup> Red downward arrows indicate downregulated expression.

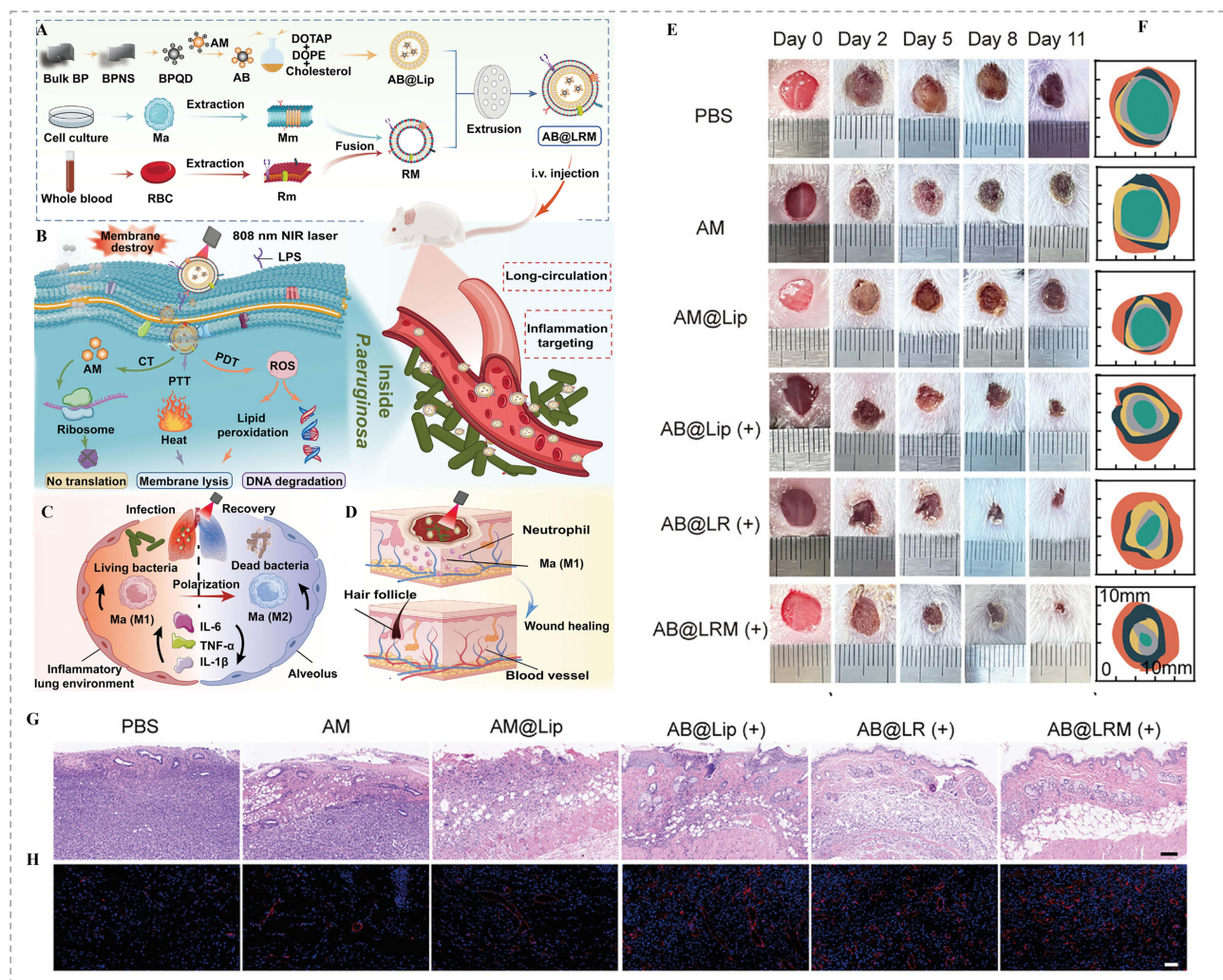
(SA) encapsulating an antibacterial agent (reuterin) and immobilized Concanavalin A (Con A) along with NO molecules. These nanoparticles specifically recognize bacterial polysaccharides on the surface to achieve targeted antibacterial effects (Figure 5B).<sup>124</sup> The results showed that RE@SA-Con A/SNO NPs effectively targeted and bound to the surface of *Staphylococcus aureus*. In contrast, when Con A protein was replaced with bovine serum albumin (BSA), the nanoparticles lost their ability to target harmful bacteria (Figure 5C). These findings confirm the targeted ability of RE@SA-Con A/SNO NPs, as Con A interacts with mannose and glucose residues on the bacterial surface. In vitro experiments indicated that RE@SA-Con A/SNO NPs exhibited excellent bacterial clearance, consistent with the antibacterial results, and showed the best biofilm clearance effect against *Staphylococcus aureus* (Figure 5D and E). Due to the synergistic antibacterial effect of reuterin and NO molecules, the biofilm clearance rate reached  $78.13 \pm 1.48\%$ . Therefore, combining the natural targeting ability of cell membranes with the efficient drug delivery capability of nanoparticles may enhance the delivery efficiency and targeting of nanoparticles, paving the way for the development of targeted drug delivery nanoplatforms for chronic wound microenvironments.

## Phototherapy Combined Treatment

Phototherapy combined treatment is a strategy that integrates phototherapy with other therapeutic approaches to enhance treatment efficacy. In the field of tumor treatment, immunotherapy combined with phototherapy is often used to strengthen the effects of tumor immunotherapy. Currently, the combination of cell membrane-coated nanoparticles (CNNPs) with phototherapy has synergistically enhanced tumor immunotherapy. For instance, using natural killer (NK) cell membranes combined with photosensitizer-loaded nanoparticles has endowed the nanoparticles with the ability to specifically target cancer cells. While undergoing photodynamic therapy (PDT), this combination induces M1 macrophage polarization, producing an antitumor immune response, thus enhancing the antitumor immune efficacy of NK cell membrane-coated nanoparticles.<sup>125</sup> A key question arises: can CNNPs and phototherapy be applied together for the treatment of refractory wounds? This issue is worth attention, as numerous preclinical studies have combined phototherapy with nanotechnology to develop photothermal-sensitive nanoparticle platforms, which could help improve bacterial clearance in refractory wounds.

Photothermal therapy (PTT) primarily relies on photosensitizers generating heat under near-infrared (NIR) light irradiation to damage bacterial membrane structures and cause irreversible damage to bacterial proteins, thereby killing the bacteria. However, while PTT provides heat to tissues, the local high temperatures can lead to excessive reactive oxygen species (ROS) production in the body, causing oxidative stress damage to the skin tissue and severely hindering normal wound healing. To address this, researchers have developed bio-nanomaterials with excellent photothermal conversion properties, which help promote wound healing and resist oxidative stress, thereby protecting healing tissues from damage caused by oxidation.<sup>132</sup> For example, molybdenum disulfide-cerium oxide (MoS<sub>2</sub>-CeO<sub>2</sub>) nanocomposites not only possess photothermal antibacterial properties through polyethylene glycol (PEG)-modified MoS<sub>2</sub> nanosheets but also have antioxidant activity through cerium oxide nanoparticles (CeO<sub>2</sub> NPs). These materials can eliminate excessive ROS around diabetic ulcer wounds and, through the inherent antibacterial activity of CeO<sub>2</sub> nanoparticles, MoS<sub>2</sub>-CeO<sub>2</sub> nanocomposites exhibit excellent PTT antibacterial properties under 808 nm laser irradiation, demonstrating reduced wound infection risks for both Gram-positive and Gram-negative bacteria.<sup>127</sup>

Recently, Xiong et al introduced a macrophage membrane-coated cascade-targeting photothermal nanosystem that can accurately target and eradicate intracellular bacterial infections in a cascade manner.<sup>133</sup> Liu et al used the fusion of red blood cell membranes and macrophage cell membranes to form a composite cell membrane shell, which further encapsulated drug-loaded liposomes to create a biomimetic liposome (AB@LRM). Specifically, photosensitizer black phosphorus quantum dots (BPQDs) and the classic antibiotic amikacin (AM) were loaded into AB@LRM (Figure 6A). Through the guidance of the macrophage membrane and the long-term retention ability of the red blood cell membrane, the system can accurately target inflammation sites, ultimately exhibiting effective antibacterial activity (Figure 6B). This biomimetic liposome is applied for precise antibacterial treatment, effectively treating *Pseudomonas aeruginosa* infections in both pneumonia (Figure 6C) and wounds (Figure 6D).<sup>126</sup> Furthermore, due to the excellent photothermal and photodynamic properties of BPQDs, when exposed to NIR laser irradiation, BPQDs act as effective antibacterial agents, significantly increasing bacterial sensitivity to antibiotics. In infection wound models, wounds treated with AB@LRM (+) for 11 days showed significantly faster healing effects (Figure 6E and F). H&E staining images revealed that the infection areas treated with AB@LRM (+) exhibited



