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Cell membrane-derived nanovesicles as extracellular vesicle-mimetics in wound healing

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ABSTRACT

Cell membrane-derived nanovesicles (NVs) have emerged as promising alternatives to extracellular vesicles (EVs) for wound healing applications, addressing the limitations of traditional EVs, which include insufficient targeting capability, low production yield, and limited drug-loading capacity. Through mechanical cell extrusion methods, NVs exhibit superior characteristics, demonstrating enhanced yield, stability, and purity compared to natural EVs. These NVs can be derived from various membrane sources, including single cell types (stem cells, blood cells, immune cells, and bacterial membranes), hybrid cell membranes and cell membranes mixed with liposomes, with each offering unique therapeutic properties. The integration of genetic engineering and surface modifications has further enhanced NV functionality, enabling precise targeting and improved drug delivery capabilities. Recent advances in NV-based therapies have demonstrated their potential across multiple biomedical applications. Although challenges persist in terms of standardization, storage stability, and clinical translation, the combination of natural cell-derived functions with artificial modification potential positions NVs as a promising platform for next-generation therapeutic delivery systems, thereby offering new possibilities in wound healing applications. Finally, we explore the challenges and future prospects of translating NV-based therapeutics into clinical practice, providing insights into the future development of this innovative approach in wound healing and tissue repair.

1. Introduction

The skin functions as a protective barrier against environmental factors, including extreme temperatures and pathogenic invasions. Nevertheless, it remains susceptible to trauma-induced damage and may experience impaired healing, particularly in individuals with underlying

Abbreviations: 4OI, 4-octyl itaconate; aEVs, artificial EVs; ANVs, ADSC-derived NVs; AIE, aggregation-induced emission; ADSCs, adipose-derived stem cells; bFGF, basic fibroblast growth factor; BMSCs, bone marrow mesenchymal stem cells; BNVs, bacteria-derived NVs; BSA, bovine serum albumin; CNPs, cerium oxide NPs; CXCR4, C-X-C motif chemokine receptor 4; ECs, endothelial cells; ECM, extracellular matrix; EGF, epidermal growth factor; EMNVs, engineered macrophage-derived NVs; ES, embryonic stem cells; EVs, extracellular vesicles; GelMA, Gelatin Methacryloyl; HDF, human dermal fibroblast; iECs, iPSC-derived ECs; IL-6, interleukin-6; IL-10, interleukin-10; iPSCs, induced pluripotent stem cells; LPC, lysophosphatidylcholine; LPCAT, LPC acyltransferase; MAPK, mitogen-activated protein kinase; M2BNVs, M2 macrophage-derived bioinspired NVs; MSC-NVs, NVs derived from MSCs; MSCs, mesenchymal stem cells; NIR, near-infrared; NPs, nanoparticles; NVs, nanovesicles; OMVs, outer membrane vesicles; OXA, oxaliplatin; PDGF, platelet-derived growth factor; RBC, red blood cell; RC-Lip, RBC membrane-mimicking liposomes incorporating curcumin; R-SeNPs, RBC membrane vesicles-SeNPs nanosystems; ROS, reactive oxygen species; SC-NVs, stem cell-derived NVs; SeNPs, selenium NPs; TGF-β, transforming growth factor β; THB, 4-(2-(5-(4-(diphenylamino)phenyl)thiophen-2-yl)vinyl)-1-(2-hydroxyethyl) pyridin-1-ium bromide; THB@ANVs, THB-functionalized ANVs; TNF-α, tumor necrosis factor-α; TPNVs, NVs with TIGIT (T cell immunoreceptor with Ig and ITIM domains)-expressing cell membranes and platelet cell membranes; UCMSCs, umbilical cord mesenchymal stem cells; VEGF, vascular endothelial growth factor.

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conditions such as diabetes. The compromised healing of dermal wounds and ulcers significantly affects millions of individuals, leading to psychological distress, pain, suffering, and diminished quality of life, while imposing substantial costs on healthcare providers and insurers [1]. Skin ulcers represent the leading cause of diabetes-related amputations, posing serious challenges for affected patients [2]. Due to their considerable social and medical implications, chronic wounds continue to constitute a significant healthcare challenge requiring focused attention. Prompt and efficient wound closure is crucial for maintaining skin integrity, which is essential in preventing systemic pathogenic invasion.

Wound healing represents a complex and dynamic physiological process comprising four well-coordinated, sequential, and overlapping phases: hemostatic, inflammatory, proliferative, and remodeling. During the hemostatic phase, the formed clot protects the wound area from environmental contaminants while providing both matrix and soluble factors that facilitate cell adherence and act as chemoattractants for various cellular lineages involved in the healing process. Subsequently, the inflammatory phase is characterized by the infiltration of bone marrow-derived immune cells, which promote healing by eliminating invading pathogens, apoptotic cells, cellular debris, and damaged extracellular matrix (ECM), thus preparing the site for injury recovery [3]. During the inflammatory phase, neutrophils and macrophages generate elevated levels of superoxide and H_2O_2 through NOX, playing a vital role in bacterial eradication and preventing wound infections. Additionally, reactive oxygen species (ROS) can stimulate the release of tumor necrosis factor-α (TNF-α) and platelet-derived growth factor, facilitating the recruitment and migration of monocytes and macrophages to the wound site for pathogen elimination [4]. Finally, during the tissue remodeling phase, the remodeling of newly synthesized ECM and collagen degradation results in reduced wound thickness [3]. Simultaneously, most newly formed capillaries regress, normalizing tissue vascularity and enabling wound margin approximation through underlying connective tissue contraction [3,5].

Extracellular vesicles (EVs) are naturally occurring vesicles that exhibit a spherical structure ranging in size from 40 nm to 5 μm. These vesicles play a crucial role in intercellular signal transduction by transporting bioactive molecules, including lipids, metabolites, proteins, and nucleic acids [6,7]. EVs are generated by virtually all cell types in the body and have been successfully isolated from various biological fluids, including breast milk and urine, as well as from dissociated tissues and cell culture supernatants [8]. Ultracentrifugation represents the golden method for EV separation, owing to its accessibility, simplicity, and harvest of relatively homogeneous size groups of EVs [9]. EVs are classified into three distinct subgroups: apoptotic particles (100–5000 nm) released during apoptosis, exosomes (50–150 nm) produced by sorting endosomes, and microvesicles (100–1000 nm) derived from the cell membrane [10]. These vesicles can transport endogenous molecules or therapeutic agents to recipient cells through endocytosis or direct membrane fusion. For example, drug-loaded exosomes can traverse biological membrane barriers and enter target cells via receptor-mediated endocytosis, phagocytosis, and macropinocytosis, thereby releasing their cargoes and exerting therapeutic effects efficiently [11]. EVs present a novel opportunity for drug delivery systems, characterized by exceptional biocompatibility, minimal immunogenicity, and high bioavailability. They provide a mechanism for targeted delivery of bioactive substances to specific tissues, cells, and organs. Additionally, EVs offer advantages such as abundant availability, reduced risk of immunologic rejection, and potential for reengineering or combination with other biomaterials [12]. EVs, serving as natural mediators of intercellular communication and possessing nanoscale dimensions, facilitate bidirectional communication with cells in the wound microenvironment, thereby enhancing cellular repair mechanisms and accelerating wound recovery. In the field of wound healing, EV-based therapies have gained increasing attention. EVs can be administered directly to wounds via topical application, which not only minimizes patient discomfort but also enables the delivery of higher EV concentrations directly to the injury site [13,14]. The naturally occurring, nanoscale EVs possess several intrinsic benefits compared to traditionally synthesized NPs, such as less immunogenicity, excellent biocompatibility, increased stability in the blood, high penetration depth in deep tissue, and the ability to target specific disease sites via their homing characteristics [15]. However, the therapeutic efficacy of EVs is limited by their restricted cargo capacity. EVs confront a significant limitation in clinical applications due to their low yield under *in vitro* culture conditions. This constraint significantly hinders their industrial translation and large-scale implementation. Furthermore, low yield rates and batch-to-batch variability present significant challenges for clinical application and large-scale production. Consequently, the development of engineered and modified EVs capable of delivering enhanced therapeutic payloads has become a primary focus of translational research [16].

The facile extrusion technology for generating membrane-derived nanovesicles (NVs) presents a viable alternative to EVs, offering enhanced productivity and expanded applications [17]. NVs are generated when cells mechanically pass through microporous filters multiple times, resulting in membrane fragmentation and subsequent spontaneous reassembly into nanometer-sized vesicles [18]. These NVs retain cellular components, including RNAs and proteins, from their source cells. Compared to EVs, NVs demonstrate comparable biofunctionalities while offering distinct advantages, including higher yield, shorter production time, and improved cost-effectiveness (Fig. 1A) [19]. The scalable production potential of NVs may advance the management of conditions requiring substantial cellular or therapeutic material quantities, including diabetic and infectious wound healing. Consequently, they are emerging as significant facilitators of the healing process [20].

Jang et al. first reported the application of a mechanical extrusion method to generate NVs with enhanced yield, consistent stability, and improved purity [18]. NVs produced through serial cell extrusion demonstrate membrane structures and dimensions similar to those of exosomes. As artificial exosome analogs created through sequential cell extrusion across porous membrane filters [21,22], cell-based NVs achieve a 250 flod increase in yield and demonstrate significant enrichment in protein content and RNAs compared to exosomes [23]. In comparison with naturally secreted EVs, these NVs offer superior productivity, substantially reducing large-scale production costs [24]. Consequently, NVs are anticipated to demonstrate greater efficiency in biomolecule transfer and therapeutic efficacy within recipient cells compared to exosomes, indicating enhanced clinical potential [25]. Moreover, NVs exhibit exceptional targeting capabilities. Targeted drug delivery systems have shown promise in modifying unfavorable microenvironments to promote disease remission while minimizing adverse effects on surrounding organs and tissues [26].

Cell-based NVs have recently emerged as promising innovative vesicles for targeted drug delivery and direct therapeutic applications. Surface modification with targeting ligands enhances therapeutic efficiency while minimizing adverse effects. Biomimetic nanoparticles (NPs) with cell membrane coatings have attracted considerable attention. These membrane-encapsulated NPs inherit the surface properties of their source cells, conferring advantages such as extended circulation half-life [27], immune modulation [28], homotypic targeting [29], and the capacity to neutralize pathological molecules [30]. These NPs are synthesized through coextrusion of cultured cell plasma membranes with prefabricated NPs [31]. Several successful applications demonstrate this approach's potential. For instance, red blood cell (RBC) membrane-coated NPs exhibit prolonged circulation time following intravenous administration and mitigate hemolytic effects of membrane-compromising toxins on healthy RBCs [32]. Similarly, neutrophil membrane-coated NPs function as effective decoys for inflammatory factors, providing broad-spectrum inhibition of inflammatory cascades during disease progression [33]. Moreover, platelet

A

	NVs	EVs	LNP
Size	Adjustable, typically 50-300 nm	50–5000 nm	Adjustable, typically 50–200 nm
Yield	++	+	+++
Scalability	+++	+	++
Cargo loading	+++	+	++
Immunogenicity	++	+++	+

B

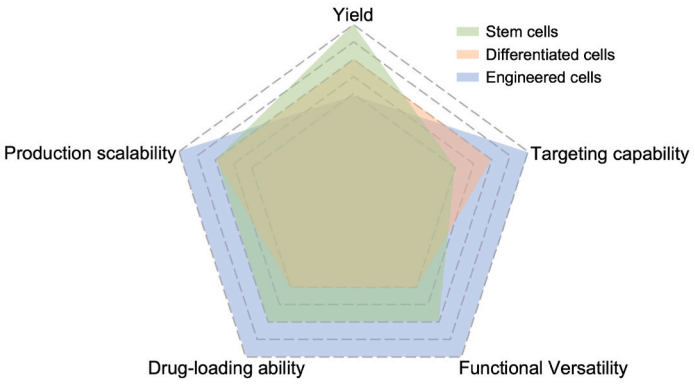


Fig. 1. Comparative Analysis of NVs, EVs, and LNP. **(A)** Summary of the characteristics of NVs, EVs, and LNPs, highlighting differences in size, yield, scalability, cargo loading, and immunogenicity. The levels of each characteristic are denoted by "+++" for high, "++" for medium, and "+" for low. **(B)** Spider plot illustrating the different features of NVs derived from three distinct cell types: stem cells, differentiated cells, and engineered cells.

membrane-camouflaged NPs enable targeted delivery of thrombolytic agents to thrombotic sites, enhancing thrombolytic activity and therapeutic outcomes [34].

In this review, we examine the current evidence supporting cell membrane-based NVs as regenerative therapy for wound healing acceleration (see Scheme 1). We first classify NVs according to their membrane sources, emphasizing single cell membrane type-derived NVs from stem cells, blood cells, immune cells, and bacterial membranes, as well as hybrid cell membrane type-derived NVs (see Table 1). We evaluate the advantages and potential applications of each type, highlighting their specific properties in wound healing contexts. Subsequently, we explore key strategies for enhancing NV functionality, including genetic modification of source cells and surface chemical modifications, designed to improve the therapeutic efficacy of NV-based drug delivery systems. We then present recent advances in NV-based therapeutics, encompassing drug loading strategies and targeted delivery mechanisms. Furthermore, we discuss the biomedical applications of cell membrane-based NVs, emphasizing their therapeutic potential across various fields. The review concludes with an analysis of challenges and prospects in translating NV-based therapies to clinical applications.

2. Classification of the NVs based on membrane sources

2.1. Single cell membrane type-derived NVs

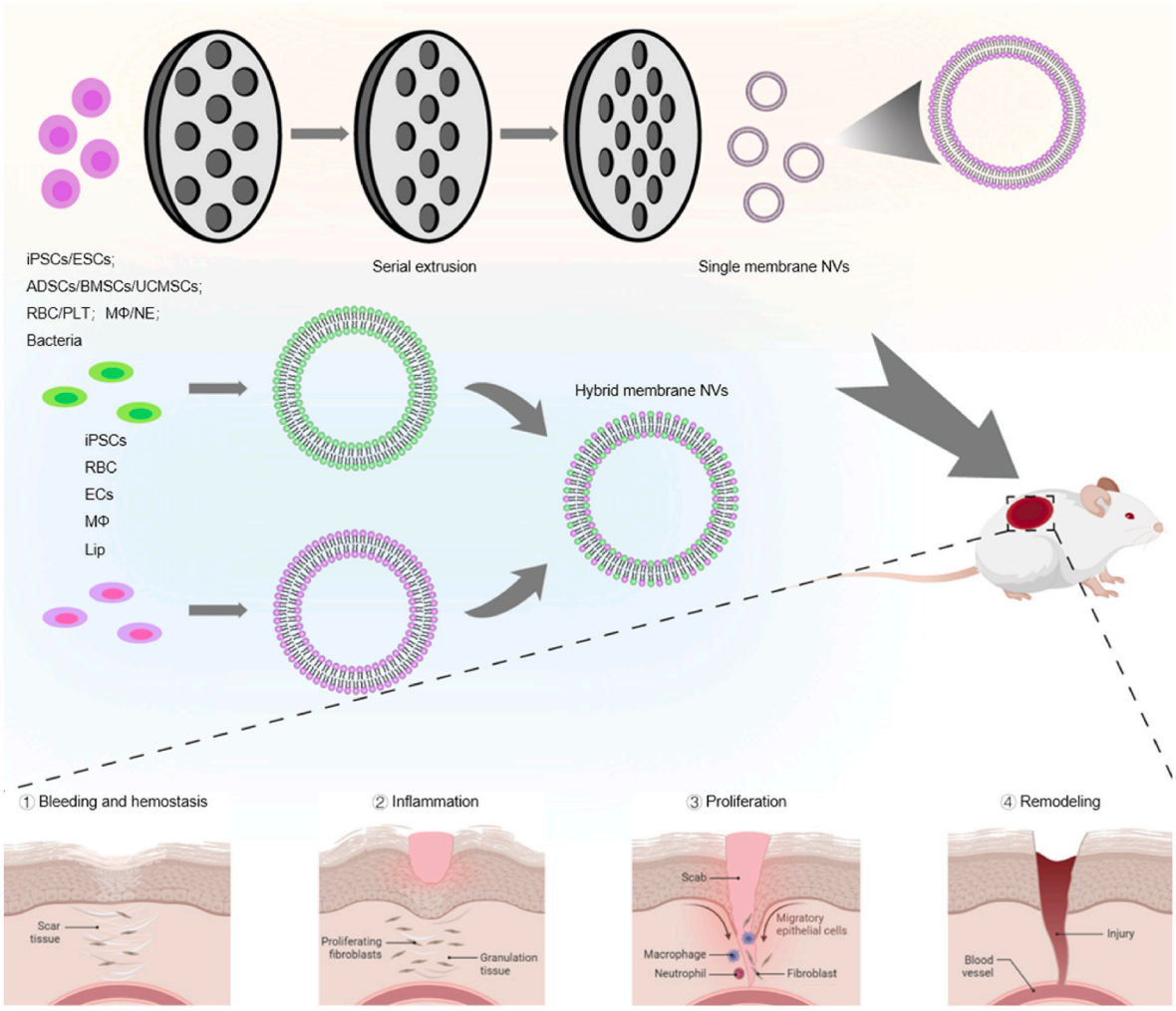
2.1.1. Stem cell–derived NVs

Stem cells are undifferentiated cells characterized by multiple capabilities, including multilineage differentiation, self-renewal capacity, and paracrine bioactivity [35]. These cells are abundant in various sources, including bone marrow, adipose tissue, epidermis, and placenta [36]. Numerous studies have demonstrated the efficacy of stem cell-based therapies in treating neurological, circulatory, orthopedic, and other systemic diseases [37,38]. However, stem cell therapies continue to face significant challenges, including low cell viability rates, inherent tumorigenic risks, and ethical concerns regarding donor sources [39]. In addressing these limitations, researchers have determined that stem cell-derived NVs (SC-NVs) retain many beneficial properties of stem cells while avoiding risks associated with whole-cell transplantation, thus offering a safer and more effective alternative to cell-based therapies [40]. Specifically, SC-NVs promote multilayered restoration through various beneficial effects, including immune polarization modulation, endothelial regeneration, anti-inflammatory activity, revascularization, oxidative stress-induced damage attenuation, and enhanced collagen remodeling during wound healing [41]. Moreover, SC-NVs demonstrate exceptional expandability and plasticity. Their therapeutic efficacy can be significantly enhanced through pharmacological pretreatment of source stem cells, physical methods, or targeted modification of EV active components [42].

Given the limitations of EVs, NVs derived from various stem cell sources, including umbilical cord mesenchymal stem cells (UCMSCs), adipose-derived stem cells (ADSCs), bone marrow mesenchymal stem cells (BMSCs), induced pluripotent stem cells (iPSCs), and embryonic stem (ES) cells, have demonstrated efficacy in wound healing applications. Stem cell derived-NVs can be rich in a variety of growth factors and have significant advantages in promoting cell proliferation (Fig. 1B). Their natural ability to promote angiogenesis, and enhance proliferation makes them highly versatile, as detailed in the following sections.

2.1.1.1. iPSC-derived NVs. iPSCs are generated from adult cells through *in vitro* pluripotency induction. These cells demonstrate pluripotent characteristics, maintain self-renewal capacity, and possess the ability to differentiate into any adult cell type. Because iPSCs originate from adult somatic cells rather than embryos, they avoid the ethical concerns associated with ES cell usage. These cells can be readily obtained from skin fibroblasts, eliminating the need for invasive collection procedures such as bone marrow or adipose tissue biopsies. Significantly, iPSCs exhibit the unique capability to differentiate into all cell types present in normal skin [43]. As iPSCs can theoretically be derived from virtually any adult tissue, their potential source cell reservoir substantially exceeds that of other stem cell types. Moreover, iPSCs enable autologous transplantation, thereby minimizing immunogenicity, reducing immune rejection risk, and enhancing *in vivo* survival [44,45].

Angiogenesis plays a critical role in wound recovery by restoring blood flow to damaged tissues and providing essential nutrients. However, this process is commonly impaired in chronic wounds, particularly in diabetic patients. The long-term and excessive hypoxic environment



Scheme 1. Schematic diagram of NVs classification based on the different sources of membrane components, which includes NVs made by a single cell membrane and NVs made by a fusion of cell membrane and liposome or another cell membrane. The NVs regulated four phases of wound healing including bleeding and hemostasis, inflammation, proliferation, and remodeling.

characteristic of chronic wounds inhibits angiogenesis, while diabetic patients exhibit reduced capacity for endothelial progenitor cell migration to wound sites, subsequently compromising their angiogenic function. In this process, endothelial cells (ECs) serve a fundamental role as essential mediators of vascular endothelial growth factor (VEGF) expression and vascular formation. Based on these considerations, researchers have investigated the potential of ECs derived from human-iPSCs to enhance wound healing [46]. Zhang et al. developed an innovative approach utilizing bioinspired NVs derived from iPSC-derived ECs (iECs) [47]. A conventional serial extrusion technique was employed to generate NVs from iPS-ECs, which demonstrated characteristics closely resembling their source cells, notably a high abundance of C-X-C motif chemokine receptor 4 (CXCR4). The elevated expression of this membrane chemokine receptor conferred targeting capabilities to ECs, while their endothelial similarity enhanced their cellular accumulation. These NVs function as exosome mimetics, facilitating targeted delivery of dapagliflozin, a sodium-glucose cotransporter 2 inhibitor (Fig. 2A). Furthermore, these iPS-EC NVs were utilized to deliver dapagliflozin to ECs, promoting wound healing in diabetic conditions and enhancing angiogenesis through the hypoxia-inducible factor-1α/VEGFA signaling pathway. This study demonstrates the efficacy of engineered NVs as a viable approach for promoting angiogenesis and accelerating wound healing in diabetic conditions, presenting novel therapeutic possibilities for chronic wound treatment [48].