**Figure 6** (A) The preparation process of AB@LRM NPs. (B) The synergistic therapeutic mechanisms against bacterial infections. Applications of AB@LRM (+) in the treatment of (C) bacterial pneumonia and (D) bacteria-infected wound healing caused by *P. aeruginosa*. (E) Representative photographs of infected wounds on days 0, 2, 5, 8, and 11. (F) Monitoring of wound closure during 11 d treatments in each group (G). H&E staining of the infected wound tissues (scale bar = 100  $\mu$ m). (H) Representative immunofluorescence images of angiogenesis (CD31) (scale bar = 50  $\mu$ m) and the quantifications of vessel density (n = 5).<sup>126</sup>

a marked reduction in inflammatory cells and complete epithelial regeneration in the wound areas, showing typical skin morphological features with hair follicles and blood vessels (Figure 6G). Additionally, immunofluorescence at the wound site in the AB@LRM (+) group showed the best vascular formation and density (Figure 6H).

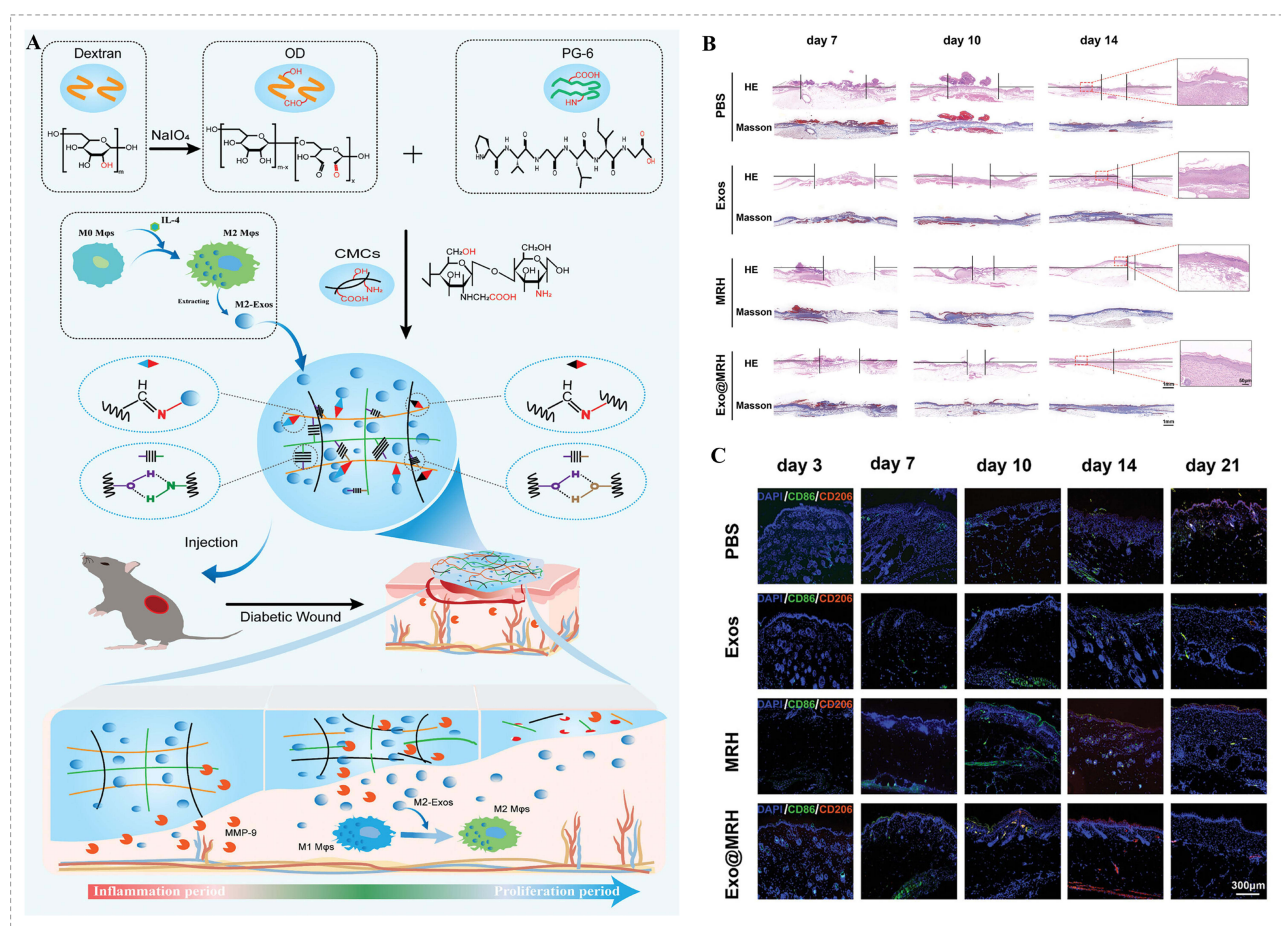
Therefore, the strategy of combining cell membrane-coated nanoparticles with phototherapy to exert antibacterial effects offers a highly feasible approach for treating refractory wounds. The synergistic effects of photothermal therapy (PTT), photodynamic therapy (PDT), and biomimetic targeting provide an innovative solution for the management of complex wounds.

## Intelligent Response to the Wound Microenvironment

Recently, stimulus-responsive drug delivery nanoparticle systems (DDS) based on multifunctional nanoparticles have garnered significant attention due to their ability to release drugs on demand at specific sites in response to external or internal signals. These intelligent nanocarriers can be customized to respond to various stimuli, such as redox potential, pH changes, light, or enzyme activation, and even to multiple or dual stimuli simultaneously.<sup>23,134</sup> Therefore, drug delivery carriers used to promote wound healing also need to respond to the specific characteristics of the wound microenvironment, such as pH changes or the presence of enzymes, by designing stimulus-responsive nanocarriers for controlled drug release.

As previously mentioned, during the inflammatory process, the inflammatory microenvironment rich in cytokines and proteases (such as matrix metalloproteinases, MMPs) plays a crucial role, as these components typically increase after wound formation and during the inflammatory response. This suggests that MMPs may serve as biomarkers of the wound inflammatory microenvironment. Based on this, Meng et al developed an MMP-9-responsive exosome delivery system (Exo@MRH).<sup>128</sup> This system is formed by the cross-coupling of oxidized dextran, matrix metalloproteinase (MMP)-9 sensitive peptide and carboxymethyl chitosan containing M2 macrophage-derived exosomes (M2-exOS). The on-demand release of M2-exOS promotes the polarization of macrophages from the M1 phenotype to the M2 phenotype at the molecular level. M2-Exos may regulate polarization signaling pathways (such as STAT6, PPAR $\gamma$ , etc.) within macrophages by delivering specific mirnas or proteins, thereby affecting the expression of downstream inflammatory factors (such as TNF- $\alpha$ , IL-6, IL-10, etc), and thus promoting the transition from the inflammatory phase to the proliferative phase. And it accelerated the healing of diabetic wounds (Figure 7A). Histological analysis using H&E and Masson staining on day 14 showed (Figure 7B) that the Exo@MRH group had well-organized epidermis and more uniform dermal collagen deposition. Immunofluorescence staining (Figure 7C) shows that Exo@MRH effectively promotes the transformation of M $\phi$  from M1 to M2, reduces chronic inflammation and promotes the healing of diabetic wounds.