Aging skin demonstrates impaired wound repair capacity due to age-related defects. During aging, metabolic regulation in accumulated senescent cells becomes critical for tissue homeostasis. This phenomenon is particularly pronounced in diabetic conditions, where senescent cells accumulate at wound sites, inhibiting the wound healing process [49]. Consequently, senescent cell rejuvenation through EVs has emerged as a potential therapeutic strategy for enhancing senescent tissue restoration [50]. Addressing this challenge, Lee et al. developed an innovative approach utilizing human iPSC-derived NVs [51]. The iPSC-NVs were generated through serial extrusion of iPSCs [52] across membrane filters with decreasing pore diameters, followed by density-gradient ultracentrifugation purification (Fig. 2B). Significantly, the iPSC-NVs displayed characteristics comparable to iPSC-derived exosomes while achieving substantially higher production yields. The investigators confirmed that iPSC-NVs contained human iPSC-specific mRNA, including Nanog and Oct4. Nanog and Oct4 are key transcription factors that maintain the pluripotency and self-renewal capacity of ES cells. During the generation of iPSCs, these factors reprogram somatic cells into a pluripotent state by activating or repressing the expression of specific genes [53]. iPSC-NV treatment enhanced proliferation and migration in both young and aged human dermal fibroblasts (HDFs). Moreover, iPSC-NVs demonstrated the capacity to reverse age-related gene expression alterations. These vesicles significantly reduced senescence-associated β-galactosidase activity in aged HDFs and suppressed the expression of p21 and p53, which are essential regulators in signaling pathways governing cell cycle arrest, apoptosis, and cellular senescence [54].

Table 1
Summary of cell-derived NVs.

Classifications	Membrane source	Preparation	Encapsulation	Functions	References
Single cell membrane type-derived NVs	Induced pluripotent stem cell	Extrusion approach	Dapagliflozin	Targeted delivery of dapagliflozin.	[47]
	Induced pluripotent stem cell	Extrusion approach	/	Stimulate the proliferation and migration of HDFs.	[51]
	Mesenchymal stem cell	Extrusion approach	/	Programmable regulation of ROS and comprehensive promotion of tissue regeneration.	[69]
	Bone marrow mesenchymal stem cell	Extrusion approach	/	Promote the polarization of macrophages toward the M2 phenotype.	[216]
	Umbilical cord mesenchymal stem cell	Extrusion approach	/	Promoted fibroblast growth, angiogenesis, and collagen formation.	[80]
	Embryonic stem cell	Extrusion approach	/	Enhance the cell proliferation rate.	[83]
	Red blood cell	Extrusion approach	SeNPs	Reduce the inflammatory response in wounds.	[89]
	Red blood cell	Extrusion approach	Fe_3O_4	A photothermal therapy and bacterial toxin adsorption strategy.	[93]
	Platelet	Extrusion approach	Cerium oxide	Release CNPs and provide a regenerative microenvironment.	[103]
	Macrophages cell	Extrusion approach	MLN4924	Inhibited macrophage M1 polarization, and promote their transition to the M2 reparative phenotype.	[118]
	Neutrophil	Extrusion approach	/	Release substantial amounts of bactericidal proteins.	[126]
	Bacteria	Extrusion approach	/	The LPC molecule stimulates the proliferation of vascular smooth muscle cells through the MAPK pathway.	[133]
Hybrid cell membrane type-derived NVs	iPSC-derived endothelial cells and M1-type macrophage	Extrusion approach	4OI	Dual-targeted delivery of 4OI into both M1 macrophages and endothelial cells.	[142]
	Red blood cell and liposome	Extrusion approach and thin-film hydration	Curcumin	Neutralize toxins and mediate the immune response.	[147]
	Liposome, bacteria and macrophage	Extrusion approach	Curcumin	Enhance macrophages' capacity to phagocytize and eliminate intracellular bacteria	[217]

2.1.1.2. Mesenchymal stem cell (MSC)-derived NVs. MSCs are important adult stem cells characterized by their plastic adherence properties and differentiation potential. These cells can be isolated from various sources, including umbilical cord, adipose tissue, and periodontal ligaments [55]. Due to their self-renewal capacity and extensive developmental potential, MSCs have emerged as viable candidates for tissue regeneration and restoration, particularly in wound healing, where they are expected to significantly impact the treatment of non-healing wounds [56,57]. However, increasing evidence indicates that MSC-derived EVs effectively overcome challenges associated with MSC-based cellular therapy, including host immune rejection in dermatological repair processes. These vesicles demonstrate multiple therapeutic benefits for skin tissue regeneration [58]. Functioning as 'Trojan horses,' EVs facilitate the delivery of beneficial biological effectors to target cells through both engineered and natural mechanisms. As an innovative cell-free therapeutic approach, MSC-derived EV therapy offers several advantages, including enhanced biosafety, reduced immunogenicity, and improved stability. Furthermore, it demonstrates superior therapeutic efficacy in scar repair and wound healing compared to conventional MSC-based treatments [59]. Despite these advantages, the limited yield of EVs under *in vitro* culture conditions restricts their clinical application, making therapeutic use in humans impractical. To overcome this limitation, researchers have developed cell-engineered NVs as a viable alternative to EVs [60]. Compared to MSCs, MSC-derived NVs present several distinct advantages: NVs can directly integrate with target cells, inducing robust biological responses. Their lipid bilayer structure effectively protects cargo from degradation. Moreover, NV concentration, dosage, and administration methods can be controlled with greater precision. NV-based therapy may prevent immune rejection risks and tumor formation potential associated with cell transplantation. These advantages establish MSC-derived NVs as a promising alternative to MSCs for future therapeutic applications in wound healing and tissue regeneration [61].

Given the promising potential of MSC-derived NVs, researchers have actively investigated their applications in wound healing. Neupane and colleagues presented compelling evidence supporting the efficacy of MSC-derived NVs in these applications. In their investigation, NVs were generated as EV mimetics through cell shearing methodology, providing a more efficient approach while maintaining comparable size and zeta potential to naturally secreted EVs. The study revealed that MSC-NVs replicated EVs in terms of essential canonical proteins associated with critical biological functions necessary for wound healing, including cell adhesion and proliferation. These NVs activated the mitogen-activated protein kinase (MAPK) signaling pathway in HDFs, enhancing both HDF proliferation and migration toward wound sites. Additionally, they increased the secretion of cell proliferation markers, growth factors, and ECM proteins from HDFs. Collectively, these effects accelerated wound healing in both *in vitro* and *in vivo* models [62]. Han et al. reported the development and characterization of cell-engineered NVs derived from MSCs (MSC-NVs), demonstrating a production yield exceeding 300 times that of natural EVs. The production process involves mechanical generation of MSC-NVs through repeated cell passage through microporous filters, resulting in membrane fragmentation and subsequent reconstitution into nanometer-sized vesicles [18]. These MSC-NVs incorporate cellular components from their parent cells, including RNAs and proteins, enabling the transmission of cellular functional properties similar to EVs. To evaluate their efficacy, the researchers conducted comparative analyses between MSC-NVs and MSC-EVs in their therapeutic application to syngeneic primary skin fibroblasts. *In vitro* studies demonstrated that MSC-NV treatment enhanced primary skin fibroblast proliferation and migration more effectively than natural MSC-EV treatment. Furthermore, MSC-NV application to skin fibroblasts induced upregulation of transforming growth factor β (TGF-β) and VEGFA [60].

2.1.1.2.1. ADSC-derived NVs. ADSCs, a subset of MSCs, are adult stem cells characterized by their multipotent potential and self-proliferation capabilities [63]. ADSCs have garnered significant attention in regenerative medicine due to their distinctive characteristics and therapeutic potential. A primary attribute of ADSCs is their immunomodulatory capacity. Upon introduction to injured sites, ADSCs interact with immune cells and regulate local immune responses through the secretion of chemokines and cytokines [64]. Additionally, they secrete essential growth factors and cytokines, including VEGF, TGF-β, and IL-10, which enhance cell proliferation for re-epithelialization and promote collagen synthesis and deposition via the ERK/β-catenin pathways [65]. The therapeutic efficacy of ADSCs in regenerative medicine is further enhanced by their low immunogenicity and, notably, their immunomodulatory capabilities [66]. These properties establish

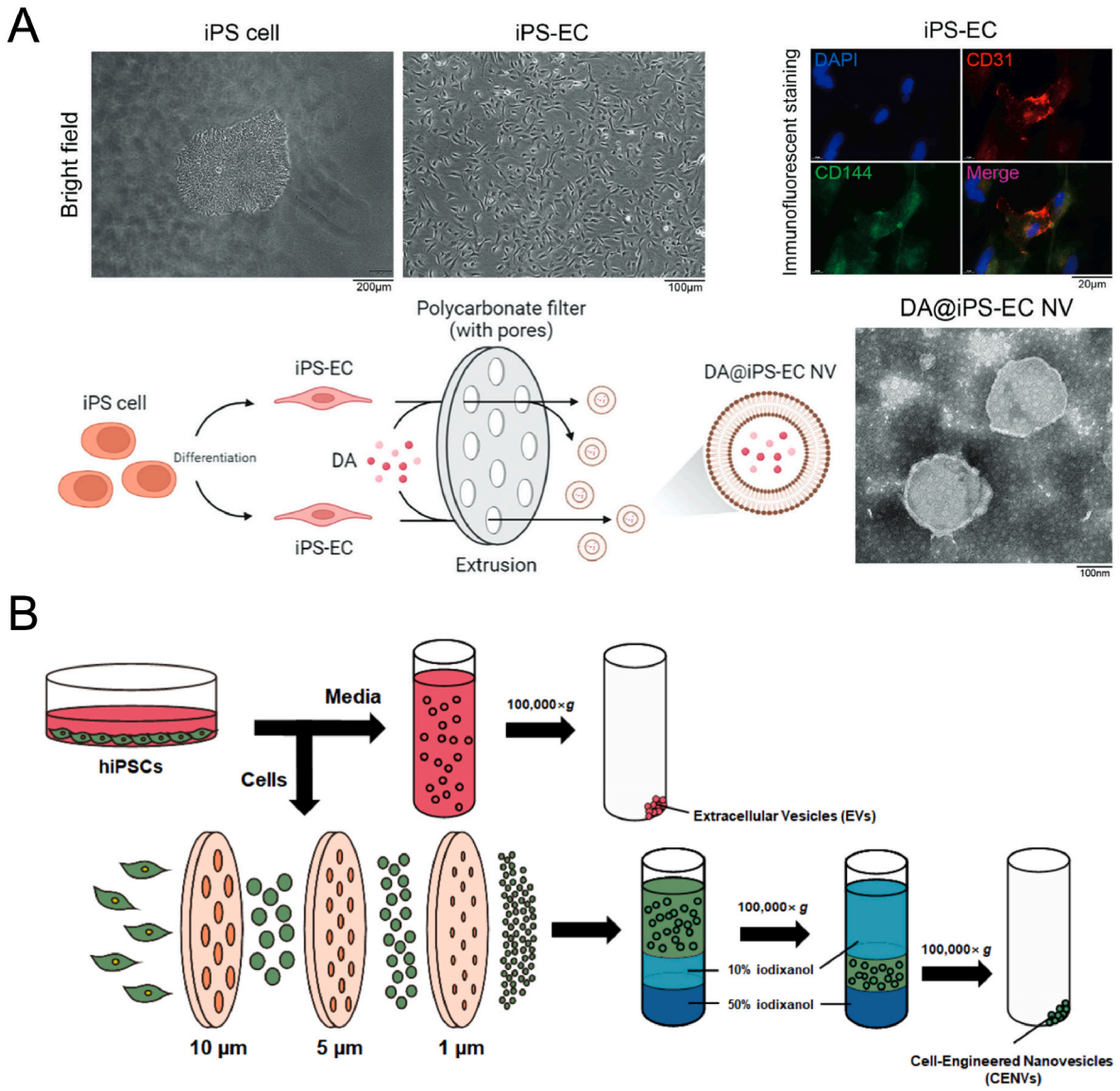


Fig. 2. Generation of NVs from iPSCs for wound healing. **(A)** iPSCs and iPS-ECs with endothelial markers. Schematic of dapagliflozin-loaded NV (DA@iPS-EC NV) production and TEM image. Adapted with permission [47], Copyright 2022, Wiley-VCH. **(B)** Preparation of EVs and cell-engineered NVs from iPSCs. EVs isolated by ultracentrifugation; cell-engineered NVs produced by serial extrusion and density gradient purification. Adapted with permission [51], Copyright 2020, MDPI.

ADSCs as particularly suitable candidates for diverse clinical applications. In comparison with other multipotent somatic stem cells, ADSCs present several practical advantages. They can be efficiently isolated and purified from adipose tissues throughout various anatomical locations in the human body. This accessibility, coupled with the capacity for isolation and expansion without ethical constraints, renders ADSCs an attractive option for both research and clinical applications [67]. In conclusion, among adult stem cells, ADSCs are distinguished by their accessibility, robust secretory functions, and immunomodulatory properties, establishing them as a viable candidate for cell-based therapy [68].

Despite the numerous advantages of ADSCs, their direct application in wound healing is limited by factors including poor survival rates and potential tumorigenicity. To overcome these limitations while maintaining the beneficial properties of ADSCs, researchers have investigated the application of ADSC-derived NVs (ANVs). These NVs maintain many therapeutic properties of ADSCs while providing enhanced stability and safety profiles. Zhao et al. [69] developed an innovative ADSC NV-embedded dual-layered hydrogel system for tissue regeneration and programmable regulation of ROS to normalize the burn wound healing process. Traditional wound treatments, such as gauze and bandages, focus on covering wounds and absorbing exudates but often fail to maintain a moist environment, which is essential for healing, and may disrupt tissues during dressing changes. In contrast, hydrogels provide a moist, protective environment that promotes cell proliferation, prevents infection, and supports healing. Biocompatible and customizable, hydrogels can also deliver therapeutic agents like antibiotics or growth factors, making them a superior option for managing chronic or complex wounds [70]. This system incorporates NVs derived from ADSCs extracted from inguinal adipose tissues. The system's key component, MTB@ANVs, combines ADSC properties with a photosensitizer [69]. MTB (2-(2-(5-(4-(bis(4-methoxyphenyl)amino)phenyl)thiophen-2yl) vinyl)-3-ethylbenzo[d]thiazol-3-ium hexafluorophosphate), an aggregation-induced emission (AIE) photosensitizer, generates ROS under 633 nm laser irradiation for photodynamic antibacterial therapy. The investigators synthesized these functional AIE photosensitizer-functionalized ANVs through co-extrusion of MTB NP solution and ANVs using a liposome extruder (Fig. 3A). Characterization studies demonstrated that MTB@ANVs maintained a protein profile consistent with that of ADSCs. Additionally, both ANVs and MTB@ANVs

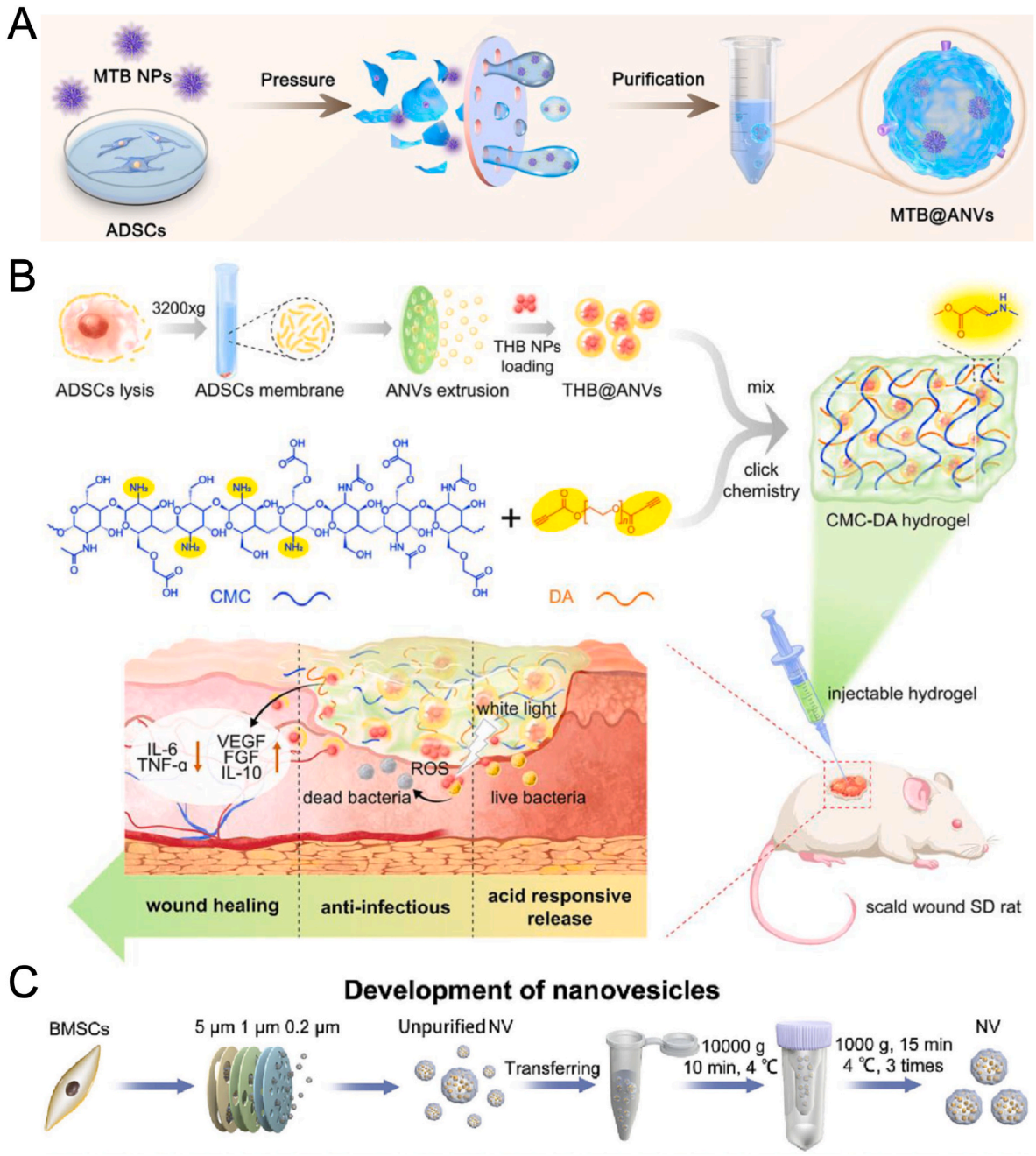


Fig. 3. Generation of stem cell-derived NVs for wound healing applications. **(A)** Preparation of MTB-loaded ANVs (MTB@ANVs) through co-extrusion of ADSCs and MTB NPs. Adapted with permission [69], Copyright 2024, Wiley-VCH. **(B)** Fabrication of THB-loaded ANVs (THB@ANVs) by co-incubating THB NPs with ANVs and subsequent extrusion. Incorporation into a CMC-DA hydrogel for multifunctional wound healing. Adapted with permission [17], Copyright 2024, MDPI. **(C)** Production of BMSC-derived NVs using serial extrusion and purification steps. Adapted with permission [216], Copyright 2023, Elsevier.

expressed TSG101 and CD9, indicating the preservation of features characteristic of ADSC-derived exosomes [71]. The dual-layered hydrogel system was engineered to respond to different wound healing phases. During the infectious stage, the hydrogel's inner layer released MTB@ANVs in response to bacteria-secreted hyaluronidase. These released NVs performed multiple functions: regulating inflammation through the TICAM-1 pathway, enhancing cell proliferation, migration, and neovascularization, while also participating in inflammation regulation and cellular process activation through paracrine factors. The MTB@ANVs effectively encapsulated MTB NPs while preserving the beneficial components of ADSCs. This innovative system maintained the regenerative properties of ADSCs while incorporating efficient ROS production capabilities during laser irradiation, thereby providing a comprehensive approach to burn wound treatment [69].