In addition, researchers have further enhanced the efficacy of nanoparticles in chronic wound treatment by combining photothermal therapy with nanotechnology. For example, Zha et al prepared a near-infrared (NIR)/pH dual-responsive copper nanoparticle (Cu-NP)-polyvinyl alcohol (PVA) hydrogel film loaded with macrophage recruitment agent SEW2871 (SEW) for the treatment of bacterial-infected skin wounds. The results showed that humic acid (Has) promoted M2 macrophage polarization in a dose-dependent manner. Through NIR-induced local thermal therapy, Cu-



**Figure 7** (A) Schematic diagram of Exo@MRH facilitating diabetic wound healing by guiding timely switch of M1-M2 M $\phi$ s. (B) Representative images of scar widths stained by H&E and collagen fibers stained by Masson. (C) Immunofluorescence costaining.<sup>128</sup>

HAs nanoparticles successfully eradicated bacterial infection. This PVA@Cu-HAs NPs@SEW hydrogel film improved tissue regeneration by promoting M2 macrophage polarization, alleviating oxidative stress, enhancing angiogenesis, and promoting collagen deposition.<sup>129</sup> Currently, inflammation microenvironment-responsive CNNPs have shown progress in the treatment of septic arthritis.<sup>130</sup> Thus, future development of cell membrane-coated nanoparticles with intelligent responsiveness to the wound microenvironment could enable the timely, on-demand, and controlled release of drugs, offering promising prospects for chronic wound management.

## Cell Membrane-Coated Nanoparticles Promote Chronic Refractory Wound Healing Through Multiple Mechanisms

Chronic refractory wounds, despite having different etiologies, share common characteristics in their wound microenvironment, including persistent inflammation, bacterial infection, bacterial biofilm formation, and elevated levels of proteases and ROS. These factors are intertwined, leading to tissue necrosis, defects in epithelial regeneration, and reduced angiogenesis. As an emerging drug delivery platform, cell membrane-coated nanoparticles (CNNPs) can exert therapeutic effects through various mechanisms. Their potential therapeutic mechanisms include inhibiting infection, promoting angiogenesis, improving the local inflammatory environment, and promoting tissue regeneration. These mechanisms together make CNNPs a promising platform for tissue engineering and drug delivery (Table 2).

**Table 2** Mechanisms and Representative Cases of Cell Membrane-Coated Nanoparticles (CNNPs) in Chronic Refractory Wound Healing

Nanoparticle System	Mechanism	Target/Effect	Application Model	Key Outcome	Ref.
Macrophage membrane-coated photothermal NPs	Cascade-targeting to intracellular bacteria	Intracellular bacteria	Infection model	Precise bacterial clearance, anti-biofilm	[133,135]
Hybrid neutrophil + <i>E. coli</i> -derived MVs (LNP-N@HMV)	Dual-targeted antibiotic delivery; humoral + cellular immunity	Gram-negative bacteria, inflammatory vascular cells	In vitro/ infection sites	Enhanced antimicrobial activity, biofilm disruption	[34]
Cationic albumin NPs	Electrostatic binding to bacterial membranes	Bacteria	In vitro	Antibacterial, biofilm disruption	[136]
Multifunctional CNNPs targeting bacteria/toxins/ cytokines	Toxin neutralization and pathogen targeting	Bacteria, toxins, inflammatory cytokines	Bone infection mouse model	Improved antimicrobial and anti-inflammatory activity, tissue repair	[137,138]
Functionalized CMNPs with phage lyases/AMPs/ quorum sensing inhibitors	Biofilm penetration and bacteria killing	<i>P. aeruginosa</i> , MRSA	Chronic wound	Anti-biofilm, microbial balance regulation	[34,133,135]
Platelet membrane-coated PLGA NPs	Promote endothelial proliferation and migration	Endothelial cells	Ischemic limb model	Enhanced angiogenesis and tissue perfusion	[139]
Liposome-coated NPs delivering miR-21	Angiogenesis promotion	Endothelial cells	Wound healing	Re-epithelialization, neovascularization	[140]
Hybrid cell membrane (NGF + VEGF aggregation)	Stimulate MSC neurovascular differentiation	MSCs	Bone defect model	Enhanced angiogenesis and neurogenesis	[141]
Macrophage membrane-coated PLGA NPs with MLN4924	Reduce inflammation, promote endothelial function	Macrophages, endothelial cells	Diabetic wound	Enhanced angiogenesis and wound closure	[142]
Macrophage + platelet membrane hybrid NPs (FM@HA@VAN)	pH-responsive antibiotic release; immune modulation	Macrophages, bacteria	Septic arthritis	Anti-inflammatory, selective bacterial killing, M1→M2 shift	[130]

(Continued)

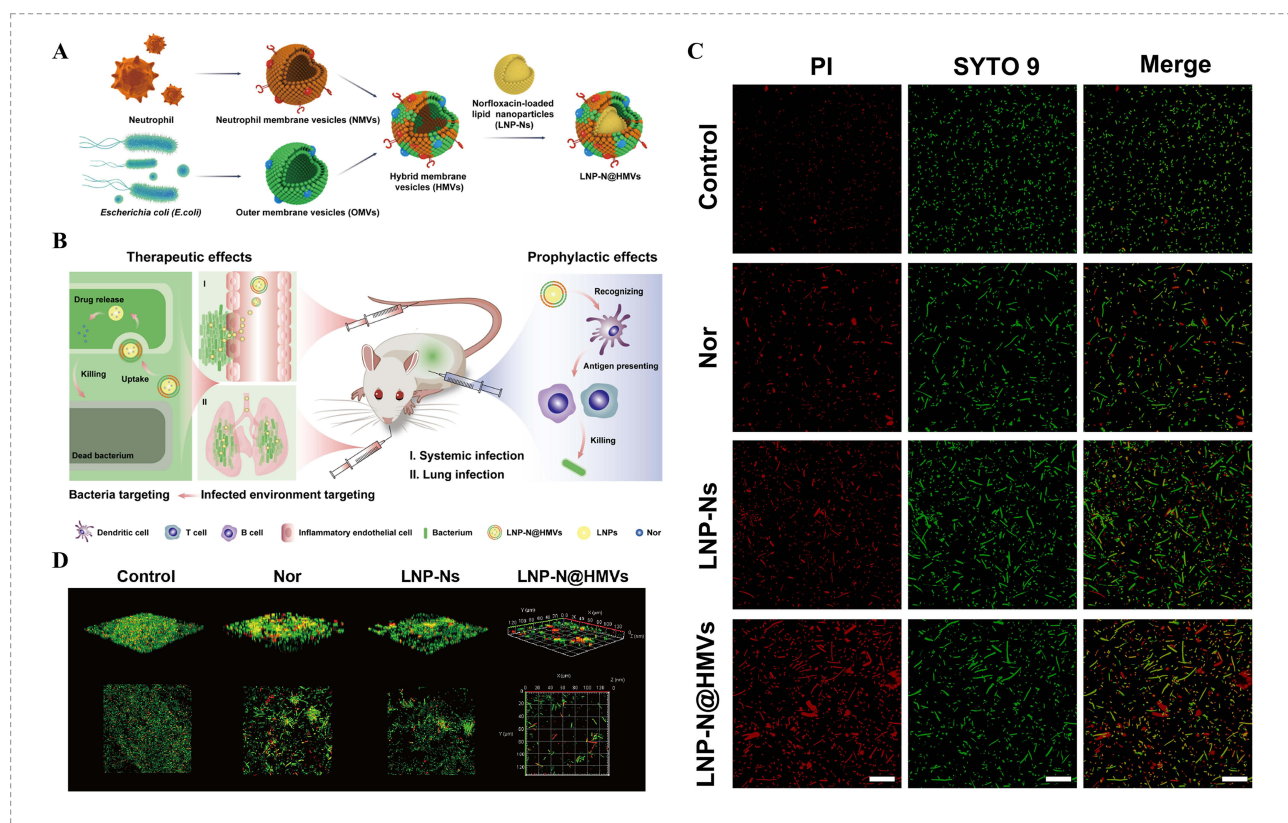
Table 2 (Continued).