Chen's research group replicated ADSC exosome functions by generating ANVs through a direct extrusion method [72]. Using rat ADSCs as the cellular source, they reconstituted fragmented cell membranes into NVs through sequential extrusion across polycarbonate membranes with nanoscale pores, enabling precise control over NV dimensions. To enhance the therapeutic efficacy of these ANVs, the researchers incorporated an AIE photosensitizer, 4-(2-(5-(4-(diphenylamino)phenyl)thiophen-2-yl)vinyl)-1-(2--hydroxyethyl) pyridin-1-ium bromide (THB), recognized for its exceptional photodynamic properties. THB-functionalized ANVs (THB@ANVs) were synthesized through co-incubation of THB NPs with 400 nm ANVs, followed by extrusion through a 200 nm polycarbonate

membrane (Fig. 3B). Characterization studies of THB@ANVs demonstrated their capacity to maintain essential stem cell components while exhibiting properties similar to native vesicles. Notably, these NVs preserved both stem cell-specific functions and THB properties, showing potential for wound healing promotion and antimicrobial activity. The effectiveness of THB@ANVs was evaluated across multiple aspects of wound healing. The NVs exhibited significant antibacterial activity against Gram-positive bacteria and demonstrated beneficial effects on tissue remodeling, including enhanced cell migration, increased cell proliferation, and immunomodulation. To evaluate their therapeutic potential further, the researchers developed a THB@ANVs hydrogel and assessed its efficacy in a rat model of second-degree burn wounds. The results demonstrated significant effects in bacterial growth inhibition, inflammation regulation, and neovascularization promotion.

2.1.1.2.2. BMSC-derived NVs. BMSCs are multipotent stem cells that possess several critical characteristics advantageous for therapeutic applications, including the production of diverse biologically active molecules, multi-lineage differentiation potential, and self-renewal capacity [73]. The regenerative properties of BMSCs in tissue repair have been extensively documented in numerous studies [74]. Their beneficial effects on wound healing are primarily attributed to paracrine actions on key cellular populations involved in the recovery process, including vascular ECs, keratinocytes, and fibroblasts [75]. Through the secretion of various cytokines and growth factors, BMSCs facilitate wound healing processes [76].

Although BMSCs have demonstrated significant potential in wound healing applications, their clinical implementation faces several challenges, including complex regulatory requirements, potential immunogenicity, and invasive harvesting procedures. These limitations have led researchers to investigate alternative approaches that capitalize on the therapeutic benefits of BMSCs while addressing their practical limitations. An innovative strategy involving BMSC-derived NVs maintains many regenerative properties of the parent cells while offering enhanced safety profiles and operational advantages. This transition from cell-based to cell-free therapies represents a significant advancement in regenerative medicine, potentially expanding the applications of BMSC-derived treatments. Wu et al. developed an innovative approach for diabetic wound healing through the creation of a novel hydrogel dressing material. This biomaterial, designated as NV@BSA-GEL, integrates continuous NV delivery with a reinforced gelatin hydrogel structure [77]. The hydrogel, derived from bovine serum albumin (BSA)-bridged gelatin, provides a stable matrix for incorporating BMSC-derived NVs. The researchers generated NVs from BMSCs through serial extrusion (Fig. 3C), replicating exosome properties while preserving beneficial components of the parent cells. Characterization studies confirmed the exosome-like properties of the NVs. Western blotting analysis revealed that both BMSCs and NVs expressed exosome surface markers CD9 and CD63. However, calnexin expression was detected exclusively in BMSCs, not in NVs, further validating the exosome-like nature of the NVs [21]. Proteomic analysis revealed that these BMSC-derived NVs contained numerous growth factors essential for wound healing. Significantly, both NV@BSA-GEL and NVs exhibited immunosuppressive effects by promoting macrophage polarization toward the M2 phenotype, potentially enhancing the healing process.

2.1.1.2.3. UCMSC-derived NVs. In the pursuit of more effective and accessible regenerative therapies, researchers have directed their attention toward the human umbilical cord. UCMSCs have gained significant recognition in the scientific community due to their unique combination of biological properties and practical advantages. UCMSCs exhibit exceptional self-renewal capacity and multipotency. Under specific conditions, they differentiate into various cell types, including osteoblasts, adipocytes, and chondrocytes, contributing to diverse organ and tissue regeneration. Furthermore, these cells secrete cytokines crucial for tissue repair and cellular response modulation. UCMSCs demonstrate additional therapeutic advantages, including abundant tissue availability, significant proliferation capacity, and minimally invasive collection procedures [78]. Their non-invasive harvesting method and low immunogenicity provide distinct advantages in clinical applications, reducing cell transplantation-associated risks [79]. Ma and colleagues generated UCMSC-derived NVs through serial extrusion filtration. The effects of UCMSC-NV on HUVEC and L929 fibroblast migration were evaluated using wound healing assays and Transwell analysis. The results demonstrated enhanced migration of both L929 fibroblasts and HUVECs in response to UCMSC-NV treatment. Further investigation of UCMSC-NV effects on HUVECs through tube formation assays revealed increased tube length and total loop formation following 8-h UCMSC-NV exposure, indicating enhanced angiogenesis. UCMSC-NV-treated db/db mice exhibited significantly increased expression of CD31, collagen I and III, and αSMA, with accelerated healing compared to control mice, validating UCMSC-NV efficacy in skin wound repair. These findings demonstrated that UCMSC-NV promotes fibroblast migration, angiogenesis, and collagen formation [80]. UCMSC-NVs were effectively generated as EV analogs using a cell-shearing and extrusion method by Neupane and his colleagues [62]. These NVs triggered the MAPK signaling pathway in HDFs, promoting their proliferation and migration toward the wound site. Additionally, they increased the secretion of markers associated with cell proliferation, growth factors, and ECM proteins from HDFs. The study showed that UCMSC-NVs, acting as EV analogs, facilitated angiogenesis in human dermal microvascular endothelial cells co-cultured with HDFs within a 3D PEG-fibrin scaffold *in vitro*. Furthermore, this research highlighted that UCMSC-NVs possess the ability to stimulate HDFs to enhance the production of growth factors and ECM proteins in the surrounding microenvironment.

2.1.1.3. ES cell-derived NVs. Studies have demonstrated that exosomes secreted by ES cells can enhance early pluripotent gene expression and promote adult stem cell proliferation [81]. Based on this understanding, Jeong et al. developed a technique to generate cell-derived NVs that mimic exosomes through the extrusion of live ES cells across micro-filters (Fig. 4A). These NVs were found to contain ES cell-derived proteins and RNAs. Additionally, they demonstrated the capacity to traverse skin fibroblast plasma membranes, facilitating efficient cargo delivery to target cells [82]. To evaluate the effects of these NVs on cell proliferation, Jeong et al. examined gene and protein expression patterns in treated fibroblasts. PCR analysis revealed elevated expression levels of TGF-β, proliferation-related growth factors, and VEGFA. These findings indicate that NVs activate cells to enhance growth factor production, potentially influencing ECM production and cellular proliferation rates. A scratch closure assay further demonstrated that NVs enhance cell migration in skin fibroblasts, a crucial aspect of the proliferation process. Collectively, these results demonstrate that ES cell-derived NVs promote proliferation in primary murine skin fibroblasts, paralleling the effects observed with natural exosomes [83].

2.1.2. Blood cell-derived NVs

2.1.2.1. RBC-derived NVs. The treatment of infectious wounds has traditionally relied on multiple drug combinations to enhance anti-infective and anti-inflammatory effects [84]. However, prolonged administration of high drug doses can lead to the emergence of drug-resistant bacteria, diminishing therapeutic efficacy [85]. Selenium, an essential trace mineral element for most living organisms, exhibits multiple biological activities in NP form, including antiviral, antioxidant, antibacterial, and antitumor effects *in vivo* [86]. Significantly, antimicrobial studies of selenium NPs (SeNPs) have not demonstrated bacterial resistance, making them an attractive option for infectious wound treatment. Nevertheless, a primary challenge in SeNP application for wound treatment remains the extension of systemic circulation time to maximize therapeutic efficacy. To address this limitation, researchers have explored biomimetic strategies. RBCs and their

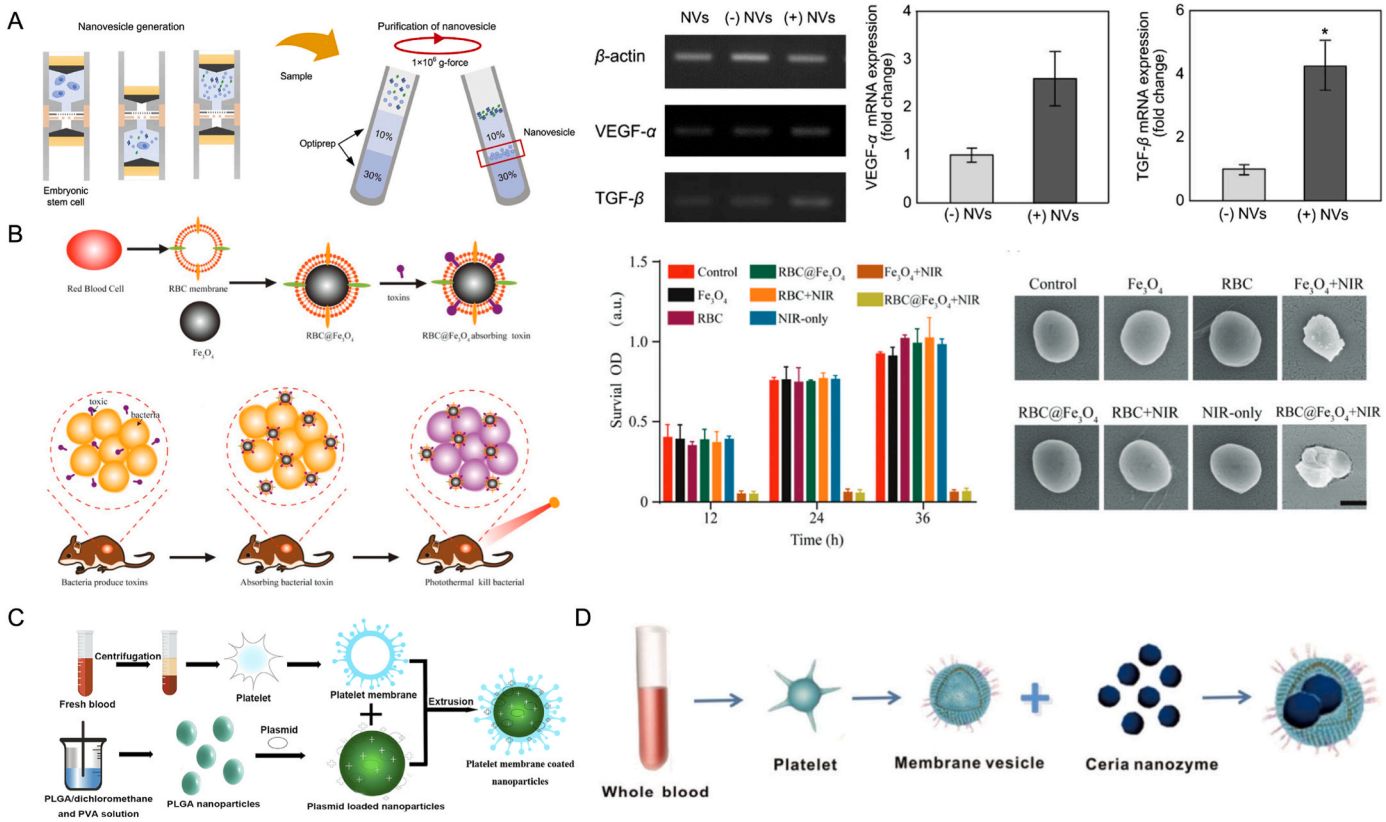


Fig. 4. NVs from ES cells, RBCs, and platelets for wound healing applications. **(A)** Generation of ES cell-derived NVs and their effects on fibroblasts. Left: Schematic of NV production through extrusion. Right: PCR analysis showing upregulation of growth factors in NV-treated fibroblasts. Adapted with permission [83], Copyright 2014, Elsevier. **(B)** RBC membrane-coated Fe_3O_4 NPs for photothermal therapy of bacterial infections. Left: Schematic of NP preparation and application. Right: *In vivo* photothermal sterilization effects and scanning electron microscopy images of bacterial viability. Adapted with permission [93], Copyright 2021, Royal Society of Chemistry. **(C)** Platelet membrane-coated NPs for gene delivery in wound healing. Left: Preparation process. Right: Blood perfusion imaging of wound sites at different time points. Adapted with permission [102], Copyright 2023, Elsevie. **(D)** Platelet membrane-coated NPs in hydrogel for diabetic wound healing. Left: Fabrication process. Adapted with permission [102], Copyright 2023, Elsevie.

membranes demonstrate prolonged blood circulation without inducing thrombosis, inflammation, or other adverse reactions [87,88]. RBC-derived NVs are distinguished by their low immunogenicity and excellent biocompatibility. While they do not contain bioactive components for direct tissue regeneration, their ability to transport oxygen and their robust membrane stability render them beneficial for mitigating hypoxic conditions, including persistent wounds or ischemic regions. Utilizing these properties, Fang et al. investigated a biomimetic system incorporating RBC membrane vesicles to encapsulate SeNPs for infectious wound healing [89]. They established a protocol for producing RBC membrane vesicles-SeNPs nanosystems (R-SeNPs) by combining RBCs from 1 mL of blood with 1 mL of SeNPs solution, followed by sequential sonication, filtration, and extrusion processes. The system's efficacy was validated through multiple experimental approaches. Fluorescence microscopy and flow cytometry analyses revealed decreased immune cell internalization of R-SeNPs, indicating enhanced immune evasion and suggesting prolonged systemic circulation. Furthermore, immunostaining and blood analysis demonstrated that the R-SeNPs treatment group exhibited reduced levels of pro-inflammatory factors, including interleukin-6 (IL-6) and TNF-α. These results indicate that R-SeNPs effectively suppress wound-associated inflammatory responses, potentially enhancing healing outcomes. This approach, combining SeNPs' antibacterial properties with RBC membranes' extended circulation capabilities, addresses both bacterial resistance concerns and therapeutic efficacy requirements, thereby achieving improved infectious wound treatment [89].

Bacterial infections represent a significant health threat, with bacterial toxins serving as major virulence factors. While photothermal sterilization utilizing materials with high photothermal conversion efficiency [90] has emerged as an effective treatment approach, significant challenges remain. Residual bacterial toxins and photothermal materials can compromise host safety, potentially inducing inflammation and adverse reactions [91]. Therefore, developing new materials that efficiently eliminate residual toxins while maintaining optimal biocompatibility is crucial [92]. To address these challenges, Chen and colleagues synthesized biomimetic RBC membrane-coated Fe_3O_4 NPs (RBC@Fe_3O_4). The fabrication process involved hydrothermal synthesis of Fe_3O_4 NPs and hypotonic preparation of RBC membranes. The RBC membrane coating was selected specifically to enhance circulation time and biocompatibility. The final RBC@Fe_3O_4 NPs were generated through component integration followed by sequential extrusion through 400 nm and 200 nm polycarbonate porous membranes using a microextruder. The researchers conducted comprehensive experiments to evaluate NP efficacy. Bacteria were incubated with various NP formulations under different treatment conditions, with optical density measurements over 36 h demonstrating superior treatment efficacy of near-infrared (NIR)-irradiated RBC@Fe_3O_4 NPs. These results highlighted the synergistic effects of combined photothermal therapy and bacterial toxin absorption. *In vivo* evaluation involved treating bacteria-infected mouse wound surfaces with different materials followed by 808 nm laser irradiation. RBC@Fe_3O_4 NPs demonstrated exceptional bacterial toxin absorption capacity. Scanning electron microscopy revealed significant surface shrinkage in bacteria treated with RBC@Fe_3O_4 + NIR and Fe_3O_4 + NIR post-irradiation, while control groups maintained intact surface morphology (Fig. 4B). This structural deterioration indicated severe bacterial cell damage, confirming

therapeutic efficacy. Furthermore, RBC@Fe_3O_4 NPs exhibit recyclability, reducing experimental costs while enabling magnetic separation and material reuse, thereby preventing environmental contamination and establishing their potential as an environmentally sustainable therapeutic agent [93].

2.1.2.2. Platelet-derived NVs. The incorporation of platelet membranes onto NP surfaces represents a novel strategy that aims to replicate platelets' natural targeting and cell-specific binding capabilities [94]. Platelets possess distinctive surface proteins enabling selective cellular recognition and interaction, a characteristic that enhances the therapeutic efficacy of targeted nanomedicines. This biomimetic approach has improved NP localization and accumulation at disease sites, demonstrating promising outcomes in the treatment of arterial diseases, ischemic heart disease, and cancer [95,96]. The efficacy of this approach derives from platelets' multifunctional properties. Platelet granules contain diverse bioactive compounds, including antimicrobial peptides and various growth factors such as platelet-derived growth factor, TGF, insulin-like growth factor, and VEGF. These components modulate immune responses through regulation of immune cell migration and adhesion mechanisms, playing crucial roles in immunological regulation [97]. Additionally, platelets significantly contribute to wound healing processes by supporting skin cell regeneration, collagen synthesis, angiogenesis, and fibroblast proliferation. Although platelets exhibit substantial therapeutic potential, their direct clinical application remains limited due to potential immunological complications [98]. To address this limitation, researchers have developed platelet activation methods utilizing $CaCl_2$ or freeze/thaw techniques. These activation protocols induce platelet alpha granule degranulation, resulting in growth factor release [99]. Among these released factors, platelet-derived EC growth factor merits particular attention, as it stimulates collagen deposition and functions as a chemotactic agent for monocytes, neutrophils, and macrophages, thereby enhancing wound healing processes. The integration of platelet membrane properties into NP design presents a promising strategy for developing enhanced targeted therapeutics and wound healing treatments. This biomimetic approach, combining platelet targeting capabilities with NP versatility, effectively addresses both precise drug delivery requirements and tissue regeneration promotion.

Wang et al. investigated an innovative approach to wound healing through the development of a novel platelet membrane-coated NP (PM@gene-NP) complex delivery system for targeted delivery of VEGFA genes and basic fibroblast growth factor (bFGF) into deep burn wounds. The research protocol initiated with the insertion of bFGF and VEGFA genes into plasmid vectors. Subsequently, the assembled plasmids were loaded onto NPs to form gene-loaded NP complexes, which underwent platelet membrane encapsulation. The synthesis protocol involved ultrasonic treatment of NPs/pEGFP complexes, followed by integration with an equivalent volume of platelet membrane solution. The resulting mixture underwent ten iterations of filtration through a porous syringe filter to generate the final PM@gene-NP complexes [100,101]. Multiple experimental outcomes validated the system's efficacy. Blood perfusion analyses demonstrated superior wound blood flow in PM@gene-NP-treated rats at 1, 2, and 3 weeks post-burn injury. These findings indicate that PM@gene-NP complexes enhance wound revascularization, a crucial component of burn wound healing. Additionally, cells treated with these complexes exhibited enhanced EGFP fluorescence expression intensity and elevated bFGF and VEGFA protein levels compared to control groups. These results demonstrate that PM@gene-NP complexes effectively facilitate gene expression and delivery (Fig. 4C). The research findings highlight the potential of PM@gene-NP complexes as an effective strategy for enhanced drug delivery to burn sites and wound healing promotion. These complexes demonstrate efficacy in accelerating skin cell growth, migration, vascular reconstruction, and overall wound recovery. Although the research presents promising results for burn wound healing, this technology remains in its early developmental stages. Several challenges require resolution before clinical implementation, including platelet availability limitations, potential immunological responses, and scale-up manufacturing considerations [102].

Dong et al. developed an innovative multifunctional hydrogel designed to promote angiogenesis and optimize wound microenvironment [103]. The dressing was synthesized using a PLTm-cloaked cerium oxide NP-loaded GelMa hydrogel (PLTm@CNPs/Gel), incorporating platelet membrane-coated cerium NPs within a gelatin methacryloyl framework (Fig. 4D). Compared to conventional antioxidant enzymes and molecules, CNPs demonstrate several advantages, including simplified synthesis procedures, superior biocompatibility, broad-spectrum effectiveness against various toxic ROS, and enhanced stability [104,105]. Previous research has established the significant anti-inflammatory properties of cerium oxide nanoenzymes [106,107]. To evaluate the anti-inflammatory effects of PLTm@CNPs/Gel, macrophages were stimulated with LPS to simulate an inflammatory response [108]. CNP treatment resulted in significant reductions in IL-6 and TNF-α secretion, demonstrating decreases of 49.7 % and 52.8 %, respectively, compared to control groups. PLTm@CNPs/Gel exhibited comparable anti-inflammatory efficacy to unmodified CNPs, indicating effective inflammation mitigation through CNP release. Wound neovascularization was assessed through VEGF/CD31 immunofluorescence staining, which revealed significantly enhanced blood vessel formation and VEGF expression in the PLTm@CNPs/Gel treatment group. Collagen formation at wound surfaces was evaluated using Masson staining. Analysis demonstrated that collagen fibers in the PLTm@CNPs/Gel group exhibited increased elongation and more organized structural arrangement, indicating enhanced wound healing progression and superior tissue regeneration quality [103].