Nanoparticle System	Mechanism	Target/Effect	Application Model	Key Outcome	Ref.
Neutrophil membrane-coated ROS-responsive NPs (SNM-NPs + Edv)	Target inflammation and oxidative stress; ROS-responsive drug release	ROS, inflammatory sites	Cerebral ischemia-reperfusion injury	Anti-ROS, anti-inflammatory, site-specific delivery	[143]
Stem cell membrane-coated ZIF-8 NPs	Target MSCs; sustained Zn <sup>2+</sup> release	MSCs	Bone repair	Enhanced osteogenic differentiation	[144]
Macrophage + MSC hybrid membranes	Inflammatory modulation and osteogenic promotion	MSCs	Bone defect repair	Anti-inflammatory, promotes tissue regeneration	[145]
Dual siRNA-loaded hybrid cell membrane (sipFMs)	Local gene therapy for vascular and neural differentiation	MSCs, HUVECs	Bone repair matrices	Promotes vascular and neural differentiation	[146]
Fibroblast membrane-coated Au NPs loaded with IL-4 ((Au+IL-4)@MFM)	Anti-inflammatory, fibroblast→myofibroblast differentiation	Fibroblasts, endothelial cells, macrophages	Skin wound	Accelerated wound closure, angiogenesis, immune modulation	[147]
Multi-layer stage-adaptive CNNPs (pH/ROS/enzyme responsive)	Sequential on-demand drug release (antibacterial → anti-inflammatory → pro-angiogenic → ECM regulation)	Multiple wound healing targets	Chronic wound (proposed design)	Simulate natural healing, improve treatment efficiency and prognosis	[148–150]

## Inhibition of Bacterial Infection

CNNPs have been reported to cleverly evade immune system recognition, precisely target pathogenic bacteria, neutralize harmful toxins, and deliver antibiotics to combat bacterial infections.<sup>151,152</sup> Due to the close interaction between pathogens and cell membranes, various cell membrane-mimicking nanostructures have been used as decoys to alleviate pathogen infection, such as liposomes and cell membrane-derived nanostructures.<sup>30,100,151</sup> Given the diversity of these cell membrane components, their functions also vary. For example, leukocyte membrane-coated biomimetic nanoparticles possess immune evasion and inflammatory chemotaxis properties. Xiong et al utilized this feature by coating photothermal nanoparticles with macrophage cell membranes to successfully create an intelligent cascading-targeting nanomaterial system. This system can precisely target and completely eliminate intracellular bacterial infections through a cascading mechanism.<sup>133,135</sup>

Additionally, bacterial membrane vesicles (MVs) have also been widely studied as potential therapeutic delivery systems for bacterial infections. The pathogen-associated molecular patterns (PAMPs) on the surface of MVs can activate the human immune system, and through a “bacteria-suppressing-bacteria” strategy, MVs can effectively inhibit the progression of bacterial infection.<sup>153</sup> To overcome the non-specificity issue of MVs as drug carriers, Peng et al combined neutrophils with *E. coli*-derived MVs to prepare hybrid cell membrane vesicles targeting the inflammatory microenvironment. Antibiotic norfloxacin (Nor) was loaded into these hybrid vesicles (LNP@HNV), forming a therapeutic nanoparticle system (LNP-N@HNV) (Figure 8A). This dual-targeted system can deliver antibiotics and activate both humoral and cellular immunity, precisely targeting inflammatory vascular cells and Gram-negative bacteria, significantly enhancing accumulation at infection sites, and showing remarkable potential in preventing Gram-negative bacterial infections (Figure 8B).<sup>34</sup> In vitro experiments showed that LNP-N@HNV exhibited good antimicrobial and biofilm-disrupting activity, with bactericidal assays demonstrating superior antimicrobial efficacy (Figure 8C). Furthermore, live/dead cell staining showed that LNP-N@HNV at a Nor concentration equivalent to 0.5 µg/mL almost completely eliminated all bacteria from the biofilm (Figure 8D). Moreover, CNNPs can achieve selective targeting through electrostatic interactions with bacterial membranes. Cationic albumin nanoparticles, for example, can bind to bacterial cell wall components, demonstrating significant antibacterial activity and biofilm disruption.<sup>136</sup>



**Figure 8** (A) Construction of hybrid cell membrane-coated antibiotic delivery system LNP-N@HMVs. (B) Application of LNP-N@HMVs in dual-targeted treatment and prophylaxis of bacterial infections. (C) Confocal microscopic images of *E. coli* ( $\sim 10^8$  CFU mL $^{-1}$ ) with different treatments at the equivalent Nor concentration of 0.24  $\mu$ g mL $^{-1}$  and stained with Live/Dead BacLight bacterial viability kit (green, all the bacteria; red, dead bacteria). Scale bar, 20  $\mu$ m. (D) Confocal microscopic images of *E. coli* biofilm with different treatments at the equivalent Nor concentration of 0.5  $\mu$ g mL $^{-1}$  for 24 hours and stained with Live/Dead BacLight bacterial viability kit.<sup>34</sup>

The protein toxins secreted by pathogens break through the cell membrane barrier through various complex mechanisms to exert their virulence.<sup>154</sup> Given the destructive nature of toxins and their key role in various pathophysiological processes, targeting toxins is undoubtedly a rational strategy for treating diseases. By neutralizing toxins, the pathogenic mechanisms that directly cause many severe symptoms can be effectively alleviated.<sup>155,156</sup> In the treatment of sepsis, multifunctional CNNPs have demonstrated strong therapeutic effects by precisely targeting pathogens, toxins, and inflammatory cytokines.<sup>137</sup> This strategy has shown improved therapeutic outcomes in bacterial infection mouse models. In a mouse model of bone infection, CNNPs synthesized through electroporation preserved the integrity of the membrane structure and the correct functioning of protein, thus exhibiting excellent recognition and adsorption capabilities for bacteria, toxins, and inflammatory cytokines. This approach significantly enhanced antimicrobial and anti-inflammatory activity, promoting bone tissue repair.<sup>138</sup>

It is worth noting that the difficulty in healing chronic wounds is closely related to specific bacterial communities and the biofilms they form, especially the complex biofilm barriers composed of key pathogenic bacteria such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA),<sup>157,158</sup> It is an important reason for the failure of traditional antibiotic treatment. In recent years, CMNPs have demonstrated cutting-edge advantages in anti-biofilm and regulating the ecological balance of wound microbiota. Through functionalized membrane surface modifications (such as integrating phage lyases, antimicrobial peptides or quorum sensing inhibitors), CMNPs can precisely identify and bind to the above-mentioned specific pathogenic bacteria, thereby penetrating the biofilm matrix and releasing the carried drugs to directly kill the residual bacteria inside<sup>34,133,135</sup>. In addition, some CMNPs designs interfere with the bacterial quorum sensing system, inhibit the expression of genes related to biofilm formation, and promote the disintegration of mature biofilms rather than merely killing bacteria, which helps to reduce the development of drug resistance. At the level of microbiota regulation, the precise targeting of CMNPs enables them to eliminate

dominant pathogenic bacteria while minimizing disturbance to the symbiotic beneficial flora of the wound, or by delivering prebiotics, postbiotics and other components, actively reshape the microecology conducive to host healing,<sup>159</sup> and promote the repair of chronic wounds in a coordinated manner from the perspective of restoring microbial balance.

## Promotion of Angiogenesis

Angiogenesis is a crucial process in wound healing, especially in chronic wounds where insufficient angiogenesis leads to hypoxia and restricted nutrient supply, delaying tissue repair.<sup>50,51</sup> Therefore, stimulating angiogenesis at the wound site is an important strategy for treating chronic wounds. Firstly, CNNPs can promote the proliferation and migration of endothelial cells by providing a stable microenvironment, thereby accelerating angiogenesis. For example, recent studies have found that platelet membrane-coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles effectively promote endothelial cell proliferation and migration, significantly improving tissue perfusion and promoting angiogenesis in ischemic limb models.<sup>139</sup> These innovative approaches provide new ideas and directions for the treatment of ischemic changes in refractory wounds.