2.1.3. Immune cell-derived NVs

2.1.3.1. Macrophages cell-derived NVs. Macrophages function as primary phagocytic cells within the innate immune system, performing crucial roles in tissue repair, pathogen defense, and immune regulation [109]. These multifunctional cells manifest two principal phenotypes: M1 and M2, each serving distinct functions in wound healing processes. M1-type macrophages predominate during early wound healing stages, maintaining localized hypoxic conditions and facilitating rapid antigen clearance. In contrast, M2-type macrophages facilitate subsequent tissue remodeling by secreting various growth factors and cytokines, promoting cellular proliferation and migration [110]. The appropriate temporal transition from M1 to M2 phenotype is fundamental for optimal wound repair [111]. The M2 phenotype is characterized by reparative properties, including modulation of ROS and reduced inflammatory mediator expression. It exhibits enhanced expression of anti-inflammatory cytokines, including IL-1 receptor antagonist, IL-1 type II decoy receptor, IL-10, and TGF-β. Additionally, M2 macrophages enhance the expression of growth factors such as epidermal growth factor (EGF), VEGF, and platelet-derived growth factor, which contribute collectively to tissue regeneration [112]. Macrophages express diverse surface receptors enabling biological signal response and directed migration toward inflammatory and tumorigenic sites. Their membranes incorporate self-recognition features preventing phagocytosis by other immune cells, while surface ligands facilitate interaction with injury site receptors. These distinctive characteristics have inspired the development of biomimetic nanosystems for targeted imaging and drug delivery. Macrophage membrane-camouflaged NPs have been engineered to exploit these biological advantages. These NPs demonstrate immune signal recognition capabilities and potential anti-tumor immunity activation [113]. The integration of nanomaterial versatility with macrophage biological functions enhances targeted delivery efficiency. Specifically, M2 macrophage membrane-coated NVs maintain critical

anti-inflammatory properties through the retention of TGF-β, interleukin-10 (IL-10), and chemokine receptors derived from M2 macrophages [114]. This strategy preserves M2 macrophage functional properties while maximizing nanocarrier advantages. Therefore, macrophages cell-derived NVs are notably efficient in immune regulation, attributed to their inclusion of cytokines (e.g., IL-10) and their inherent capacity to induce macrophage polarization towards the M2 phenotype. This renders them particularly apt for alleviating persistent inflammation and wounds linked to infections.

Recent studies have demonstrated the efficacy of biomimetic nanosystems for targeted delivery of imaging and therapeutic agents to tumor sites, inflammatory regions, and infected areas [115]. Zhang et al. utilized gradient extrusion methodology to synthesize M2 macrophage-derived bioinspired NVs (M2BNVs), which were subsequently incorporated into biocompatible Gelatin Methacryloyl (GelMA) hydrogels for acute wound healing applications. The synthesis protocol involved sequential extrusion of M2-type macrophage cells through a pneumatic extruder equipped with polycarbonate filter membranes of decreasing pore sizes (1.2 μm, 0.6 μm, and 0.22 μm) for three iterations. The extruded material underwent ultracentrifugation purification, yielding the final M2BNVs.The distinctive endogenous cargo of M2BNVs enables M1 macrophage reprogramming, facilitating phenotypic transformation toward the M2 phenotype, which is associated with enhanced healing promotion and anti-inflammatory properties. Consequently, M2BNVs effectively modulate the pro-inflammatory wound microenvironment. Furthermore, M2BNVs promote tissue regeneration and angiogenesis in wound sites. The integration of M2BNVs with GelMA hydrogels demonstrated enhanced wound healing properties *in vivo* [116].

Recent studies have elucidated strategies for enhancing wound healing in diabetic patients through reduction of M1 macrophage polarization and mitigation of chronic inflammation. M1 macrophages are characterized by their pro-inflammatory properties [117]. Zeng et al. developed macrophage-membrane-coated PLGA NPs (M-NPs/MLN4924), a biomimetic drug delivery system [118]. The synthesis protocol involved initial fabrication of porous PLGA nanospheres through nanoprecipitation methodology. Subsequently, macrophage membrane isolation was achieved through 11 sequential extrusions using an Avanti mini extruder, followed by integration onto the porous PLGA nanospheres. The incorporated macrophage membranes retain essential protein receptors, including IL-6 Receptor, Toll-like Receptor 4, and TNF Receptor 1. These receptors interact with endotoxin LPS and inflammatory cytokines (TNF-α and IL-6), effectively neutralizing these inflammatory mediators.Neddylation, a post-translational protein modification analogous to ubiquitination, regulates diverse biological processes by modulating target protein functionality, activity, stability, and subcellular localization [119]. MLN4924 functions as a neddylation inhibitor at low concentrations. The investigation examined therapeutic effects of MLN4924-mediated neddylation inhibition on macrophage differentiation and diabetic wound recovery through both *in vitro* and *in vivo* analyses. Macrophage activation phenotype polarization (M1 or M2) was evaluated through quantification of inducible nitric oxide synthase as an M1 marker and arginase 1 as an M2 marker. Immunofluorescence analysis of skin sections revealed significantly decreased inducible nitric oxide synthase expression and markedly enhanced arginase 1 fluorescence intensity in the GelMA@M-NPs/MLN4924 group compared to the hyperglycemia group. The experimental results demonstrate that PLGA NPs incorporating MLN4924, combined with the biomimetic membrane system, effectively reduced wound inflammation in diabetic mice, suppressed M1 macrophage polarization, and promoted transition toward the reparative M2 phenotype (Fig. 5A). M-NPs/MLN4924 release inhibited pro-inflammatory M1 macrophage polarization, thereby reducing excessive inflammatory responses and accelerating wound healing processes [118].

2.1.3.2. Neutrophils-derived NVs. Neutrophils represent the predominant immune cell population in the circulatory system and function as primary responders to infection and inflammation [120]. Their recruitment to affected sites occurs through complex molecular signaling cascades. This recruitment process involves elevated cytokine expression, enhanced adhesion molecule regulation, and increased chemokine production at lesion sites, which interact with specific neutrophil membrane antigens [121]. Following migration to inflammatory sites, neutrophils function as potent immune response mediators, releasing multiple pro-inflammatory factors including ROS, proteases, cytokines, chemokines, and neutrophil extracellular traps [122]. At wound sites, recruited neutrophils execute two fundamental functions: foreign debris clearance and antimicrobial defense [123]. Inflammatory stimuli enhance neutrophil defensive capabilities through degranulation, enabling rapid release of diverse antimicrobial molecules [124]. This mechanism constitutes a critical component of immediate host defense against microbial invasion. However, neutrophil functionality is constrained by their limited *in vivo* lifespan (<7 h) and

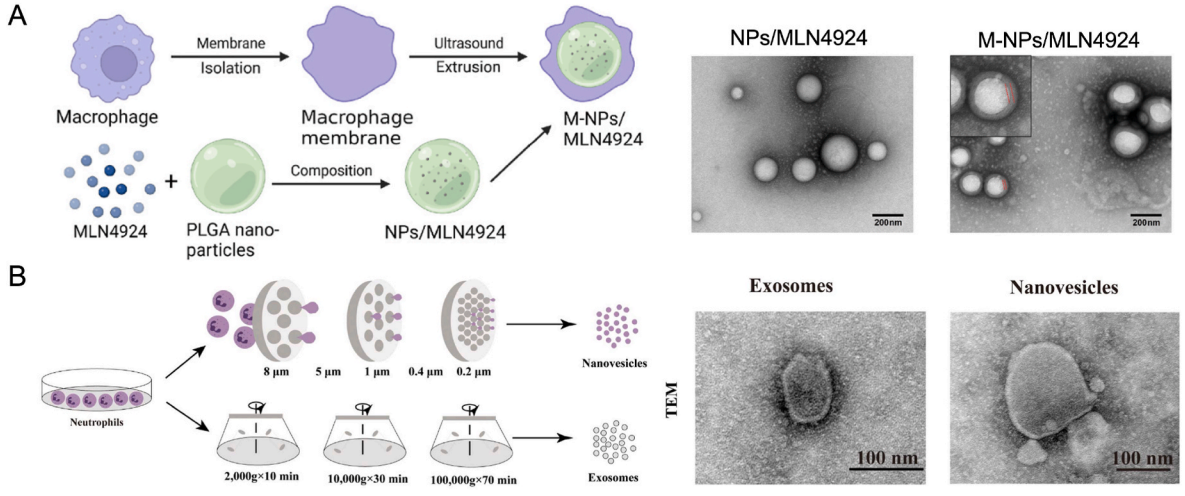


Fig. 5. NVs derived from macrophages, neutrophils, and bacteria for wound healing applications. **(A)** Macrophage membrane-coated NPs (M-NPs/MLN4924): Schematic of synthesis process and TEM images of NPs/MLN4924 and M-NPs/MLN4924. Adapted with permission [118], Copyright 2024, Elsevier. **(B)** Neutrophil-derived NVs: Illustration of NV and exosome preparation methods, with corresponding TEM images. Adapted with permission [126], Copyright 2024, Oxford Academic.

inherent pro-inflammatory characteristics. To address these limitations while preserving beneficial neutrophil properties, researchers have engineered neutrophil membrane-fused nanosystems. These biomimetic constructs maintain the neutralizing capabilities and inflammation-targeting properties of native neutrophils while minimizing pro-inflammatory effects and extending functional durability [125]. This biomimetic strategy presents significant potential for developing targeted therapeutic approaches that effectively localize to inflammatory and infectious sites, potentially enhancing treatment outcomes for various inflammatory and infectious conditions.

Jin et al. established a protocol for engineering neutrophil-derived vesicles. The methodology involved extraction of neutrophils from peripheral blood followed by *in vitro* activation through phorbol myristate acetate stimulation [126]. Activated neutrophils demonstrated rapid release of substantial bactericidal protein quantities. The researchers generated engineered neutrophil-derived vesicles through sequential extrusion of activated neutrophils and ultracentrifugation (Fig. 5B). Membrane integrity assessment of *E. coli* and *S. aureus* under various experimental conditions was conducted using EthD-III live/dead fluorescent staining assay and DMAO. Treatment with engineered neutrophil-derived vesicles induced significant green and red fluorescence overlap, indicating membrane compromise in both *S. aureus* and *E. coli* populations. While these vesicles exhibited morphological characteristics and particle dimensions similar to exosomes, they demonstrated significantly enhanced bactericidal protein enrichment. Comparative analysis of TNF-α expression revealed significantly elevated levels in the control and Exos groups compared to the NVs group, indicating inflammatory conditions at the wound site. Additionally, VEGF immunostaining demonstrated markedly increased expression in the NVs group relative to both Exos and control groups, suggesting enhanced angiogenic activity. *In vitro* analyses demonstrated pronounced bactericidal effects of engineered NVs, attributed to enrichment of proteins including lysozyme. Lysozyme, a naturally occurring glycosidic bond-cleaving enzyme, exhibits bactericidal properties primarily through N-acetylmuramoylhydrolase activity, facilitating peptidoglycan hydrolysis and subsequent bacterial cell lysis [127]. Deep tissue administration of NVs via multipoint injection enhanced pathogen elimination efficiency. These NVs accelerated wound healing processes, characterized by inflammatory marker downregulation, significant bacterial load reduction, and enhanced collagen deposition in a full-thickness infectious skin defect model. The neutrophil-derived NVs demonstrate significant therapeutic potential for infectious wound treatment due to their robust bactericidal capabilities.

Yu et al. developed a methodology for synthesizing exosome mimetics from polymorphonuclear neutrophils through an extrusion process. The synthesis protocol initially involved processing lipopolysaccharide-activated polymorphonuclear neutrophils through multilayer filtration membranes, yielding activated neutrophil exosome mimetics (aPMNEM), a novel category of exosome mimetics [47,128]. Subsequently, VEGF encapsulation within aPMNEM was achieved through ultrasound-assisted incorporation, generating VEGF-aPMNEM constructs. The final phase involved integration of VEGF-encapsulated aPMNEM into the ECM to produce a VEGF-aPMNEM-ECM hybrid hydrogel system designed for chronic wound treatment. The investigation demonstrated significant antibacterial properties of aPMNEM through colony formation assays on LB plates and infected wound animal models. The results revealed that aPMNEM exhibited antibacterial efficacy comparable to PMNExo, effectively reducing wound inflammatory factor concentrations. Functioning as biological delivery vehicles, exosome mimetics protect VEGF from enzymatic degradation, facilitate sustained VEGF release kinetics, and extend therapeutic duration [129].

2.1.4. Bacterial membrane-derived NVs

Inner membrane vesicles produced by the removal of the bacterial outer membrane are referred to as protoplast-derived NVs or cytoplasmic membrane vesicles. Cytoplasmic membrane vesicles produced by the physical extrusion of protoplasts exhibit higher uniformity compared to those generated through alternative methods, as the vesicle size can be precisely controlled during the extrusion process. These vesicles encompass the fundamental components of the bacterial inner membrane or plasma membrane, along with cytoplasmic contents, including nucleic acids and proteins. For gram-negative bacteria, the outer membrane and peptidoglycan layer are removed using lysozyme. In gram-positive bacteria, the peptidoglycan layer is removed to form protoplasts, which are then subjected to physical extrusion to generate cytoplasmic membrane vesicles (alternatively referred to as protoplast-derived NVs) [130] (Fig. 6A). Photosynthetic bacteria, categorized as facultative anaerobes, possess photosynthetic capabilities. These organisms exhibit significant therapeutic potential as both therapeutic agents and drug delivery systems due to their antioxidant properties and photothermal characteristics [131]. However, several inherent limitations, including substantial cellular dimensions, elevated immunogenicity, and reduced biosafety profiles, impede their therapeutic applications. To overcome these constraints, researchers have engineered bacteria-derived NVs (BNVs). These NVs, generated through controlled extrusion processes, effectively circumvent the limitations associated with intact bacterial cells. Current research initiatives focusing on BNVs primarily emphasize *E. coli*, investigating vesicle dimensional characteristics, morphological properties, and biological functionalities [132].

Xiao et al. developed a methodology for BNV synthesis through bacterial cell micropore traversal [133]. The BNV preparation protocol involves initial lysozyme treatment of photosynthetic bacteria, followed by sequential extrusion through polycarbonate membrane filters (pore diameters: 1 μm, 600 nm, and 400 nm) with two iterations per diameter. The final product undergoes ultrafiltration and storage at either 4 °C or −80 °C. During this process, bacterial cell membrane extension occurs due to adhesive tension, resulting in lipid bilayer fragment release into the aqueous phase. These fragments spontaneously form vesicles due to their amphiphilic properties. The high lysophosphatidylcholine (LPC) concentration in BNVs is particularly significant, as LPC mediates cell proliferation and activates downstream signaling pathways promoting angiogenesis and epithelialization. LPC induces ECM protein production through the AKT pathway while promoting vascular smooth muscle cell proliferation via the MAPK pathway [134]. Furthermore, LPC undergoes conversion to phosphatidylcholine through LPC acyltransferase, supporting cell proliferation and activating downstream pathways involved in epithelialization and angiogenesis [135]. Both BNVs and outer membrane vesicles (OMVs) enhanced NIH 3T3 cell proliferation, with BNVs demonstrating superior efficacy (Fig. 6B). Similarly, while both OMVs and BNVs promoted NIH 3T3 cell migration, BNVs exhibited enhanced effects. BNV-associated exogenous LPC metabolizes to phosphatidylcholine through LPC acyltransferase 1 activity, inducing membrane structural modifications. These alterations activate the EGFR signaling pathway [136], subsequently triggering the downstream PI3K/AKT cascade. This pathway activation enhances cell proliferation and migration, accelerating wound healing processes [137]. Western blot analysis revealed increased expression levels of EGFR, PI3K, and AKT following BNV and OMV treatment, with BNVs demonstrating superior effects. The study established that BNV-associated LPC facilitates NIH 3T3 cell proliferation and migration through EGFR/PI3K/AKT signaling pathway activation. Consequently, LPC-enriched BNVs demonstrate significant potential as therapeutic agents for wound healing enhancement.

2.2. Hybrid membrane type-derived NVs

Hybrid membrane NVs, generated through the fusion of membrane components derived from natural secretion or artificial synthesis, enable simultaneous execution of diverse functions and applications [138].

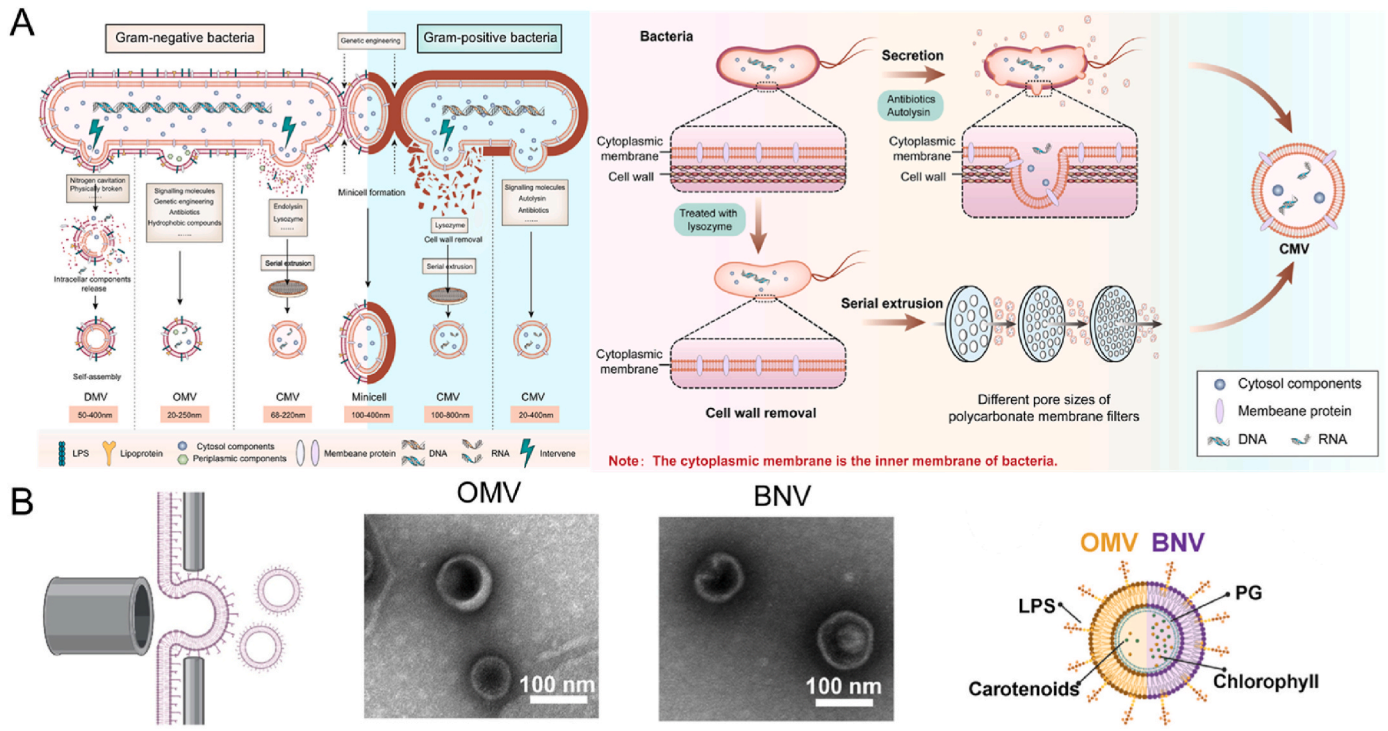


Fig. 6. **(A)** Bacterial-derived NVs encompass the fundamental components of the bacterial inner membrane or plasma membrane, along with cytoplasmic contents, including nucleic acids and proteins. The peptidoglycan layer of gram-positive bacteria is removed to form protoplasts, which are then subjected to physical extrusion to generate cytoplasmic membrane vesicles. Adapted with permission [130], Copyright 2022, Elsevier. **(B)** Bacterial-derived NVs: Schematic of BNV preparation, TEM images of OMVs and BNVs, and diagram comparing OMV and BNV structures. Adapted with permission [133], Copyright 2024, Elsevier.

Hybrid membrane NVs constitute a significant advancement in therapeutic delivery systems. These engineered structures permit large-scale production through accessible methodologies, including membrane filter extrusion and sonication. The development of hybrid membrane NVs has expanded the therapeutic potential of natural EVs in drug delivery and clinical applications. These hybrid constructs serve as effective EV alternatives, providing sophisticated platforms for therapeutic and diagnostic agent delivery [139]. Compared to conventional simplex EVs, hybrid membrane NVs demonstrate superior characteristics, including enhanced circulation stability, improved physiological persistence, precise targeting capabilities, and augmented antiphagocytic properties [140]. These attributes significantly expand their potential biological applications. The integration of natural cellular functions with artificial modification capabilities enhances the versatility of hybrid membrane NVs. This combination results in improved targeting precision, enhanced drug loading capacity, sufficient production yields, and expanded multifunctional capabilities. Furthermore, hybrid membrane NV functionality can be enhanced through biomolecular chemical modifications or genetic engineering approaches, either within the NVs or on their surface. This customization enables the development of tailored platforms with defined compositions, offering exceptional versatility, safety, and adaptability.

Rapid advancement in manufacturing technologies has generated diverse hybrid membrane NVs variants. These can be systematically classified based on membrane component origins, encompassing hybrid membrane NVs generated through cell membrane fusion, and those produced through cell membrane-liposome integration. Hybrid membrane NVs represent an innovative frontier in nanomedicine, combining natural cellular component advantages with artificial system flexibility. Their customization potential and targeted delivery capabilities establish them as significant tools for future therapeutic and diagnostic applications, advancing the fields of personalized medicine and precision therapeutics.

2.2.1. *Hybrid cell membrane-derived NVs*

Hybrid membrane NVs represent advanced nanoscale architectures engineered through the fusion of diverse cell membrane types via sonication or extrusion methodologies. Notably, fused hybrid membrane NVs derived from distinct cell types exhibit integrated biological properties and functionalities from both parental cell populations. Hybrid membrane NVs derived from distinct cellular lineages exhibit integrated biological characteristics and functionalities inherited from their parent cells. These sophisticated constructs integrate multiple biological functions derived from cellular sources, facilitating the synergistic combination of distinct cellular properties. The incorporation of membrane components from multiple cell types enables these hybrid NVs to exhibit comprehensive functionalities, generating versatile nanoplatforms with enhanced therapeutic delivery capabilities and expanded applications.

The simultaneous regulation of EC dysfunction and macrophage polarization necessitates targeted intervention of both macrophages and endothelium. iECs exhibit significant homology with native ECs in the expression of endothelial function-associated genes [141]. Biomimetic NVs derived from iECs maintain characteristic iEC membrane properties [48], establishing their potential for homologous targeting applications. In their investigation, Zhang et al. utilized iEC and M1-type macrophage membranes to synthesize hybrid membrane NVs. Through established extrusion techniques, they developed hybrid membrane (iEC-M) structures encapsulating 4-octyl itaconate (4OI), generating 4OI@iEC-M NVs (Fig. 7A). 4OI, an itaconate metabolite derivative, has garnered significant interest due to its potent anti-inflammatory properties. The cell membrane coating strategy represents an innovative biomimetic approach for drug delivery, enabling the transfer of source cell characteristics for diverse biomedical applications. To achieve dual-regulation of macrophage polarization and endothelial cell dysfunction, macrophage-targeting and endothelium-targeting are both required. The researchers further incorporated these bioinspired 4OI@iEC-M NVs into injectable, multifunctional gelatin methacryloyl hydrogels for diabetic wound repair and regeneration. These bioinspired NVs achieved

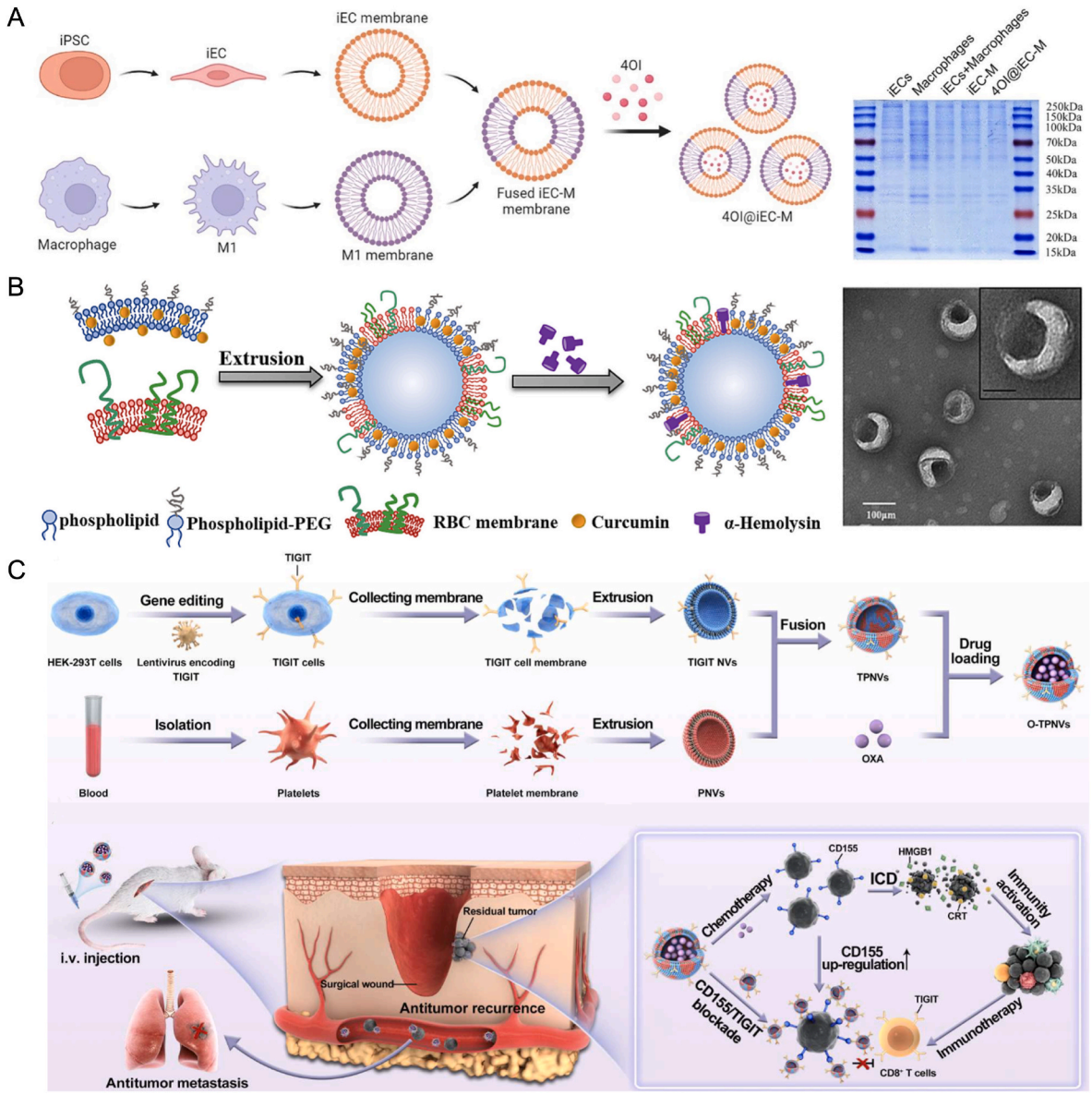


Fig. 7. Hybrid membrane NVs and their applications in wound healing. **(A)** Preparation of hybrid membrane-coated NVs (4OI@iEC-M) using iPSC-derived EC and M1 macrophage membranes. Adapted with permission [142], Copyright 2023, Springer Nature. **(B)** Fabrication of red blood cell membrane and curcumin-loaded liposomes for diabetic wound healing, with TEM images showing the nanostructure. Adapted with permission [147], Copyright 2023, Elsevier. **(C)** Schematic of TIGIT-expressing cell and platelet membrane fusion NVs (O-TPNVs) for cancer immunotherapy, illustrating their preparation and antitumor effects against recurrence and metastasis after surgery. Adapted with permission [159], Copyright 2022, AAAS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

dual-targeted delivery of 4OI to ECs and M1 macrophages, promoting macrophage polarization while providing EC protection. The NV-loaded hydrogels enhanced neovascularization through immunomodulatory and anti-inflammatory effects, demonstrating superior efficacy in diabetic wound repair and regeneration processes [142].

2.2.2. *Cell membrane-liposome derived NVs*

Although cell membrane-derived hybrid NVs demonstrate extensive applications in biomedical fields, several challenges limit their advancement, including stability constraints, insufficient drug loading capacity, and complex manufacturing protocols. Liposomes, representing synthetic vesicular structures engineered through established methodologies such as ultrasonic dispersion, thin-film hydration, and microfluidic systems, exhibit stable bilayer architectures analogous to EVs. Their well-established synthesis protocols, superior drug-carrying capabilities, adaptable characteristics, and minimal systemic toxicity establish liposomes as fundamental components in hybrid NV engineering [143]. The versatile nature of liposomes facilitates their integration with diverse cellular membranes for hybrid NV synthesis.

Curcumin, a polyphenolic compound extracted from turmeric, exhibits anti-inflammatory properties through enhanced M2 macrophage polarization [144]. However, its therapeutic efficacy is limited by poor aqueous solubility [145]. To address this limitation and enhance cellular targeting specificity, liposomal delivery systems have emerged as effective carriers. Tang et al. engineered RBC membrane-mimicking liposomes incorporating curcumin (RC-Lip) for diabetic wound treatment. Surface protein analysis confirmed successful RC-Lip fabrication through RBC-liposomal membrane fusion. Research findings demonstrated that RC-Lips effectively suppressed M1 macrophage-derived inflammatory mediators and proteases, modulating the wound microenvironment through reduced inflammatory responses and minimized migration-associated cellular damage [146]. Furthermore,

RC-Lips exhibited dual regulatory effects on inflammatory responses by inhibiting M1 polarizing factors while promoting M2 polarizing components (Fig. 7B). This mechanism reverses inflammatory cytokine dysregulation and abnormal growth factor expression patterns. Analysis on day 10 revealed significant upregulation of M2-type polarization and angiogenesis markers, including CD206, PPAR-γ, and VEGF mRNA levels. These findings indicate that RC-Lips enhance M2-type polarization within appropriately modulated inflammatory microenvironments, facilitating infection-associated wound healing processes. Additionally, RC-Lips demonstrated efficient curcumin delivery to macrophages, mediating their polarization from M0 to M2 phenotype, resulting in significantly enhanced wound healing outcomes in diabetic mouse models [147].

Che et al. developed an innovative hierarchically structured delivery system incorporating macrophage-like NVs for enhanced diabetic wound healing applications. The NVs were synthesized through the fusion of macrophage membranes with synthetic lipids via sonication, followed by sequential extrusion through 100 nm membrane filters. The hierarchically structured delivery system was engineered through microfluidic-based encapsulation of these NVs within hydrogel microspheres. The integration of macrophage membranes with synthetic lipid membranes generated NVs that retained the cytokine-neutralizing properties of their parent macrophages. These NVs exhibited therapeutic efficacy in wound healing through significant attenuation of inflammatory responses while promoting angiogenesis and collagen synthesis within the wound tissue. The hydrogel microsphere matrix provided protection and controlled release of the encapsulated NVs within the oxidative stress environment characteristic of diabetic wounds. This bioinspired hierarchically structured delivery system demonstrated significant enhancement of HUVEC migration and tube formation capabilities [148].

Jiang et al. developed multifunctional EC-derived biomimetic hybrid NVs for enhanced infected diabetic wound healing [149]. The hybrid NVs were synthesized through the integration of EC extrusion-derived NVs with rhamnolipid liposomes. Rhamnolipid, a nonionic surfactant exhibiting antibacterial properties, demonstrates efficacy as a cutaneous delivery nanocarrier with superior skin tolerance [150]. The engineered hybrid NVs exhibited significant biocompatibility and achieved endothelium-targeted delivery through membrane CXCR4-mediated homologous homing mechanisms. The rhamnolipid modification enhanced both tissue penetration capabilities and antibacterial properties of the hybrid NVs, mitigating the adverse microenvironment characteristic of infected diabetic wounds. This synergistic combination enables hybrid NVs to achieve enhanced penetration into compromised ECs through targeted delivery while reducing antibiotic dependence and subsequent resistance development [151,152].

3. Modifications of cell membrane-based NVs

Cell membranes have emerged as significant drug delivery platforms in therapeutic applications, attributable to their intrinsic biocompatibility and minimal immunogenicity. However, natural EVs face significant limitations in clinical translation, including restricted targeting capabilities, insufficient production yields, and inadequate drug-loading capacity. Although various cell membrane NVs have been developed, these systems continue to encounter substantial challenges, including limited targeting efficiency, reduced therapeutic efficacy, and potential adverse effects. Zhang et al. pioneered the development of erythrocyte membrane-derived NVs, which retain multiple advantageous properties of erythrocyte membranes, including superior biocompatibility, procedural simplicity, and cost-effectiveness [153]. Nevertheless, critical limitations persist, particularly regarding targeting capabilities and therapeutic efficacy. The insufficient targeting ability results in rapid systemic clearance post-administration, leading to reduced circulation half-life. Consequently, the engineering of multifunctional NVs with enhanced adaptability and versatility has become essential for expanding the therapeutic applications of extravesicular particles [140].

To maximize the therapeutic potential of NVs as delivery systems, various modification strategies have been investigated. Cell membrane modification, particularly surface engineering, has emerged as a predominant approach [154]. Surface engineering encompasses both genetic and chemical modifications designed to enhance the functionality of cell membrane NVs. Genetic engineering has significantly advanced the therapeutic applications of cell membrane NVs, facilitating the development of genetically modified NV-based therapeutics. Recent developments have yielded cell membrane NVs functionalized with diverse proteins through genetic engineering approaches [155]. Through strategic implementation of genetic or chemical modifications to either internal biomolecules or surface membrane components, these NVs serve as customizable platforms for specific therapeutic applications, offering enhanced safety profiles with superior versatility and adaptability.

3.1. Genetic editing of source cells

Genetic engineering represents a predominant methodology for cellular modification through exploitation of intrinsic cellular biosynthetic machinery, establishing itself as an efficient approach for cell membrane modification [156]. Current genetic engineering techniques enable selective expression of specific peptides or proteins on cell membranes, enhancing both therapeutic efficacy and targeting capabilities of cell membrane NVs [157]. Compared to alternative modification strategies, including hydrophobic insertion, electrostatic interactions, and click chemistry, genetic engineering demonstrates significant advantages in maintaining cellular activity and preserving native protein bioactivity on cell membrane NVs. The precise regulation of target protein gene expression ensures preservation of native protein structure, orientation, and biological function. Furthermore, genetically engineered stable cell lines facilitate large-scale production capabilities and extended storage potential [158].

Yu et al. engineered fusion NVs incorporating TIGIT (T cell immunoreceptor with Ig and ITIM domains)-expressing cell membranes and platelet cell membranes (TPNVs) loaded with oxaliplatin (OXA) to generate a targeted drug delivery system (O-TPNVs), as illustrated in Fig. 7C. The platelet-derived membrane components of O-TPNVs demonstrated selective targeting to postoperative cancer wounds. OXA administration resulted in direct elimination of residual cancer cells while simultaneously stimulating immune responses and inducing immunogenic cell death. The platelet membrane-mediated active targeting properties of O-TPNVs, combined with controlled OXA release, enhanced anticancer immune responses and promoted immunogenic cell death in malignant cells. The TIGIT components of O-TPNVs specifically interacted with CD155 expressed on cancer cell surfaces, suppressing CD155-TIGIT signaling pathways and restoring $CD8^+$ T cell activity. This therapeutic strategy effectively inhibited post-surgical cancer recurrence and metastasis, leading to improved overall survival outcomes. The system represents an innovative approach to combination therapy, wherein platelet-derived membrane components enable precise targeting of both postoperative wounds and circulating tumor cells by O-TPNVs [159].

TNF-α functions as a critical inflammatory mediator in dermal injury. Following binding to TNF-R1, TNF-α initiates severe inflammation and adverse outcomes through NF-κB signaling pathway activation. Although monoclonal antibodies show therapeutic potential, their clinical application is constrained by complex manufacturing processes, high costs, and non-specific cellular targeting, potentially leading to systemic toxicity and adverse effects.To overcome these limitations, Xi et al. employed genetic bioengineering strategies to modify TNF-R1 expression on cell membrane-derived NVs [160]. The methodology involved culturing HEK 293T cells expressing elevated levels of mouse-derived TNF-R1, followed by membrane isolation and sequential filtration through 0.45, 0.22, and 0.1 μm filters for sterilization.

Spherical cell membrane NVs were subsequently generated through physical extrusion processes. The investigators demonstrated that TNF-R1 NVs maintained consistent TNF-R1 surface expression and effectively interacted with TNF-α, competitively inhibiting its biological activity through ligand-receptor interactions. Furthermore, TNF-R1 NVs significantly reduced healing time and scar formation by enhancing fibroblast proliferation and migration while attenuating inflammation, as evidenced in both *in vitro* studies and a scalded mouse model. Surface-expressed TNF-R1 on TNF-R1 NVs effectively sequestered TNF-α cytokines, blocking the TNF-α/TNF-R1/NF-κB immune activation pathway (Fig. 8A). This TNF-α sequestration by TNF-R1 NVs decreased pro-inflammatory cytokine accumulation and enhanced wound healing in severe burn injuries. These results establish TNF-R1 NVs as promising acellular therapeutic candidates for attenuating TNF-α-mediated pro-inflammatory signaling and promoting tissue regeneration. Brain therapy presents a considerable challenge due to the necessity for drug delivery systems to traverse the blood-brain barrier (BBB), an exceptionally selective membrane that limits the passage of most therapeutic agents. To overcome this limitation, Liu et al. utilized extrusion methods on HEK293T cells expressing ANG-TRP-PK1 to generate functional, engineered NVs. These NVs successfully crossed the BBB and specifically targeted brain tumors, offering a potential strategy for glioblastoma therapy [161].

3.2. Chemical surface modifications of membrane-based NVs

Membrane NVs, as an emerging drug delivery platform, have demonstrated significant potential in modulating cellular physiological and pathological processes through surface chemical modifications of functional molecules, enabling diverse therapeutic applications. The chemical modification of cellular membranes involves covalent conjugation of chemical residues to membrane-associated polysaccharides and proteins [162]. Chemical modification of NVs facilitates stable protein attachment to their surfaces, offering efficient and versatile methodological approaches for various applications [163]. Through strategic chemical modification of membrane components and surface biomolecules, NVs can be engineered into customizable platforms that incorporate specific therapeutic agents, providing enhanced safety profiles and adaptability. Cell membrane surface molecules, including sulfhydryl, carboxyl, and amino groups, present multiple active sites for chemical modification. These modifications can be classified based on their binding mechanisms, primarily differentiated into covalent and noncovalent interactions.