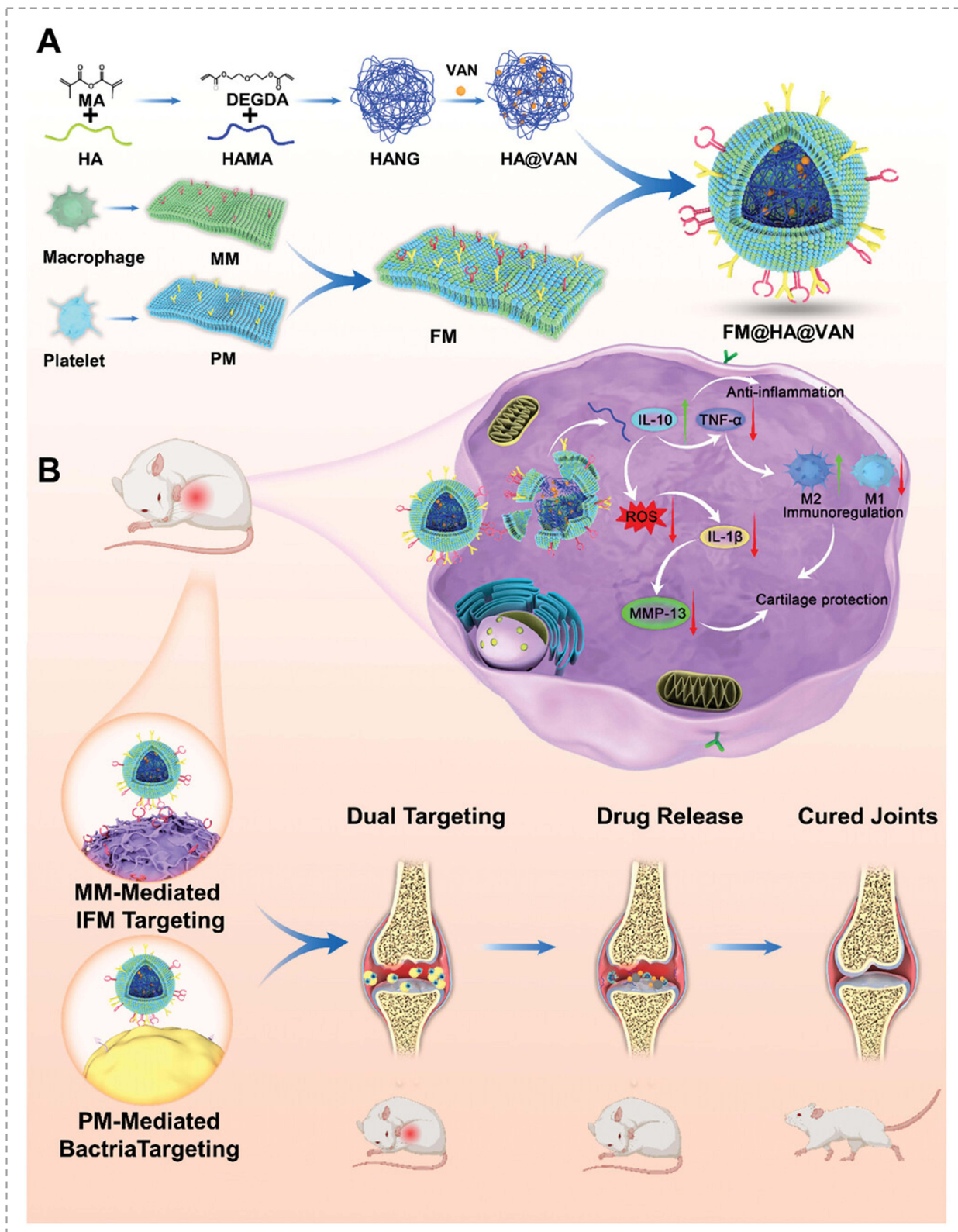
Significant progress has also been made in the use of CNNPs to promote angiogenesis in wound healing. CNNPs can serve as drug delivery systems, directly delivering angiogenesis-promoting factors to the wound site. For example, liposome-coated nanoparticles can effectively deliver angiogenesis-related microRNAs (such as miR-21), promoting reepithelialization, dermal reconstruction, and neovascularization at the wound site.<sup>140</sup> In addition to drug delivery, local enrichment of growth factors is also an innovative approach. For instance, Qiao et al designed a hybrid cell membrane with specific surface receptors that could aggregate neurotrophic growth factor (NGF) and vascular endothelial growth factor (VEGF). This approach enhanced the neurovascular differentiation of mesenchymal stem cells (MSCs), stimulated the osteogenic differentiation of MSCs via paracrine signaling related to nerves and blood vessels, and further promoted angiogenesis and neurogenesis around bone defects.<sup>141</sup>

Finally, CNNPs can promote angiogenesis by modulating the inflammatory response. Certain nanoparticles can regulate the expression of inflammatory cytokines, drive macrophage polarization towards the M2 phenotype, enhance angiogenesis, and promote tissue repair. For example, the neddylation inhibitor MLN4924 can suppress the production of pro-inflammatory cytokines, enhance endothelial cell formation, and promote angiogenesis in diabetic wound healing. Based on this, Zeng et al developed a macrophage membrane-coated PLGA nanoparticle drug delivery system (M-NPs/MLN4924) loaded with MLN4924, which protects the drug from clearance, reduces local inflammation, and promotes wound healing in diabetic mice.<sup>142</sup> Further evaluation of the effects of M-NPs/MLN4924 on human umbilical vein endothelial cell (HUVEC) proliferation and angiogenesis revealed that it enhanced cell proliferation, migration, and angiogenesis.

## Modulation of the Inflammatory Microenvironment

Inflammation is a critical stage in wound healing; however, excessive or prolonged inflammation can lead to the formation of chronic wounds. Therefore, regulating the inflammatory response to maintain immune balance is one of the key strategies for promoting wound healing.<sup>160,161</sup> Additionally, macrophages play a central role in wound healing, as their polarization state determines the progression of inflammation and the efficiency of tissue repair.<sup>162</sup> By mimicking the biological functions of natural cell membranes, CNNPs can effectively interact with the immune system, demonstrating great potential in the treatment of inflammation-related diseases.<sup>123,163</sup> CNNPs can efficiently bind with various types of cytokines through the respective cytokine receptors on the cell membrane. Cytokine neutralization can inhibit the activation of downstream macrophages and prevent the propagation of immune cascades, thus alleviating inflammation.<sup>130</sup>

In the treatment of septic arthritis, Yu et al designed a multifunctional nanoparticle drug delivery system based on macrophage membrane and platelet membrane hybrid membranes (FM@HA@VAN) (Figure 9A). The nanoparticles utilize macrophage-mediated inflammatory homing and platelet-guided bacterial targeting, exhibiting long-lasting retention and selective targeting of the infection site. Upon responding to pH changes at the infection site, the encapsulated vancomycin and hyaluronic acid are rapidly released, generating strong bactericidal and anti-inflammatory effects, and



**Figure 9** (A) Schematic of the two main steps in the preparation of FM@HA@VAN nanoparticles: 1) The HAMA is prepared by functionalizing HA through methacrylation and is subsequently copolymerized with DEGDA to fabricate HANG, which is then loaded with vancomycin to prepare HA@VAN. 2) FM is prepared by fusing MM and PM using the co-extrusion technique, and subsequently co-extruded with HA@VAN. (B) The mechanisms of action of the FM@HA@VAN nanoparticles for dual-targeted therapy of septic arthritis in vitro and in vivo (The rat image was created in BioRender. Zeping, (Y) (2024) <https://BioRender.com/y23n096>).<sup>130</sup> The original figure contained a spelling error “bactria”. Green upward arrows indicate upregulated expression, while red downward arrows indicate downregulated expression. **Abbreviations:** MA, methacrylic anhydride; HAMA, methacrylated hyaluronic acid; HA, hyaluronic acid; DEGDA, di(ethylene glycol) diacrylate; HANG, hyaluronic acid nanogel; VAN, vancomycin; FM, fused membrane; MM, macrophage membrane; PM, platelet membrane; IFM, inflammation.

protecting articular cartilage (Figure 9B).<sup>130</sup> Immunofluorescence analysis showed that FM@HA@VAN co-cultures reduced iNOS expression while increasing the CD206 level in macrophages. Furthermore, Western blot (WB) analysis also confirmed the potential of FM@HA@VAN in inducing the M1 to M2 macrophage phenotype shift.