3.2.1. Covalent chemical modification

Covalent chemical modification of NVs encompasses the incorporation of exogenous functional groups and bioactive molecules onto NV surfaces through chemical bond formation. The abundant thiol groups present on cell membrane surfaces enable conjugation with functional molecules through thiol-maleimide reactions [164]. Michael addition

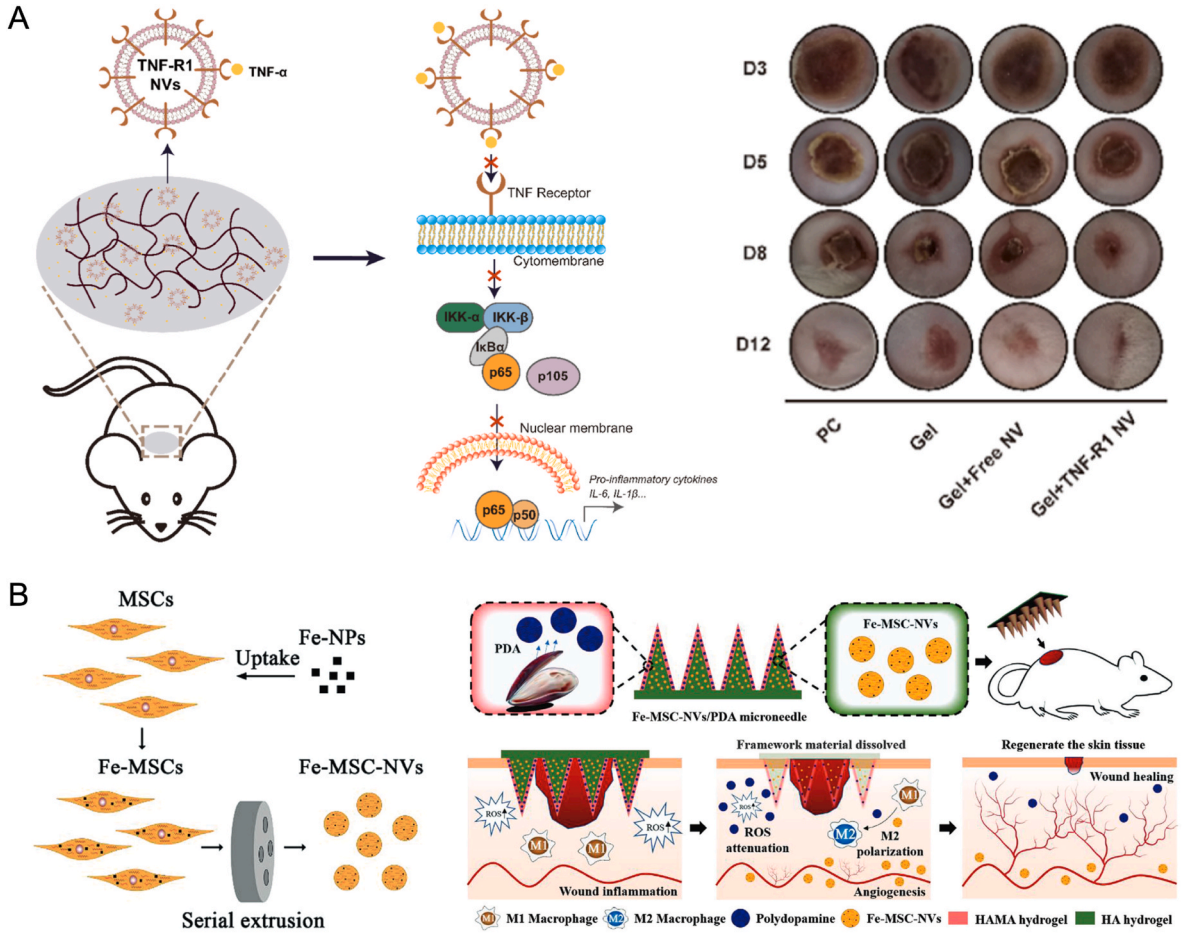


Fig. 8. Engineered NVs for wound healing and inflammation modulation. **(A)** TNF-R1 NVs for burn wound healing: schematic of preparation from genetically modified cells, mechanism of TNF-α neutralization, and representative images of scald repair in mice. Adapted with permission [160], Copyright 2023, American Chemical Society. **(B)** Fe-MSC-NVs/PDA microneedle patch for diabetic wound healing: preparation process of Fe-MSC-NVs, design of the microneedle patch, and illustration of the wound closure process. These approaches demonstrate the versatility of engineered NVs in targeting specific inflammatory pathways and promoting tissue regeneration for enhanced wound healing outcomes. Adapted with permission [181], Copyright 2022, Wiley-VCH.

reactions between sulfhydryl and maleimide groups facilitate selective and efficient protein site modification while maintaining protein integrity on NV surfaces. Cheng et al. achieved NV surface functionalization by incorporating succinimidyl-[(N-maleimidopropionamido)-polyethylene glycol] ester, followed by thiolated human recombinant hyaluronidase conjugation via thiol-maleimide reactions. This approach enables successful integration of functional molecules onto NV surfaces through maleimide-sulfhydryl coupling, maintaining structural integrity and biological functionality [165]. N-hydroxysuccinimide forms irreversible, spontaneous bonds with membrane protein amines, enabling efficient pre-conjugation of functional molecules [166]. Click chemistry represents a prevalent methodology for protein peptide and antibody attachment to NV surfaces. Notably, Cai et al. enhanced the targeting capabilities of T-cell membrane-derived NVs through click chemistry applications [167]. Azide-alkyne cycloaddition serves as a key click chemistry reaction for bioconjugating functional moieties to cell membranes [168]. Kang et al. demonstrated metabolic la beling of cell-surface glycoproteins using azide sugars, followed by conjugation with dibenzocyclooctyne-bearing molecules through biorthogonal click chemistry [169]. This methodology demonstrates superior efficiency, reaction kinetics, and conjugation site specificity compared to maleimide-thiol coupling. In a particular study, mannosylerythritol lipids, a potent suppressor of inflammatory mediators, were linked to PEG using a thiol-maleimide reaction and subsequently coextruded with HaCaT cells (human epidermal keratinocytes) to produce NVs. These NVs demonstrated elevated cellular internalization and exhibited significant anti-inflammatory effects, aiding in the preservation of the skin barrier [170]. For targeted cellular delivery, various functional nanomaterials, such as peptides and aptamers, have been utilized to modify cells and endow NVs with targeting abilities. For instance, Lee et al. [171] covalently modified apoptotic fibroblasts with dextran and ischemic heart-homing peptide (CHP) before preparing NVs. Dextran and CHP are recognized for their specific targeting of macrophages and ischemic heart tissue. The targeted delivery of these NVs substantially diminished inflammatory responses through M2 polarization of macrophages, thus reducing adverse cardiac remodeling.

3.2.2. Noncovalent chemical modification

The membrane structure of NVs, analogous to cell membranes, primarily consists of phospholipids, glycolipids, and cholesterol. Amphiphilic molecules containing diverse functional groups can be integrated into NV surfaces through hydrophobic interactions. Liu et al. demonstrated successful incorporation of cholesterol-modified aptamers—short nucleotide sequences characterized by high specificity and binding affinity for target ligands—into NV surfaces via cholesterol-mediated insertion. NVs engineered through hydrophobic insertion methods demonstrated effective anticancer activity [172]. In a related study, Zhang et al. successfully functionalized NV surfaces with cyclic (ARG--GLY-ASP) peptides through noncovalent chemical modification, resulting in enhanced tumor accumulation [173]. The inherent negative surface charge of NVs enables attachment of cationic nanocomplexes through electrostatic interactions. Zhang et al. utilized this principle to incorporate positively charged nanocomplexes onto cell membranes, enhancing targeting efficiency. However, the instability of electrostatic noncovalent bonds may compromise the therapeutic efficacy of this approach [174].

4. Biomedical applications of cell membrane-based NVs

Biological barriers, particularly the nonspecific distribution of NPs and the phagocytosis of the immune system, significantly restrict the clinical translation of nanomedicine. To address these challenges, researchers have implemented biomimetic and bioengineering approaches. Cell membrane-based biofunctionalized NPs have emerged as promising candidates, combining cell surface mimetic properties with tailored nanomaterial characteristics. These hybrid nanocarriers demonstrate substantial potential for diverse therapeutic agent delivery [175]. Biomimetic strategies utilize cell membrane-derived NVs to camouflage NPs, addressing various limitations inherent to nanoscale materials. This cell membrane-coating technology, derived from natural intercellular interaction mechanisms, enhances targeted delivery to specific sites, improving therapeutic efficacy and safety profiles. Furthermore, the natural biocompatibility of cell membranes enables efficient navigation through biological barriers and immune clearance evasion, resulting in prolonged circulation times and reduced *in vivo* toxicity [115]. The integration of natural cell membranes onto NP surfaces combines the advantages of biomimetic interfaces with versatile material chemistry [176]. Specifically, cell membrane-mediated biofunctionalization of NP surfaces facilitates immune evasion through reduced opsonic protein adsorption and presentation of "self" markers via surface proteins [177]. This biofunctionalization approach endows synthetic NPs with inherent targeting capabilities, providing a platform for active targeting modifications [178]. Additionally, cell membrane-derived lipid components on NP surfaces enhance colloidal stability and function as molecular barriers, modulating drug release kinetics [179].

Stem cell membrane-based nanotechnology represents an innovative drug delivery platform that integrates the advantages of both natural and synthetic components. Stem cell membranes, as biological entities, exhibit distinctive surface characteristics, including site-specific targeting capabilities to damaged tissues. Additionally, the synthetic NP cores enable drug encapsulation for diverse therapeutic applications.These advantageous properties position stem cell membrane-coated NPs as superior candidates for clinical translation compared to alternative stem cell-based delivery systems. Nevertheless, advancement in stem cell membrane-coating methodologies remains crucial. Surface ligands present on stem cell membranes play fundamental roles in cellular targeting and homing mechanisms. While conventional membrane coating techniques rely on extrusion or sonication, emerging approaches incorporating microfluidic systems and electroporation [138] demonstrate potential for optimizing both membrane functionality and coating efficiency.

4.1. Drug loading and targeted delivery using cell membrane-based NVs

Cell membrane-based NVs have emerged as promising carriers for therapeutic cargo delivery, offering unique advantages in drug loading and delivery efficiency. These biomimetic platforms can accommodate diverse therapeutic agents, ranging from nucleic acids to proteins, while maintaining their biological functions. Recent studies have demonstrated significant advances in utilizing these NVs for various therapeutic applications, particularly in wound healing and tissue regeneration. Two notable examples illustrate the versatility and effectiveness of these delivery systems in addressing complex therapeutic challenges.

Tao et al. investigated high-yield EV-mimetic NVs as a delivery system for long noncoding RNA H19 (LncRNA-H19). The researchers examined the therapeutic potential of engineered macrophage-derived NVs (EMNVs) enriched with LncRNA-H19 (H19EMNVs) in diabetic wound management through competing endogenous RNA mechanisms [180]. The study demonstrated H19EMNVs' capacity to counteract hyperglycemia-induced inhibition of tissue regeneration. These NVs effectively restored EC functions, including proliferation, migration, and tube formation capabilities, which were previously impaired by elevated glucose conditions. The investigators identified LncRNA-H19 suppression as a critical regulatory element in this process. Glucose-induced suppression of LncRNA-H19 impairs angiogenesis through inhibition of Akt activation. Thus, H19EMNVs represent a potential precision-medicine approach targeting the underlying pathophysiology of chronic diabetic wounds. To evaluate *in vivo* angiogenic and wound healing efficacy, alginate hydrogel-encapsulated H19EMNVs were applied as wound dressings in an experimental model. Results

demonstrated that H19EMNV administration significantly enhanced wound blood perfusion, promoted re-epithelialization, and accelerated wound healing processes. These findings highlight the dual significance of EMNVs as a bioengineered delivery platform for biomacromolecules and demonstrate LncRNA's role as an epigenetic regulator through competing endogenous RNA network modulation in tissue regeneration and wound healing.

Ma et al. developed a novel core-shell hyaluronic acid microneedle patch incorporating polydopamine NPs and ferrum-mesenchymal stem cell-derived artificial NVs (Fe-MSC-NVs) within the needle tips for wound healing applications [181]. The experimental protocol involved co-culturing MSCs with Fe NPs for 24 h, followed by magnetic separation of Fe-MSCs. Subsequently, Fe-MSCs underwent sequential extrusion through porous membranes to generate functional MSC NVs (Fig. 8B). MSC-derived NVs overcome the limitations associated with MSC applications, including storage challenges and reduced cell viability within biomaterials, while demonstrating enhanced therapeutic efficacy in animal models. Fe NP exposure significantly augments the therapeutic cytokine expression capacity of MSC NVs. Real-time quantitative PCR analysis revealed significantly elevated expression levels of therapeutic growth cytokines in Fe-MSC-NVs, including hepatocyte growth factor, VEGF, TGF-β3, angiopoietin-1, hypoxia-inducible factor-1α, and fibroblast growth factor 2. These findings indicate Fe-MSC-NVs' superior angiogenic potential compared to unmodified MSC-NVs. The microneedle design incorporates multifunctional therapeutic cytokine-containing Fe-MSC-NVs within the hyaluronic acid core at the needle tips to promote angiogenesis. Fe-MSC-NVs notably enhance the migration, proliferation, and tube-forming ability of HUVECs. *In vivo* studies demonstrate significant efficacy of the Fe-MSC-NVs/PDA microneedle patch in accelerating diabetic wound healing.The adoption of biomimetic approaches utilizing cell membrane-based nanosystems derives from the intrinsic properties of cellular membranes, including their complex compositional architecture, natural tissue interaction capabilities, and inherent biocompatibility. The NV generation process maintains cell membrane functional integrity, preserving essential membrane proteins crucial for biological functions. Cell membrane-derived NVs demonstrate superior targeting capabilities through enhanced payload capacity and extended bloodstream stability. This versatility enables the delivery of diverse therapeutic agents, ranging from small molecule drugs to proteins, establishing their adaptability across multiple therapeutic applications.

Cell membrane-based NPs and cell membrane-derived NVs represent an emerging paradigm in targeted drug delivery systems, particularly for challenging therapeutic applications. This approach integrates the distinctive properties of multiple cellular membrane sources with advanced fabrication technologies to generate biomimetic NPs that effectively replicate endogenous cellular functions.

This biomimetic strategy represents a significant advancement in cellular membrane-based drug delivery systems. The approach is exemplified in cell membrane-coated NPs, which demonstrate enhanced biocompatibility, targeted delivery capabilities, reduced immunogenicity, and improved barrier penetration, particularly across the blood-brain barrier. In comparison with conventional liposomal systems utilizing synthetic lipid bilayers for drug encapsulation, cell membrane-based nanosystems exhibit several distinctive advantages, including enhanced biocompatibility, targeted delivery capabilities, functional mimicry, advanced preparation techniques, and versatility with multifunctionality [182]. A key advantage of these systems lies in their ability to replicate the natural functionalities of their source cells. For example, nanocarriers derived from cells capable of blood-brain barrier penetration inherit this intrinsic capability, facilitating direct therapeutic agent delivery to brain tissues. Surface membrane proteins and receptors play crucial roles in this process, as they can be engineered for specific target recognition and binding, thereby enhancing delivery efficiency and specificity. This targeted approach results in minimized systemic side effects and improved therapeutic indices of encapsulated drugs [182].

4.2. Applications in cancer therapy

Cancer represents a significant global public health challenge, posing substantial threats to human life and wellbeing [183]. Current conventional clinical treatments, primarily comprising chemotherapy, radiotherapy, and surgery, are limited by low selectivity, severe toxic side effects, and insufficient tumor specificity, thus compromising the potential for complete tumor eradication. Consequently, the development of safe and effective oncological treatments remains an urgent medical necessity. Phototherapy, primarily consisting of photothermal therapy and photodynamic therapy, has attracted significant research attention due to its minimally invasive nature, therapeutic efficacy, and precise spatiotemporal control capabilities [184]. The selective destruction of cancer cells through phototherapy is achieved by modulating light parameters, including spatial distribution, temporal exposure, and dosage, with NIR radiation being particularly advantageous due to its superior tissue penetration properties. While nanomaterial-mediated phototherapy demonstrates promising advances in tumor treatment, its clinical translation and therapeutic efficacy remain constrained by inherent limitations of phototherapeutic agents, including inadequate targeting, limited stability, and immunological clearance. The implementation of biomimetic strategies that replicate cell membrane interactions with the cellular environment enhances the biological properties of nanomaterials. This approach maintains the optical characteristics of phototherapeutic agents while simultaneously improving tumor targeting specificity, immune evasion capabilities, and biocompatibility, thereby significantly enhancing phototherapeutic efficacy. Sun et al. [185] leveraged the abundant Fe^{2+} present in erythrocytes and reacted it with H_2S gas to produce FeS nanocomposites as photothermal agents. Catalytic erythrocyte-derived NVs, enriched with endogenous ADA, were subsequently prepared through sequential extrusion. These biofunctional NVs exhibited tumor-targeting properties and triggered immunogenic cell death via the photothermal effects of FeS. The intrinsic ADA within the NVs efficiently converted adenosine to inosine, mitigating the immunosuppressive impact of adenosine on tumor-infiltrating immune cells and thereby amplifying the antitumor immune response.

Recent advances in cell membrane biomimetic technology have addressed the limitations inherent to conventional surface modification approaches in biomedical applications. Biomimetic nanomaterials derived from cell membranes acquire the surface characteristics of their source cells, endowing phototherapeutic agents with specific biological functions, including prolonged circulation time, enhanced biocompatibility, homologous targeting, and immune evasion capabilities [186]. The co-extrusion methodology has emerged as the primary technique for membrane-nanomaterial fusion. Multiple cell membrane types have been successfully utilized for photothermal therapeutic agent modification, including RBC membranes [187], cancer cell membranes [188], macrophage membranes [189], platelet membranes [190], mixed cell membranes [191], and engineered cell membranes [192]. These cell membrane biomimetic phototherapeutic agents integrate the photo-responsive properties of nanomaterials with the antigenic diversity of source cells [193]. The cell membrane biomimetic approach optimizes nanomedicine biodistribution to enhance phototherapeutic efficacy while simultaneously inducing antitumor immune responses, thereby amplifying the overall therapeutic effect against cancer [194]. Additionally, synergistic antitumor strategies combining chemotherapy [189], Radiotherapy, immunotherapy, and sonodynamic therapy have been developed to maximize phototherapeutic benefits and address tumor heterogeneity. Yuan et al. [195] anchored the nucleolin-targeting aptamer AS1411 onto the surfaces of murine dendritic cell membranes and subsequently produced ligand-modified NVs via extrusion. These NVs, loaded with chemotherapeutic agents, exhibited potent antitumor activity while minimizing severe systemic toxicity. The integration of biomimetic cell membrane strategies with passive targeting mechanisms enhances tumor-specific accumulation of NPs, enabling robust

antitumor effects with reduced nanomedicine dosages.

4.3. Potential therapeutic applications in other diseases

Pang et al. [196] engineered exosome-like MSC-NVs using sequential cell extrusion. These MSC-NVs, abundant in microRNAs that facilitate cartilage repair, were shown to enhance the differentiation, migration, and proliferation of chondrocytes and BMSCs, while also promoting M2 macrophage polarization. BMSC-NVs demonstrated significant efficacy in alleviating osteoarthritis by regulating chondrogenesis and macrophage polarization. Wu and colleagues [197] developed NVs originating from primary hepatocytes, which demonstrated biological activities similar to natural EVs in supporting liver regeneration. These NVs facilitated the production of sphingosine-1-phosphate in target hepatocytes by transferring sphingosine kinase 2, acting as a protective mechanism for the liver. Keunhee et al. [198] identified that NVs derived from mouse pancreatic β-cells could promote the differentiation of bone marrow cells into functional β-cells. In a diabetic mouse model with immune deficiency, a subcutaneous matrix platform incorporating bone marrow cells was created and subsequently treated with NVs derived from mouse pancreatic β-cells. The findings demonstrated that therapeutic insulin-secreting cells could develop from donor-derived bone marrow cells, effectively maintaining blood glucose homeostasis in diabetic mice for more than 60 days. Yang et al. [199] created macrophage-derived artificial EVs (aEVs) coated with cell membranes that overexpressed the immunosuppressive molecules PD-L1 and Gal-9. The immune-modified aEVs containing PD-L1 and Gal-9 demonstrated the capacity to induce suppressive and apoptotic effects in T cells. Their research showed that PD-L1–Gal-9 aEVs were able to promote apoptosis in T cells and support the development of Treg cells. Remarkably, PD-L1–Gal-9 aEVs effectively reversed newly diagnosed hyperglycemia in NOD mice, hindered the progression of T1D, and reduced both the proportion and activation of $CD4^+$ and $CD8^+$ T cells infiltrating the pancreas, collectively supporting the preservation of residual β-cell function and alleviation of hyperglycemia. To improve targeting efficiency, Kim et al. [22] designed high-yield NVs with magnetically steered brain-targeting properties by co-culturing human BMSCs with iron oxide NPs prior to sequential extrusion. Iron oxide NPs enriched the NVs with therapeutic growth factors. The findings revealed that systemic delivery of NVs following middle cerebral artery obstruction in rats, coupled with magnetic guidance, enhanced the accumulation of NVs in ischemic regions by 5.1-fold and stimulated anti-inflammatory, angiogenic, and antiapoptotic effects in brain injury. CD40 was displayed on the surface of genetically modified NIH 3T3 cells to produce CD40-NVs. CD40-NVs disrupted the CD40/CD40L costimulatory signaling pathway in B cells, thereby suppressing their ability to generate antibodies. Simultaneously, it restricted the proper development of germinal center structures. Additionally, this study incorporated the immunosuppressive drug mycophenolate mofetil into aEVs and demonstrated that the combined formulation could be utilized to eliminate immune cells [200].

5. Perspective and challenges

Beyond comparable therapeutic efficacy in wound healing, NVs demonstrate distinct advantages over both EVs and cells, particularly regarding production efficiency, yield, and economic considerations. A significant advantage of NV production lies in its independence from cellular vesicle secretion processes. In contrast, EV production involves a labor-intensive process yielding only minimal quantities (measured in protein content), while requiring expensive EV-free medium compared to standard cell culture media [62]. NV production demonstrates superior scalability through extrusion methods, enabling direct generation from confluent cells maintained in continuous bioreactor systems. NVs have emerged as a promising alternative to EVs, serving as sophisticated platforms for targeted delivery of diagnostic and therapeutic agent [139]. Compared to natural simplex EVs, NVs can be engineered to achieve enhanced targeting specificity, production efficiency, drug loading capacity, and multifunctionality by integrating source cell biological properties with artificial modifications. However, while numerous studies position NVs as direct EV alternatives, fundamental differences may exist between these vesicle types. Variations in essential components could significantly impact vesicular functionality [133]. Consequently, additional validation studies are essential to confirm the functional equivalence between NVs and EVs. These advanced membrane vesicles remain in early developmental stages and await clinical implementation. The progression from preclinical research to clinical translation necessitates addressing several critical challenges and limitations, as outlined below.

5.1. Stability and reproducibility

The manufacturing of NVs presents significant challenges, particularly regarding reproducibility and scalability in large-scale production. The industrial-scale production of cell membrane-based biomaterials faces substantial limitations due to the precision requirements in nanoscale engineering and inherent cell membrane variability. The development of large-scale culture methodologies for cells with limited availability remains a critical research priority [201]. Production yields, purity levels, and NV uniformity are heavily influenced by processing parameters during preparation. The current absence of standardized and economically viable methods for large-scale NV production represents a significant barrier to advancement. The implementation of good manufacturing practices for industrial-scale production constitutes a crucial step toward facilitating the clinical translation of cell membrane-based nanotherapeutics.