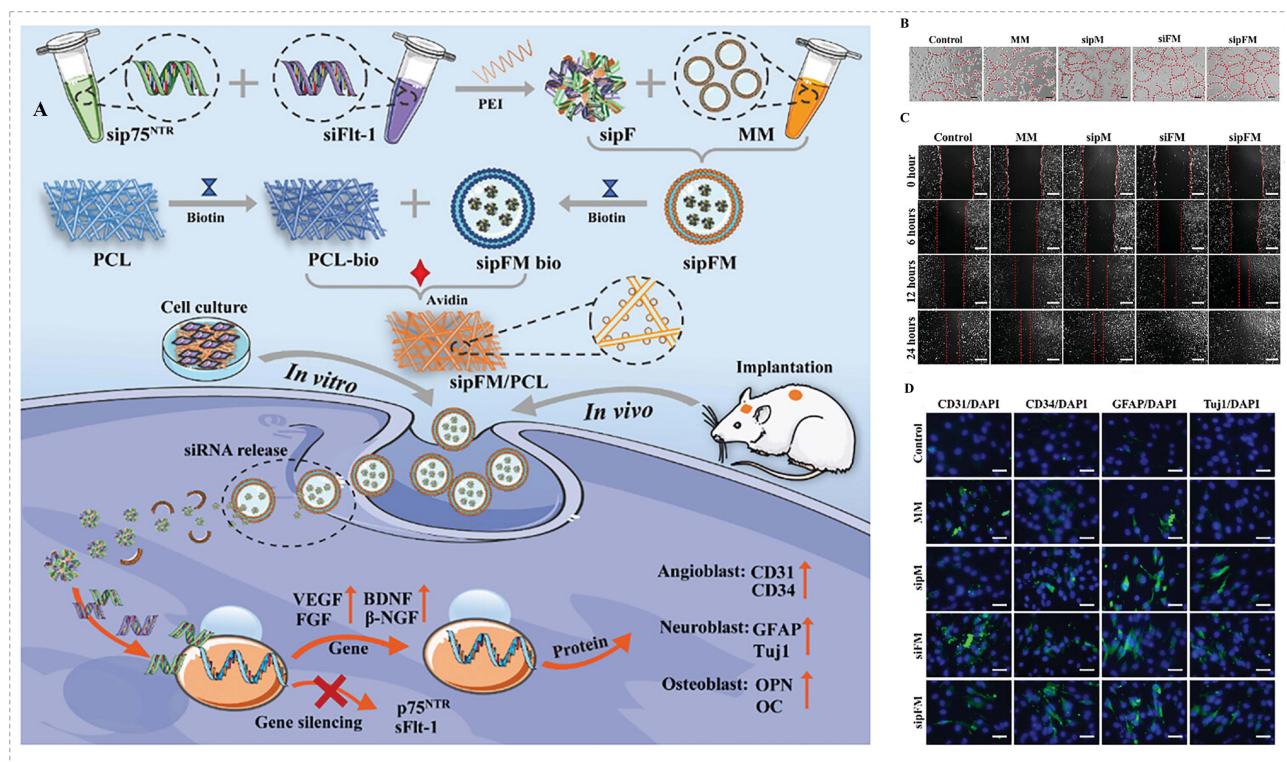
Duan et al recently developed an innovative oral formulation, where macrophage membrane-coated nanoparticles are encapsulated in enteric polymer-coated gelatin capsules. This design cleverly protects the nanoparticles from degradation in the stomach, ensuring they are accurately delivered to the colon. At the site of colonic inflammation, these nanoparticles act as “decoys” that attract and bind to macrophages while neutralizing pro-inflammatory cytokines, thus playing a pivotal role in the treatment of inflammatory bowel disease.<sup>164</sup> Overall, through design, CNNPs exhibit excellent anti-inflammatory modulation capabilities, demonstrating great potential in the treatment of inflammation-related diseases, such as chronic refractory wounds.

Oxidative stress is another key feature of chronic wounds, and inhibiting oxidative stress can promote tissue repair and regeneration, making antioxidant properties equally important in wound healing. Fortunately, CNNPs not only show potential in inhibiting excessive inflammatory responses and immune modulation but can also enhance the antioxidant capacity at the site of inflammation. For instance, in cerebral ischemia-reperfusion injury (CIRI), the accumulation of ROS leads to various oxidative damages, causing glial cell activation, infiltration of inflammatory cells, production of pro-inflammatory cytokines, and ultimately neuronal cell death. Edaravone (Edv) is a primary drug used in clinical stroke treatment to clear ROS; however, it has limitations such as low efficiency in crossing the blood-brain barrier, a short half-life, and strong toxic side effects at high concentrations. Therefore, increasing the drug concentration at the lesion site while reducing systemic toxicity is crucial. To address this, Dong et al developed a biomimetic nanoparticle system (SNM-NPs) wrapped in neutrophil membranes, which enables precise targeting of active oxygen and the inflammatory microenvironment.<sup>143</sup> By modifying with stroke-homing peptide (SHp), SNM-NPs can target damaged neurons more rapidly. Furthermore, SNM-NPs are ROS-responsive, leading to the release of edaravone (Edv), which clears ROS and inhibits neuroinflammation. This demonstrates that CNNPs not only modulate inflammation but also precisely target inflammatory sites, exhibiting excellent ROS scavenging abilities.

## Promoting Tissue Regeneration

CNNPs hold significant potential in the fields of wound repair and tissue regeneration. By simulating the unique properties of cell membranes, this technology greatly enhances the compatibility, targeting ability, and intercellular interactions of nanoparticles in the body, showcasing great potential in promoting tissue regeneration and repair at the wound site.<sup>28,76,77</sup> First, CNNPs can be integrated with stem cell therapy by delivering specific signaling molecules to promote the directional differentiation and functional activity of stem cells. In the field of bone tissue repair, Ren et al developed an innovative nanopatform that uses stem cell membranes (SCMs) to encapsulate zeolitic imidazolate framework-8 (ZIF-8) nanoparticles. This design not only improves biocompatibility but also enhances targeting capability toward mesenchymal stem cells (MSCs). The biomimetic nanoparticles regulate the sustained release of Zn<sup>2+</sup>, promoting specific internalization into MSCs, thereby significantly enhancing the osteogenic potential of the stem cells.<sup>144</sup> Studies have shown that hybrid cell membranes derived from macrophages and MSCs retain the anti-inflammatory phenotype of macrophages and promote osteogenic differentiation. By regulating the inflammatory microenvironment, they promote the repair of bone defects.<sup>145</sup> Building on this, Qiao et al prepared a dual siRNA formulation targeting soluble vascular endothelial growth factor receptor 1 (sFlt-1) and p75 neurotrophin receptor (p75NTR) for local delivery, extracted hybrid membranes as a dual siRNA gene delivery vector. These cell membrane-loaded dual siRNAs (sipFMs) enabled local gene therapy to promote the vascular and neural differentiation of bone repair matrices (Figure 10A).<sup>146</sup> SipFMs effectively promoted the differentiation and migration of human umbilical vein endothelial cells (HUVECs), and in vitro experiments demonstrated that the platform promoted vascular differentiation (Figure 10B and C) and neural differentiation (Figure 10D) of MSCs.