Current experimental research predominantly employs extrusion and sonication techniques for cell membrane generation. The quality and efficacy of the process are significantly influenced by multiple parameters, including initial cell concentration, membrane fluidity, and processing conditions, which collectively affect membrane purity, NP encapsulation efficiency, and membrane integration capabilities [202]. In the preparation of nucleated cell-derived materials, membrane isolation must achieve complete separation from organelles and nuclei to ensure optimal purity. The optimization of processing parameters and purification protocols specific to each cell type is essential for enhancing the yield of high-purity cell membranes required for large-scale uniform NV production. The development and implementation of standardized quality control assays and optimized production workflows are anticipated to address these technical challenges in the immediate future.

Although artificially assembled NVs demonstrate enhanced production yields and controllability compared to naturally secreted EVs, scalability remains a critical challenge for clinical implementation [140]. Beyond achieving adequate NV yields, extraction methodologies require careful optimization specific to their intended applications. The selection of appropriate isolation techniques, including differential centrifugation, density gradient centrifugation, and size exclusion chromatography, is crucial, as complex preparation processes can impact cell membrane protein composition and integrity. Researchers must evaluate diverse methodological approaches to establish standardized protocols, ultimately developing efficient, reliable, and reproducible manufacturing processes for large-scale NV production. Current research in this domain remains insufficient, necessitating increased focus in future investigations to advance NV-based therapeutic applications.

5.2. Cell sources

Despite advances in NV therapeutic applications, careful consideration of cell source selection is crucial prior to clinical implementation. This selection encompasses target cell identification, cellular abundance, *in vitro* culture conditions, and cell availability. The choice of

appropriate cell sources directly impacts the safety and efficacy of cell membrane-derived NV therapies. Notably, membrane characteristics vary across different growth phases and cell cycles, potentially leading to batch-to-batch variability that may affect therapeutic outcomes [203]. The development of quality control parameters and protocols for both cell sources (raw materials) and NVs (final products) requires significant attention in future research. Additionally, ensuring immunocompatibility presents a critical challenge, particularly as NVs are typically derived from allogeneic membrane sources. Two potential approaches address this challenge: utilizing autologous cells or patient-derived iPSCs as membrane sources, or developing universal cell lines through genetic elimination of potentially immunogenic antigens.

Autologous cells serve as ideal source materials for minimizing host immune responses. Patient-derived cells are particularly advantageous as they eliminate antigen mismatch concerns and reduce immune response risks associated with macrophage cell type variations [204]. However, the utilization of autologous cell sources presents limitations regarding immediate cell availability for NV production. The manufacturing of cell membrane-based drug formulations involves complex multi-step processes requiring substantial time and rigorous quality control measures. These requirements may result in treatment delays when patients must await cell isolation and product synthesis [205]. Allogeneic (donor) cells offer an alternative approach, providing readily available cell membrane sources for immediate treatment needs. However, analogous to organ transplantation protocols, antigen matching remains essential to minimize host immune responses while optimizing NV therapeutic efficacy [206]. The development of safe and effective gene delivery vectors remains a significant challenge in cell genetic modification. The selection of donor cell type significantly influences NV homogeneity. Various cell sources, ranging from blood cells (RBCs, platelets) to immune cells, cancer cells, and stem cells, have been employed in NV delivery system development. While RBCs and platelets represent predominant cell sources for membrane extraction, their anucleate nature limits their compatibility with genetic engineering approaches for membrane pre-modification [207].

Future research directions should prioritize the optimization of cell source selection and standardization of operating protocols. Critical areas for development include cell selection methodology, culture condition refinement, quality control enhancement, and immunocompatibility management. These fundamental advances will prove essential for facilitating the successful clinical translation of NV-based therapeutic platforms.

5.3. Balancing hybrid cell membrane type proportions

Comprehensive investigations of NV biological effects and molecular mechanisms are necessary, particularly considering source cell heterogeneity — which is defined as the differential distribution of molecules across single EVs. In cell membrane hybridization studies, optimal proportioning of dual cell membranes is critical for enhancing the efficacy of hybrid membrane-derived vesicles [208]. Recent studies have demonstrated hybridization success through qualitative assessments of target cell interactions and enhanced therapeutic agent pharmacological activity. However, advancing the design principles of hybrid cell membrane-derived vesicular delivery systems requires quantitative analysis of vesicle-specific compositions [206]. The incorporation of synthetic lipid membranes into NVs may generate unexpected effects on native cell membranes, potentially compromising their inherent biological functions. Further investigation is required to elucidate NV biological properties and their complex interactions with tissue- or cell-derived biomacromolecules. Careful evaluation of cell type selection and membrane proportions is essential for optimizing individual component functions (cell membrane or liposome). This systematic approach can expand the biomedical applications of biomimetic NVs in precision bioimaging, therapeutic interventions, and diagnostic procedures. Future research priorities should encompass quantitative analytical methods, evaluation of artificial component effects, and optimization of NV design parameters to maximize their biomedical potential.

Heterogeneity poses a significant challenge to the clinical application of EVs/ANVs in nanotherapeutics. We propose several strategies and viewpoints to address this issue. Enhancing resolution and achieving more precise profiling of individual EVs—revealing their inherent heterogeneity—will be crucial. Expanding and refining microfluidic-based isolation methods could transform how researchers separate and concentrate specific vesicle subsets. Advancing to a stage where these methods are widely adopted in laboratories globally would mark a substantial milestone. While microfluidic systems show great potential, their current throughput remains insufficient to generate the quantities required for downstream functional studies or *in vivo* applications. Promoting collaborative efforts and sharing knowledge. Developing and improving platforms for international cooperation and standardization will allow researchers worldwide to build upon each other's work, accelerating progress and fostering innovation in the field.

5.4. Storage

As biological entities, NVs require frozen storage conditions, which may compromise membrane integrity [209]. Research efforts must focus on developing appropriate cryoprotectant formulations to minimize membrane degradation during storage. The long-term stability of coated membranes requires thorough evaluation in various physiological buffers and *in vivo* environments, as the material-membrane interfacial adhesion may lack sufficient strength for extended storage periods [210]. The preservation of nanocarrier stability, particularly concerning structural integrity and functional properties over time, remains fundamental. The development of storage protocols that maintain NV efficacy is crucial for clinical implementation. Currently, standardized and cost-effective methods for mass production and long-term storage of NVs are lacking.

5.5. Safety and biocompatibility

The clinical translation of NVs requires systematic evaluation of their biocompatibility and potential long-term toxicity, encompassing immunogenicity, cytotoxicity, and off-target effects. For instance, the stress-triggered secretion of particular immune-regulatory factors from parental cells or the breakdown of synthetic cells could lead to the incorporation of pro-inflammatory elements within NVs, potentially causing systemic inflammatory responses [211]. Several biological characteristics of NVs, including blood circulation patterns, immune responses, biodistribution, and clearance mechanisms, remain incompletely understood. Additionally, metabolic risks associated with integrated components, such as loaded nucleic acids, encapsulated NPs, and other bioactive compounds, require careful consideration. Although biomimetic approaches enhance biocompatibility, comprehensive investigation of long-term nanocarrier safety remains essential [212]. Chemical engineering of cell membranes enhances NV functionality; however, significant challenges persist, including insufficient targeting specificity and unpredictable chemical reactions between membrane proteins and functional groups. The complex surface characteristics of NVs may reduce reaction efficiency, while covalent modifications potentially alter their structural and functional properties [213]. The incorporation of diverse active chemical groups, including azido groups, dyes, and biotin, presents additional toxicity concerns. Future research should prioritize the identification of safe and effective functional groups for chemical modification [155]. A comprehensive assessment of both acute and chronic biosafety profiles is crucial. Furthermore, elucidating the fundamental principles governing chemical-material-biological interactions in NVs is imperative for their rational design and successful clinical implementation in biomedical applications.

5.6. Clinical translation

NVs are still in the early stages of research and encounter many obstacles in clinical translation. A significant gap exists in controllable production techniques and evaluation benchmarks for NVs. In clinical practice, EVs derived from stem cells as therapeutic agents often require multiple administrations, with a single dose needing over 2×10^{10} particles/kg [211]. Compared to EVs, NVs can be manufactured in large quantities, greatly enhancing yields while reducing the frequency of cell passaging and mitigating batch-to-batch inconsistencies. However, the absence of standardized protocols across the various methods used for NV preparation and purification poses significant challenges to quality assurance. It is essential to carefully choose and refine suitable methods based on the specific use of NVs, implement standardized procedures, and minimize batch-to-batch variability. Lab-scale procedures for isolating cell membranes involve multiple steps and are tailored to individual cell types, which can lead to sample loss, functional receptor degradation, and contamination with mitochondrial, nuclear, or cytosolic components. Thus, a standardized protocol with minimal manual intervention is needed for cell membrane extraction, ensuring high yield and purity across various cell types. Enhancing the membrane stability and long-term storage conditions of NVs is essential for extending their shelf life. Lyophilized isolated cell membranes can be preserved under low-temperature conditions and rehydrated in buffers prior to application. Nevertheless, investigations into shelf life to assess the stability and functional performance of isolated cell membranes have yet to be conducted [214]. Ongoing assessment and evaluation of genetic modifications in EV and NV-producing cells, along with quantification of drug loading or transfection efficiency following cellular bioengineering, are critical to maintaining the consistency and safety of bioengineered EVs and NVs. Noncovalent alterations of NVs help preserve membrane protein functionality, though the interaction strength is relatively weak. Similarly, EVs necessitate processing for external modifications, yet the recovery and stability after these modifications are often overlooked and rarely addressed in existing preclinical research. These impacts warrant greater consideration in the development of bioengineered EVs and NVs [215].

6. Conclusion

This review examines the current evidence supporting NV applications in regenerative wound healing therapy. Cell membrane-derived NVs demonstrate significant potential for cost-effective large-scale production, establishing their role as innovative therapeutic agents for targeted delivery and direct wound healing applications, thereby advancing chronic wound management strategies. Furthermore, this review evaluates the diverse biomedical applications of cell membrane-derived NVs, highlighting their therapeutic potential across multiple domains. Future directions focus on optimizing NV-based therapeutic approaches to enhance both their efficacy and wound healing capabilities.

CRediT authorship contribution statement

Wenwen Li: Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Formal analysis. **Huihui Zhang:** Writing – original draft, Supervision, Methodology, Formal analysis. **Lianglong Chen:** Visualization, Validation, Conceptualization. **Chaoyang Huang:** Writing – review & editing, Formal analysis, Conceptualization. **Ziwei Jiang:** Validation, Supervision, Conceptualization. **Hai Zhou:** Visualization, Data curation. **Xinxi Zhu:** Writing – review & editing, Writing – original draft. **Xiaoyang Liu:** Visualization, Validation. **Zesen Zheng:** Supervision. **Qiuyi Yu:** Project administration, Investigation. **Yufang He:** Visualization, Validation, Supervision. **Yanbin Gao:** Writing – original draft, Visualization, Validation. **Jun Ma:** Software, Project administration, Conceptualization. **Lei Yang:** Writing – review & editing, Writing – original draft, Visualization, Validation.

Declaration of competing interest

The authors declare that they have no competing interests.

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Data availability

Data will be made available on request.

References

[1] C. Karimkhani, R.P. Dellavalle, L.E. Coffeng, C. Flohr, R.J. Hay, S.M. Langan, E. O. Nsoesie, A.J. Ferrari, H.E. Erskine, J.I. Silverberg, T. Vos, M. Naghavi, Global skin disease morbidity and mortality, JAMA Dermatology 153 (5) (2017) 406, https://doi.org/10.1001/jamadermatol.2016.5538.
[2] D.G. Armstrong, A.J.M. Boulton, S.A. Bus, Diabetic foot ulcers and their recurrence, N. Engl. J. Med. 376 (24) (2017) 2367–2375, https://doi.org/10.1056/NEJMra1615439.
[3] S. Guo, L.A. Dipietro, Factors affecting wound healing, Journal of Dentistry Research 89 (3) (2010) 219–229, https://doi.org/10.1177/0022034509359125.
[4] A. Joorabloo, T. Liu, Recent advances in reactive oxygen species scavenging nanomaterials for wound healing, Exploration 4 (3) (2024) 20230066. https://doi.org/10.1002/EXP.20230066.
[5] S. Rani, T. Ritter, The exosome - a naturally secreted nanoparticle and its application to wound healing, Adv. Mater. 28 (27) (2016) 5542–5552, https://doi.org/10.1002/adma.201504009.
[6] P.H. Tran, D. Xiang, T.T. Tran, W. Yin, Y. Zhang, L. Kong, K. Chen, M. Sun, Y. Li, Y. Hou, Exosomes and nanoengineering: a match made for precision therapeutics, Adv. Mater. 32 (18) (2020) 1904040, https://doi.org/10.1002/adma.201904040.
[7] L.M. Doyle, M.Z. Wang, Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis, Cells 8 (7) (2019), https://doi.org/10.3390/cells8070727.
[8] M. Yanez-Mo, P.R. Siljander, Z. Andreu, A.B. Zavec, F.E. Borras, E.I. Buzas, K. Buzas, E. Casal, F. Cappello, J. Carvalho, E. Colas, A. Cordeiro-da Silva, S. Fais, J.M. Falcon-Perez, I.M. Ghobrial, B. Giebel, M. Gimona, M. Graner, I. Gursel, M. Gursel, N.H. Heegaard, A. Hendrix, P. Kierulf, K. Kokubun, M. Kosanovic, V. Kralj-Iglic, E.M. Kramer-Albers, S. Laitinen, C. Lasser, T. Lener, E. Ligeti, A. Line, G. Lipps, A. Llorente, J. Lotvall, M. Mancek-Keber, A. Marcilla, M. Mittelbrunn, I. Nazarenko, E.N. Nolte-'t Hoen, T.A. Nyman, L. O'Driscoll, M. Olivan, C. Oliveira, E. Pallinger, H.A. Del Portillo, J. Reventos, M. Rigau, E. Rohde, M. Sammar, F. Sanchez-Madrid, N. Santarem, K. Schallmoser, M. S. Ostenfeld, W. Stoorvogel, R. Stukelj, S.G. Van der Grein, M.H. Vasconcelos, M. H. Wauben, O. De Wever, Biological properties of extracellular vesicles and their physiological functions, J. Extracell. Vesicles 4 (2015) 27066, https://doi.org/10.3402/jev.v4.27066.
[9] Y. Tian, M. Gong, Y. Hu, H. Liu, W. Zhang, M. Zhang, X. Hu, D. Aubert, S. Zhu, L. Wu, X. Yan, Quality and efficiency assessment of six extracellular vesicle isolation methods by nano-flow cytometry, J. Extracell. Vesicles 9 (1) (2020) 1697028, https://doi.org/10.1080/20013078.2019.1697028.
[10] G. Nikoloudaki, K. Creber, D.W. Hamilton, Wound healing and fibrosis: a contrasting role for periostin in skin and the oral mucosa, American Journal of Physiology-Cell Physiology 318 (6) (2020) C1065–C1077, https://doi.org/10.1152/ajpcell.00035.2020.
[11] M. Sun, M. Li, M. Hu, Y. Fan, Y. Liu, J. Sun, J. Zhang, Fully bioactive nanodrugs: stem cell-derived exosomes engineered with biomacromolecules to treat CCl(4)-and extreme hepatectomy-induced acute liver failure, ACS Nano 18 (50) (2024) 33907–33921, https://doi.org/10.1021/acsnano.4c07408.
[12] M.T. Roefs, J.P.G. Sluijter, P. Vader, Extracellular vesicle-associated proteins in tissue repair, Trends Cell Biol. 30 (12) (2020) 990–1013, https://doi.org/10.1016/j.tcb.2020.09.009.
[13] D. Ramadon, M.T.C. McCrudden, A.J. Courtenay, R.F. Donnelly, Enhancement strategies for transdermal drug delivery systems: current trends and applications,