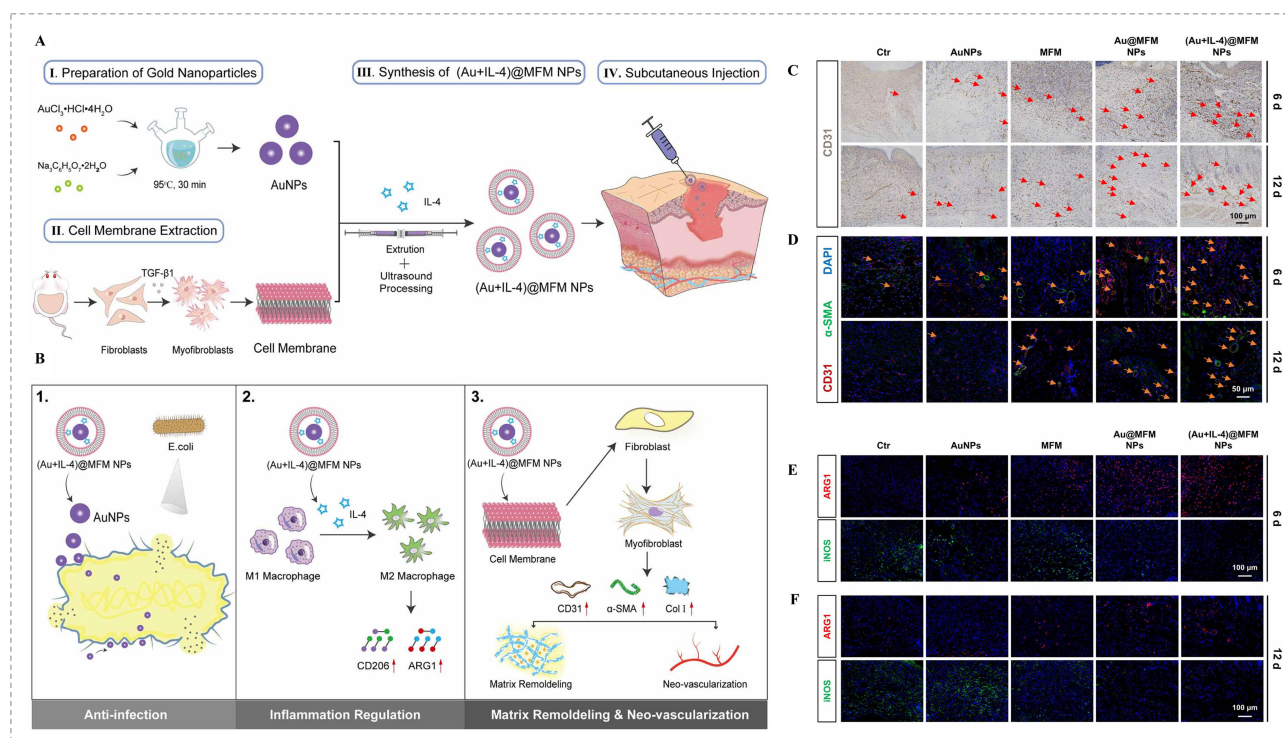
Fibroblasts play a crucial role during the proliferative phase, where they migrate along the fibrin network and initiate epithelial regeneration at the wound edges. These cells secrete large amounts of extracellular matrix (ECM) proteins at the damaged area.<sup>54,56</sup> Additionally, fibroblasts are temporarily activated into myofibroblasts, a highly contractile subtype of fibroblasts whose stress fibers consist of cytoplasmic actin and myosin, enabling them to express ECM proteins like collagen



**Figure 10** (A) Schematic illustrations of the dual siRNA-loaded cell membrane functionalized matrix facilitate bone regeneration with angiogenesis and neurogenesis. The GFMs can regulate the expression of vascular-related genes and nerve-related genes, and promote the paracrine function of vascular and nerve factors *in vitro*. The bone repair matrix based on angiogenesis and neurogenesis improves the bone defects microenvironment and achieves bone defect repair and bone integration. (B) The images of the tube formation of HUVECs. Red dotted lines indicate the tube structures identified and quantified by ImageJ during tube formation analysis. The scale bar = 200  $\mu$ m. (C) The images of wound healing assay. Red dotted lines indicate the initial wound edges used as reference for migration distance measurement at different time points. The scale bar = 50  $\mu$ m. (D) The expression of CD31, CD34, GFAP, and Tuj1 markers of MSCs cultured with siRNA@MMs for 7 days. The scale bar = 50  $\mu$ m.<sup>146</sup> Red upward arrows indicate upregulated expression.

I (Col I) and alpha-smooth muscle actin ( $\alpha$ -SMA).<sup>165</sup> Myofibroblasts provide adhesion structures to the matrix and close the wound through cell contraction.<sup>166</sup> Therefore, modulating the biological activity of myofibroblasts during the proliferative phase is a promising strategy to improve the outcome of dysregulated skin wound healing. In recent years, researchers in the field of wound repair have focused on using cell membrane-coated nanoparticle platforms to activate the transformation of fibroblasts into myofibroblasts, thus promoting skin wound healing. Additionally, by leveraging the drug delivery capabilities of CNNPs, cytokines are delivered to stimulate the proliferation and migration of key cells, such as fibroblasts and endothelial cells, to promote granulation tissue formation and epidermal regeneration. For example, Jia et al used cell membranes extracted from fibroblasts to coat gold nanoparticles and loaded them with IL-4 cytokine to promote skin wound healing (Figure 11A). This nanoparticle platform, (Au+IL-4)@MFM NPs, effectively cleared bacterial infections, modulated the inflammatory response, and promoted the transformation of fibroblasts into myofibroblasts, thereby accelerating the wound healing process (Figure 11B).<sup>147</sup> Experimental results showed that (Au+IL-4)@MFM NPs promoted the differentiation of fibroblasts into myofibroblasts and enhanced fibroblast proliferation and migration, while promoting angiogenesis in skin wounds and inducing the conversion of endogenous macrophages into an anti-inflammatory phenotype (Figure 11C–F).

As mentioned earlier, wound healing is a highly dynamic and orderly multi-stage process, involving the close connection of the inflammatory phase, proliferative phase and remodeling phase. Although existing studies have listed the independent functions of CNNPs in terms of antibacterial, anti-inflammatory, angiogenic promotion and tissue regeneration, their intelligent response and sequential treatment ability in intervening at different healing stages still need to be further clarified. The design of future CNNPs can focus on simulating the temporal nature of the natural healing process. By constructing environment-responsive nanoplateforms, on-demand release of different therapeutic drugs can be achieved<sup>148–150</sup>. For instance, multi-layer coated CNNPs with pH, ROS or enzyme responsiveness can be



**Figure 11** (A) Preparation of gold nanoparticles, derivation of myfibroblast membrane, and synthesis of (Au+IL-4)@MFM NPs. (B) Regulatory mechanism of (Au+IL-4)@MFM NPs in wound healing process. The NPs release gold nanoparticles to clear bacteria, deliver IL-4 to repolarize macrophages for accelerating inflammation, and induce myfibroblast membrane to activate fibroblast-myfibroblast transition for improving outcomes of dysregulated skin wound healing. (C) The immunohistochemical images of CD31 expression (CD31 is an endothelial cell marker) at 6 d and 12 d. Scale bar = 100  $\mu\text{m}$ . (D) The immunofluorescent images of CD31/ $\alpha$ -SMA expression (CD31 is an endothelial cell marker,  $\alpha$ -SMA is a myfibroblast marker) at 6 d and 12 d. Cell nucleus is stained with DAPI in blue, CD31 is stained in red, and  $\alpha$ -SMA is stained in green. Scale bar = 50  $\mu\text{m}$ . (E), (F) The immunofluorescent images of ARG1 (marker of M2 macrophage) and iNOS (marker of M1 macrophage) after different treatments for 6 and 12 d. Cell nucleus is stained with DAPI in blue, ARG1 is stained in red, and iNOS is stained in green. Scale bar = 100  $\mu\text{m}$ .<sup>147</sup> CD31 expression is shown, serving as an endothelial cell marker for angiogenesis.  $\alpha$ -SMA expression is shown, serving as a myfibroblast marker for myfibroblast differentiation.<sup>147</sup> Arrows indicate representative staining markers. Red upward arrows represent upregulated expression.

designed to preferentially release antibacterial drugs and anti-inflammatory factors during the inflammatory period to control infection and excessive inflammation. Subsequently, during the proliferative phase, in response to microenvironmental changes (such as elevated pH or expression of specific matrix metalloproteinases), the release of pro-angiogenic drugs (such as VEGF) or growth factors is triggered to promote granulation tissue formation and re-epithelialization; Ultimately, during the remodeling period, factors regulating the synthesis and degradation of ECM are continuously released to optimize the quality of tissue repair. Such stage adaptive CNNPs can not only precisely match the dynamic demands of the healing process, but also significantly improve the treatment efficiency and prognosis of chronic refractory wounds by reducing off-target effects and optimizing drug utilization.

## Current Challenges

In recent years, Cell Membrane-Coated Nanoparticles (CMNPs) have demonstrated significant potential in chronic wound treatment due to their superior biocompatibility, prolonged circulation, and active targeting properties. However, despite advances in basic research, this technology still faces numerous challenges, including issues related to the source and large-scale production of cell membranes, nanoparticle stability and drug release control, biocompatibility and safety evaluation, immunogenicity, personalized treatment strategies, and technical barriers to clinical translation.<sup>29,167,168</sup> Among them, quality control is the core challenge in achieving clinical transformation, especially how to ensure that each batch of products is uniformly controllable in terms of size, coating efficiency and biological activity to meet the strict standards of drug research and development.<sup>167,169</sup> Addressing these key issues will be crucial for advancing the clinical application of CMNPs.

Firstly, the large-scale production of CMNPs is constrained by the source of cell membranes. Currently, cell membranes derived from red blood cells, macrophages, platelets, stem cells, and other sources are used to coat nanoparticles, imparting different biological functions. However, large-scale extraction and purification of cell membranes still face challenges, such as high cell culture costs, membrane protein denaturation during the extraction process, and batch-to-batch variations.<sup>170</sup> Therefore, developing efficient membrane extraction and purification technologies, as well as establishing standardized quality control systems, are key steps for the industrialization of CMNPs. In terms of quality control, it is necessary to establish a series of quantifiable and repeatable evaluation criteria, ranging from the management of the cell bank at the cell source, to the monitoring of the composition and activity of membrane proteins during the membrane extraction process, and finally to the physical and chemical properties (such as size, Zeta potential, and coating integrity) and biological functions (such as targeting and immune escape ability) of the final CMNPs products.<sup>169</sup>

Secondly, the stability of CMNPs and the regulation of drug release still require further optimization.<sup>171,172</sup> Due to the fluidity and degradable nature of cell membranes, CMNPs may undergo membrane fusion or membrane protein shedding *in vivo*, affecting their functional stability. Additionally, the cell membrane may influence the drug release rate, limiting the therapeutic effect. Some studies have attempted to enhance the stability and controllable release capability of CMNPs through cross-linking modifications, freeze-drying storage, or the construction of stimulus-responsive CMNPs (eg, pH, enzyme, or redox-responsive). These optimization strategies are crucial for improving the effectiveness of CMNPs in chronic wound treatment. During this process, it is necessary to establish corresponding stability indication methods, such as monitoring particle size changes, membrane protein retention rates and drug leakage rates in accelerated stability tests, and set clear shelf life standards to ensure the consistency of product quality during storage and transportation.

Furthermore, the biocompatibility and safety evaluation of CMNPs still need in-depth research.<sup>173</sup> Although CMNPs are derived from natural cell membranes, the long-term degradation and metabolic pathways of CMNPs *in vivo* are not yet clear. Different types of cell membranes may induce distinct immune responses.<sup>171,172</sup> For example, allogeneic cell membranes may contain MHC molecules, increasing immunogenicity and affecting their clinical application. Therefore, establishing a comprehensive biocompatibility assessment system, including *in vivo* pharmacokinetic analysis, immunogenicity evaluation, and long-term toxicity studies, will aid in advancing CMNPs to clinical trials. It is particularly crucial to establish quality control indicators for safety attributes such as immunogenicity, for instance, to monitor the immune response potential of products between batches through methods like *in vitro* cytokine release tests.

Regarding personalized treatment, CMNPs hold vast potential for application. For instance, by genetically engineering surface proteins on cell membranes or using the patient's own cell membranes for nanoparticle coating, personalized drug delivery strategies can be achieved. Additionally, combining artificial intelligence and big data analysis to optimize pathological subtyping and immune status evaluation will help improve the precision and effectiveness of CMNPs in chronic wound treatment. This places higher demands on quality control, that is, it is necessary to develop a fast and efficient quality control platform that can adapt to small-batch and multi-batch production modes, ensuring that even personalized CMNPs products from self-sourced sources can meet the predetermined safety and effectiveness benchmarks.<sup>169</sup>

Despite the enormous potential shown by CMNPs in basic research, their clinical translation still faces obstacles such as production standardization, regulatory policy gaps, and safety validation issues. In the future, efforts should focus on optimizing cell membrane extraction and nanoparticle synthesis processes, developing low-immunogenicity, high-targeting CMNPs, and establishing stringent preclinical safety evaluation systems.<sup>29,167,168</sup> Among them, establishing a full-chain quality control system covering raw materials, intermediates and final products, and promoting regulatory authorities to recognize innovative quality control methods applicable to CMNPs (such as determination based on biological potency), is the inevitable way to break through the bottleneck of clinical transformation.<sup>169</sup> Additionally, exploring the combination of CMNPs with other advanced therapies, such as gene editing and stem cell therapy, may further enhance their clinical application value in chronic wound treatment. With the continuous development of nanomedicine and biotechnology, CMNPs are expected to become a key breakthrough strategy in the field of chronic wound repair.

## Future Development Directions

With the rapid development of biomedical engineering, nanotechnology, and precision medicine, the application prospects of Cell Membrane-Coated Nanoparticles (CMNPs) in chronic wound repair are becoming increasingly broad. Future research will focus on areas such as cell membrane engineering, intelligent drug delivery, 3D bioprinting, and artificial intelligence-assisted treatment decision-making, aiming to overcome current technological bottlenecks and realize more precise, efficient, and safe wound repair strategies.<sup>120,121</sup>

In terms of cell membrane engineering, enhancing the targeting ability of CMNPs through genetic or chemical modifications is a key research direction.<sup>174,175</sup> For example, modifying integrins or chemokine receptors to increase their specificity for damaged tissues, while employing multi-cell membrane coating strategies, could use red blood cell membranes to extend circulation time and macrophage membranes to enhance targeting capabilities at inflammation sites.<sup>85,109,110,112</sup> This would allow for multi-functional synergistic effects. Additionally, the construction of artificial biomimetic membranes can further improve the stability and controllability of CMNPs, enhancing their therapeutic potential.<sup>76,118</sup>

In the field of intelligent nanoparticle delivery, combining CRISPR-Cas9 and other gene-editing tools with CMNPs can enable targeted regulation of inflammatory factors in wounds (such as TNF- $\alpha$ , IL-1 $\beta$ ) or genes that promote tissue repair (such as VEGF, TGF- $\beta$ ).<sup>176</sup> A pathological microenvironment-responsive system (such as pH, oxidative stress) can be used to achieve precise drug release, while combining photosensitive or magnetosensitive materials will allow drug release to be controlled by external stimuli, improving the controllability and efficiency of treatment.<sup>23,134</sup>

The application of 3D bioprinting technology enables the integration of CMNPs with hydrogels, collagen, and other biomaterials to construct bioactive, personalized biomimetic scaffolds.<sup>177</sup> These scaffolds can be adapted to the wound morphology of different patients, providing mechanical support while continuously releasing healing-promoting factors. Furthermore, combining patient-specific cell membrane-coated nanomaterials with customized bio-inks can be achieved. High-throughput imaging analysis and computer-aided design (CAD) can precisely match the needs of wound repair.<sup>178</sup> The rapid development of Artificial Intelligence (AI) technology also presents new opportunities for the precise application of CMNPs. AI can be used for deep learning analysis of wound images (such as OCT, ultrasound, or infrared thermography) to assess the wound healing status, predict the efficacy of different treatment options, and dynamically optimize CMNP delivery strategies. AI can also be employed for large-scale screening of bioactive molecules, optimizing CMNP membrane protein modification strategies to enhance their potential in personalized treatments.<sup>179,180</sup> Despite the challenges of biocompatibility, batch production, and standardization in the clinical translation of CMNPs, interdisciplinary integration is expected to lead to breakthrough progress in chronic wound repair, providing more precise and efficient treatment options for patients.<sup>29,167,168</sup>

## Conclusion

The treatment of chronic wounds remains a major challenge in clinical medicine and biomedical engineering. Traditional therapies are limited by poor biocompatibility, low drug delivery efficiency, and the complexity of the wound micro-environment, which hinder effective healing. In recent years, cell membrane-coated nanoparticles (CMNPs) have emerged as a promising therapeutic strategy. By combining the high loading capacity of synthetic nanoparticles with the biomimetic properties of natural cell membranes, CMNPs can evade immune clearance, achieve targeted delivery, and release therapeutic agents in a controlled and stage-specific manner.

Importantly, CMNPs exhibit multiple synergistic mechanisms, including antibacterial activity, anti-inflammatory effects, promotion of angiogenesis, and facilitation of tissue regeneration, which collectively enhance wound repair. Experimental studies and animal models have demonstrated their efficacy and versatility. Despite these advances, several challenges remain for clinical translation, including large-scale production, quality control, and long-term safety.

With ongoing progress in nanotechnology, biotechnology, and precision medicine, CMNPs are expected to become a core platform for chronic wound management, providing an integrated approach that addresses the multifaceted biological processes of wound healing.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author Yuchang Wang upon reasonable request.

## Consent Statement

No individual personal data is included in the study.

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## Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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