Drug Delivery and Translational Research 12 (4) (2022) 758–791, https://doi.org/10.1007/s13346-021-00909-6.
[14] C. Wang, M. Wang, T. Xu, X. Zhang, C. Lin, W. Gao, H. Xu, B. Lei, C. Mao, Engineering bioactive self-healing antibacterial exosomes hydrogel for promoting chronic diabetic wound healing and complete skin regeneration, Theranostics 9 (1) (2019) 65–76, https://doi.org/10.7150/thno.29766.
[15] M. Li, F. Fang, M. Sun, Y. Zhang, M. Hu, J. Zhang, Extracellular vesicles as bioactive nanotherapeutics: an emerging paradigm for regenerative medicine, Theranostics 12 (11) (2022) 4879, https://doi.org/10.7150/thno.72812.
[16] X. Xu, Y. Liang, X. Li, K. Ouyang, M. Wang, T. Cao, W. Li, J. Liu, J. Xiong, B. Li, J. Xia, D. Wang, L. Duan, Exosome-mediated delivery of kartogenin for chondrogenesis of synovial fluid-derived mesenchymal stem cells and cartilage regeneration, Biomaterials 269 (2021) 120539, https://doi.org/10.1016/j.biomaterials.2020.120539.
[17] X. Chen, M. Zhao, Q. Xie, S. Zhou, X. Zhong, J. Zheng, R. Yang, X. Du, J. Xia, Y. Liao, Click-hydrogel delivered aggregation-induced emissive nanovesicles for simultaneous remodeling and antibiosis of deep burn wounds, Aggregate 5 (1) (2024) e406, https://doi.org/10.1002/agt2.406.
[18] S.C. Jang, O.Y. Kim, C.M. Yoon, D.S. Choi, T.Y. Roh, J. Park, J. Nilsson, J. Lotvall, Y.K. Kim, Y.S. Gho, Bioinspired exosome-mimetic nanovesicles for targeted delivery of chemotherapeutics to malignant tumors, ACS Nano 7 (9) (2013) 7698–7710, https://doi.org/10.1021/nn402232g.
[19] Y. Wen, Q. Fu, A. Soliwoda, S. Zhang, M. Zheng, W. Mao, Y. Wan, Cell-derived nanovesicles prepared by membrane extrusion are good substitutes for natural extracellular vesicles, Extracell Vesicle 1 (2022), https://doi.org/10.1016/j.vesic.2022.100004.
[20] B. Zhang, Y. Bi, K. Wang, X. Guo, Z. Liu, J. Li, M. Wu, Stem cell-derived extracellular vesicles: promising therapeutic opportunities for diabetic wound healing, Int. J. Nanomed. 19 (2024) 4357–4375, https://doi.org/10.2147/IJN.S461342.
[21] H.Y. Kim, H. Kumar, M.J. Jo, J. Kim, J.K. Yoon, J.R. Lee, M. Kang, Y.W. Choo, S. Y. Song, S.P. Kwon, T. Hyeon, I.B. Han, B.S. Kim, Therapeutic efficacy-potentiated and diseased organ-targeting nanovesicles derived from mesenchymal stem cells for spinal cord injury treatment, Nano Lett. 18 (8) (2018) 4965–4975, https://doi.org/10.1021/acs.nanolett.8b01816.
[22] H.Y. Kim, T.J. Kim, L. Kang, Y.-J. Kim, M.K. Kang, J. Kim, J.H. Ryu, T. Hyeon, B.-W. Yoon, S.-B. Ko, Mesenchymal stem cell-derived magnetic extracellular nanovesicles for targeting and treatment of ischemic stroke, Biomaterials 243 (2020) 119942, https://doi.org/10.1016/j.biomaterials.2020.119942.
[23] W. Jo, J. Kim, J. Yoon, D. Jeong, S. Cho, H. Jeong, Y. Yoon, S. Kim, Y. Gho, J. Park, Large-scale generation of cell-derived nanovesicles, Nanoscale 6 (20) (2014) 12056–12064, https://doi.org/10.1039/c4nr02391a.
[24] R. Molinaro, C. Corbo, J.O. Martinez, F. Taraballi, M. Evangelopoulos, S. Minardi, I.K. Yazdi, P. Zhao, E. De Rosa, M.B. Sherman, A. De Vita, N.E. Toledano Furman, X. Wang, A. Parodi, E. Tasciotti, Biomimetic proteolipid vesicles for targeting inflamed tissues, Nat. Mater. 15 (9) (2016) 1037–1046, https://doi.org/10.1038/nmat4644.
[25] A. Grangier, J. Branchu, J. Volatron, M. Piffoux, F. Gazeau, C. Wilhelm, A.K. A. Silva, Technological advances towards extracellular vesicles mass production, Adv. Drug Deliv. Rev. 176 (2021) 113843, https://doi.org/10.1016/j.addr.2021.113843.
[26] Y. Zhu, T. Zhao, M. Liu, S. Wang, S. Liu, Y. Yang, Y. Yang, Y. Nan, Q. Huang, K. Ai, Rheumatoid arthritis microenvironment insights into treatment effect of nanomaterials, Nano Today 42 (2022) 101358, https://doi.org/10.1016/j.nantod.2021.101358.
[27] C. Gao, Q. Huang, C. Liu, C.H.T. Kwong, L. Yue, J.B. Wan, S.M.Y. Lee, R. Wang, Treatment of atherosclerosis by macrophage-biomimetic nanoparticles via targeted pharmacotherapy and sequestration of proinflammatory cytokines, Nat. Commun. 11 (1) (2020) 2622, https://doi.org/10.1038/s41467-020-16439-7.
[28] Y. Zhai, J. Wang, T. Lang, Y. Kong, R. Rong, Y. Cai, W. Ran, F. Xiong, C. Zheng, Y. Wang, Y. Yu, H.H. Zhu, P. Zhang, Y. Li, T lymphocyte membrane-decorated epigenetic nanoinducer of interferons for cancer immunotherapy, Nat. Nanotechnol. 16 (11) (2021) 1271–1280, https://doi.org/10.1038/s41565-021-00972-7.
[29] Y. Qu, B. Chu, X. Wei, Y. Chen, Y. Yang, D. Hu, J. Huang, F. Wang, M. Chen, Y. Zheng, Z. Qian, Cancer-cell-biomimetic nanoparticles for targeted therapy of multiple myeloma based on bone marrow homing, Adv. Mater. 34 (46) (2022) e2107883, https://doi.org/10.1002/adma.202107883.
[30] Y. Bi, W. Duan, J. Chen, T. You, S. Li, W. Jiang, M. Li, G. Wang, X. Pan, J. Wu, Neutrophil decoys with anti-inflammatory and anti-oxidative properties reduce secondary spinal cord injury and improve neurological functional recovery, Adv. Funct. Mater. 31 (34) (2021) 2102912, https://doi.org/10.1002/adfm.202102912.
[31] R. Deng, R. Zhao, Z. Zhang, Y. Chen, M. Yang, Y. Lin, J. Ye, N. Li, H. Qin, X. Yan, J. Shi, F. Yuan, S. Song, Z. Xu, Y. Song, J. Fu, B. Xu, G. Nie, J.K. Yu, Chondrocyte membrane-coated nanoparticles promote drug retention and halt cartilage damage in rat and canine osteoarthritis, Sci. Transl. Med. 16 (735) (2024) eadh9751, https://doi.org/10.1126/scitranslmed.adh9751.
[32] C.-M.J. Hu, R.H. Fang, J. Copp, B.T. Luk, L. Zhang, A biomimetic nanosponge that absorbs pore-forming toxins, Nat. Nanotechnol. 8 (5) (2013) 336–340, https://doi.org/10.1038/nnano.2013.54.
[33] Q. Zhang, D. Dehaini, Y. Zhang, J. Zhou, X. Chen, L. Zhang, R.H. Fang, W. Gao, L. Zhang, Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis, Nat. Nanotechnol. 13 (12) (2018) 1182–1190, https://doi.org/10.1038/s41565-018-0254-4.
[34] J. Xu, Y. Zhang, J. Xu, G. Liu, C. Di, X. Zhao, X. Li, Y. Li, N. Pang, C. Yang, Y. Li, B. Li, Z. Lu, M. Wang, K. Dai, R. Yan, S. Li, G. Nie, Engineered nanoplatelets for targeted delivery of plasminogen activators to reverse thrombus in multiple mouse thrombosis models, Adv. Mater. 32 (4) (2020) e1905145, https://doi.org/10.1002/adma.201905145.
[35] W. Zakrzewski, M. Dobrzynski, M. Szymonowicz, Z. Rybak, Stem cells: past, present, and future, Stem Cell Res. Ther. 10 (1) (2019) 68, https://doi.org/10.1186/s13287-019-1165-5.
[36] L. Bacakova, J. Zarubova, M. Travnickova, J. Musilkova, J. Pajorova, P. Slepicka, N.S. Kasalkova, V. Svorcik, Z. Kolska, H. Motarjemi, M. Molitor, Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells - a review, Biotechnol. Adv. 36 (4) (2018) 1111–1126, https://doi.org/10.1016/j.biotechadv.2018.03.011.
[37] X.Y. Liu, L.P. Yang, L. Zhao, Stem cell therapy for Alzheimer's disease, World J. Stem Cell. 12 (8) (2020) 787–802, https://doi.org/10.4252/wjsc.v12.i8.787.
[38] P.K. Nguyen, J.W. Rhee, J.C. Wu, Adult stem cell therapy and heart failure, 2000 to 2016: a systematic review, JAMA Cardiology 1 (7) (2016) 831–841, https://doi.org/10.1001/jamacardio.2016.2225.
[39] L. Mazini, L. Rochette, B. Admou, S. Amal, G. Malka, Hopes and limits of adipose-derived stem cells (ADSCs) and mesenchymal stem cells (MSCs) in wound healing, Int. J. Mol. Sci. 21 (4) (2020), https://doi.org/10.3390/ijms21041306.
[40] Y. Watanabe, A. Tsuchiya, S. Terai, The development of mesenchymal stem cell therapy in the present, and the perspective of cell-free therapy in the future, Clin. Mol. Hepatol. 27 (1) (2021) 70–80, https://doi.org/10.3350/cmh.2020.0194.
[41] C. Zhou, B. Zhang, Y. Yang, Q. Jiang, T. Li, J. Gong, H. Tang, Q. Zhang, Stem cell-derived exosomes: emerging therapeutic opportunities for wound healing, Stem Cell Res. Ther. 14 (1) (2023) 107, https://doi.org/10.1186/s13287-023-03345-0.
[42] Y. Rong, Z. Wang, P. Tang, J. Wang, C. Ji, J. Chang, Y. Zhu, W. Ye, J. Bai, W. Liu, G. Yin, L. Yu, X. Zhou, W. Cai, Engineered extracellular vesicles for delivery of siRNA promoting targeted repair of traumatic spinal cord injury, Bioact. Mater. 23 (2023) 328–342, https://doi.org/10.1016/j.bioactmat.2022.11.011.
[43] J. Gorecka, V. Kostiuk, A. Fereydooni, L. Gonzalez, J. Luo, B. Dash, T. Isaji, S. Ono, S. Liu, S.R. Lee, J. Xu, J. Liu, R. Taniguchi, B. Yastula, H.C. Hsia, Y. Qyang, A. Dardik, The potential and limitations of induced pluripotent stem cells to achieve wound healing, Stem Cell Res. Ther. 10 (1) (2019) 87, https://doi.org/10.1186/s13287-019-1185-1.
[44] N. Ojeh, I. Pastar, M. Tomic-Canic, O. Stojadinovic, Stem cells in skin regeneration, wound healing, and their clinical applications, Int. J. Mol. Sci. 16 (10) (2015) 25476–25501, https://doi.org/10.3390/ijms161025476.
[45] G.T. Kirby, S.J. Mills, A.J. Cowin, L.E. Smith, Stem cells for cutaneous wound healing, BioMed Res. Int. 2015 (2015) 285869, https://doi.org/10.1155/2015/285869.
[46] K.A. Gallagher, Z.J. Liu, M. Xiao, H. Chen, L.J. Goldstein, D.G. Buerk, A. Nedeau, S.R. Thom, O.C. Velazquez, Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha, J. Clin. Investig. 117 (5) (2007) 1249–1259, https://doi.org/10.1172/JCI29710.
[47] W. Zhang, L. Wang, H. Guo, L. Chen, X. Huang, Dapagliflozin-loaded exosome mimetics facilitate diabetic wound healing by HIF-1alpha-Mediated enhancement of angiogenesis, Adv. Healthcare Mater. 12 (7) (2023) e2202751, https://doi.org/10.1002/adhm.202202751.
[48] Y. Cui, Z. Li, Y. Guo, X. Qi, Y. Yang, X. Jia, R. Li, J. Shi, W. Gao, Z. Ren, G. Liu, Q. Ye, Z. Zhang, D. Fu, Bioinspired nanovesicles convert the skeletal endothelium-associated secretory phenotype to treat osteoporosis, ACS Nano 16 (7) (2022) 11076–11091, https://doi.org/10.1021/acsnano.2c03781.
[49] M. Tomic-Canic, L.A. DiPietro, Cellular senescence in diabetic wounds: when too many retirees stress the system, J. Invest. Dermatol. 139 (5) (2019) 997–999, https://doi.org/10.1016/j.jid.2019.02.019.
[50] Y. Zhuang, S. Jiang, X. Deng, A. Lao, X. Hua, Y. Xie, L. Jiang, X. Wang, K. Lin, Energy metabolism as therapeutic target for aged wound repair by engineered extracellular vesicle, Sci. Adv. 10 (15) (2024) eadl0372, https://doi.org/10.1126/sciadv.adl0372.
[51] H. Lee, H. Cha, J.H. Park, Derivation of cell-engineered nanovesicles from human induced pluripotent stem cells and their protective effect on the senescence of dermal fibroblasts, Int. J. Mol. Sci. 21 (1) (2020), https://doi.org/10.3390/ijms21010343.
[52] M. Zou, E.Y. Baitei, R.A. Al-Rijjal, R.S. Parhar, F. Al-Mohanna, S. Kimura, C. Pritchard, H.A. BinEssa, A.S. Alzahrani, H.H. Al-Khalaf, A. Hawwari, M. Akhtar, A.M. Assiri, B.F. Meyer, Y. Shi, TSH overcomes BrafV600E-induced senescence to promote tumor progression via downregulation of p53 expression in papillary thyroid cancer, Oncogene 35 (2016) 1909–1918, https://doi.org/10.1038/onc.2015.253.
[53] R. Jaenisch, R. Young, Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming, Cell 132 (4) (2008) 567–582, https://doi.org/10.1016/j.cell.2008.01.015.
[54] M. Farnebo, V.J.N. Bykov, K.G. Wiman, The p53 tumor suppressor: a master regulator of diverse cellular processes and therapeutic target in cancer, Biochemical and biophysical research communications 396 1 (2010) 85–89, https://doi.org/10.1016/j.bbrc.2010.02.152.
[55] G. Päth, N. Perakakis, C.S. Mantzoros, J. Seufert, Stem cells in the treatment of diabetes mellitus—focus on mesenchymal stem cells, Metabolism 90 (2019) 1–15, https://doi.org/10.1016/j.metabol.2018.10.005.
[56] H.D. Zomer, A.G. Trentin, Skin wound healing in humans and mice: challenges in translational research, J. Dermatol. Sci. 90 (1) (2018) 3–12, https://doi.org/10.1016/j.jdermsci.2017.12.009.

[57] H. Jo, S. Brito, B.M. Kwak, S. Park, M.G. Lee, B.H. Bin, Applications of mesenchymal stem cells in skin regeneration and rejuvenation, Int. J. Mol. Sci. 22 (5) (2021), https://doi.org/10.3390/ijms22052410.

[58] A. Golchin, T.Z. Farahany, A. Khojasteh, F. Soleimanifar, A. Ardeshirylajimi, The clinical trials of mesenchymal stem cell therapy in skin diseases: an update and concise review, Curr. Stem Cell Res. Ther. 14 (1) (2019) 22–33, https://doi.org/10.2174/1574888X13666180913123424.

[59] D. Bian, Y. Wu, G. Song, R. Azizi, A. Zamani, The application of mesenchymal stromal cells (MSCs) and their derivative exosome in skin wound healing: a comprehensive review, Stem Cell Res. Ther. 13 (1) (2022) 24, https://doi.org/10.1186/s13287-021-02697-9.

[60] C. Han, D. Jeong, B. Kim, W. Jo, H. Kang, S. Cho, K.H. Kim, J. Park, Mesenchymal stem cell engineered nanovesicles for accelerated skin wound closure, ACS Biomater. Sci. Eng. 5 (3) (2019) 1534–1543, https://doi.org/10.1021/acsbiomaterials.8b01646.

[61] J. Huang, J. Zhang, J. Xiong, S. Sun, J. Xia, L. Yang, Y. Liang, Stem cell-derived nanovesicles: a novel cell-free therapy for wound healing, Stem Cell. Int. 2021 (2021) 1285087, https://doi.org/10.1155/2021/1285087.

[62] Y.R. Neupane, H.K. Handral, S.A. Alkaff, W.H. Chng, G. Venkatesan, C. Huang, C. K. Lee, J.W. Wang, G. Sriram, R.A. Dienzo, W.F. Lu, Y. Ali, B. Czarny, G. Pastorin, Cell-derived nanovesicles from mesenchymal stem cells as extracellular vesicle-mimetics in wound healing, Acta Pharm. Sin. B 13 (5) (2023) 1887–1902, https://doi.org/10.1016/j.apsb.2022.10.022.

[63] M. Samberg, R. Stone 2nd, S. Natesan, A. Kowalczewski, S. Becerra, N. Wrice, A. Cap, R. Christy, Platelet rich plasma hydrogels promote in vitro and in vivo angiogenic potential of adipose-derived stem cells, Acta Biomater. 87 (2019) 76–87, https://doi.org/10.1016/j.actbio.2019.01.039.

[64] R. Dai, Z. Wang, R. Samanipour, K.I. Koo, K. Kim, Adipose-derived stem cells for tissue engineering and regenerative medicine applications, Stem Cell. Int. 2016 (2016) 6737345, https://doi.org/10.1155/2016/6737345.

[65] Q. Yu, H. Sun, L. Zhang, L. Jiang, L. Liang, C. Yu, X. Dong, B. Guo, Y. Qiu, J. Li, H. Zhang, F. Yao, D. Zhu, J. Li, A zwitterionic hydrogel with anti-oxidative and anti-inflammatory properties for the prevention of peritoneal adhesion by inhibiting mesothelial-mesenchymal transition, Adv. Healthcare Mater. 12 (30) (2023) e2301696, https://doi.org/10.1002/adhm.202301696.

[66] J.A. Ankrum, J.F. Ong, J.M. Karp, Mesenchymal stem cells: immune evasive, not immune privileged, Nat. Biotechnol. 32 (3) (2014) 252–260, https://doi.org/10.1038/nbt.2816.

[67] Y. Zhu, T. Liu, K. Song, X. Fan, X. Ma, Z. Cui, Adipose-derived stem cell: a better stem cell than BMSC, Cell Biochem. Funct. 26 (6) (2008) 664–675, https://doi.org/10.1002/cbf.1488.

[68] S. Li, J. Sun, J. Yang, Y. Yang, H. Ding, B. Yu, K. Ma, M. Chen, Gelatin methacryloyl (GelMA) loaded with concentrated hypoxic pretreated adipose-derived mesenchymal stem cells(ADSCs) conditioned medium promotes wound healing and vascular regeneration in aged skin, Biomater. Res. 27 (1) (2023) 11, https://doi.org/10.1186/s40824-023-00352-3.

[69] M. Zhao, M. Kang, J. Wang, R. Yang, X. Zhong, Q. Xie, S. Zhou, Z. Zhang, J. Zheng, Y. Zhang, S. Guo, W. Lin, J. Huang, G. Guo, Y. Fu, B. Li, Z. Fan, X. Li, D. Wang, X. Chen, B.Z. Tang, Y. Liao, Stem cell-derived nanovesicles embedded in dual-layered hydrogel for programmed ROS regulation and comprehensive tissue regeneration in burn wound healing, Adv. Mater. 36 (32) (2024) e2401369, https://doi.org/10.1002/adma.202401369.

[70] V. Brumberg, T. Astrelina, T. Malivanova, A. Samoilov, Modern wound dressings: hydrogel dressings, Biomedicines 9 (9) (2021), https://doi.org/10.3390/biomedicines9091235.

[71] Y. Song, Y. You, X. Xu, J. Lu, X. Huang, J. Zhang, L. Zhu, J. Hu, X. Wu, X. Xu, Adipose-derived mesenchymal stem cell-derived exosomes biopotentiated extracellular matrix hydrogels accelerate diabetic wound healing and skin regeneration, Adv. Sci. 10 (30) (2023) 2304023, https://doi.org/10.1002/advs.202304023.

[72] X. Chen, M. Zhao, Q. Xie, S. Zhou, X. Zhong, J. Zheng, R. Yang, X. Du, J. Xia, Y. Liao, Click-hydrogel delivered aggregation-induced emissive nanovesicles for simultaneous remodeling and antibiosis of deep burn wounds, Aggregate 5 (1) (2024), https://doi.org/10.1002/agt2.406.

[73] X. He, D. Wang, Y. Yi, Y. Tan, M. Wu, H. Wang, W. Hu, H. Chen, Q. Zhang, Y. Wu, delta-Tocotrienol preconditioning improves the capability of bone marrow-derived mesenchymal stem cells in promoting wound healing by inhibiting BACH1-related ferroptosis, Cell Death Discovery 9 (1) (2023) 349, https://doi.org/10.1038/s41420-023-01653-1.

[74] L. Li, X. Chen, W.E. Wang, C. Zeng, How to improve the survival of transplanted mesenchymal stem cell in ischemic heart? Stem Cell. Int. 2016 (2016) 9682757 https://doi.org/10.1155/2016/9682757.

[75] R. Guillamat-Prats, The role of MSC in wound healing, scarring and regeneration, Cells 10 (7) (2021), https://doi.org/10.3390/cells10071729.

[76] Y. Shi, S. Wang, W. Zhang, Y. Zhu, Z. Fan, Y. Huang, F. Li, R. Yang, Bone marrow mesenchymal stem cells facilitate diabetic wound healing through the restoration of epidermal cell autophagy via the HIF-1α/TGF-β1/SMAD pathway, Stem Cell Res. Ther. 13 (1) (2022), https://doi.org/10.1186/s13287-022-02996-9.

[77] Y. Wu, M. Su, S. Zhang, L. Xiao, Y. Xiao, M. Zhang, Y. Bei, M. Li, F. Zhang, Q. Yuan, A mesenchymal stem cell-derived nanovesicle-biopotentiated bovine serum albumin-bridged gelatin hydrogel for enhanced diabetic wound therapy, Mater. Des. 230 (2023) 111960, https://doi.org/10.1016/j.matdes.2023.111960.

[78] W. Yang, J. Zhang, B. Xu, Y. He, W. Liu, J. Li, S. Zhang, X. Lin, D. Su, T. Wu, J. Li, HucMSC-derived exosomes mitigate the age-related retardation of fertility in female mice, Mol. Ther. 28 (4) (2020) 1200–1213, https://doi.org/10.1016/j.ymthe.2020.02.003.

[79] Q. Xie, R. Liu, J. Jiang, J. Peng, C. Yang, W. Zhang, S. Wang, J. Song, What is the impact of human umbilical cord mesenchymal stem cell transplantation on clinical treatment? Stem Cell Res. Ther. 11 (1) (2020) 519, https://doi.org/10.1186/s13287-020-02011-z.

[80] Y.Y. Ma, X. Zhao, J.Y. Chen, X.Y. Chen, W.J. Fan, Y. Sun, Z.W. Lin, L.Q. Fu, H. Zou, X.Z. Mou, Umbilical cord mesenchymal-stem-cell-derived nanovesicles as a novel strategy to promote wound healing in diabetes, Nano Select 4 (2) (2023) 170–180, https://doi.org/10.1002/nano.202200211.

[81] I. Cornil, D. Theodorescu, S. Man, M. Herlyn, J. Jambrosic, R. Kerbel, Fibroblast cell interactions with human melanoma cells affect tumor cell growth as a function of tumor progression, Proceedings of the National Academy of Sciences of the United States of America 88 (14) (1991) 6028–6032, https://doi.org/10.1073/pnas.88.14.6028.

[82] W. Jo, D. Jeong, J. Kim, S. Cho, S.C. Jang, C. Han, J.Y. Kang, Y.S. Gho, J. Park, Microfluidic fabrication of cell-derived nanovesicles as endogenous RNA carriers, Lab Chip 14 (7) (2014) 1261–1269, https://doi.org/10.1039/c3lc50993a.

[83] D. Jeong, W. Jo, J. Yoon, J. Kim, S. Gianchandani, Y.S. Gho, J. Park, Nanovesicles engineered from ES cells for enhanced cell proliferation, Biomaterials 35 (34) (2014) 9302–9310, https://doi.org/10.1016/j.biomaterials.2014.07.047.

[84] X. Yang, C. Zhang, D. Deng, Y. Gu, H. Wang, Q. Zhong, Multiple stimuli-responsive MXene-based hydrogel as intelligent drug delivery carriers for deep chronic wound healing, Small 18 (5) (2022) 2104368, https://doi.org/10.1002/smll.202104368.

[85] W. Weng, J. Chi, X. Wang, K. Shi, F. Ye, Y. Zhao, Ellipsoidal porous patch with anisotropic cell inducing ability for inhibiting skin scar formation, Engineered Regeneration 3 (3) (2022) 262–269, https://doi.org/10.1016/j.engreg.2022.06.003.

[86] H. Zhang, D. Xu, Y. Zhang, M. Li, R. Chai, Silk fibroin hydrogels for biomedical applications, Smart Medicine 1 (1) (2022) e20220011, https://doi.org/10.1002/SMMD.20220011.

[87] C. Hu, R. Luo, Y. Wang, Heart valves cross-linked with erythrocyte membrane drug-loaded nanoparticles as a biomimetic strategy for anti-coagulation, anti-inflammation, anti-calcification, and endothelialization, ACS Appl. Mater. Interfaces 12 (37) (2020) 41113–41126, https://doi.org/10.1021/acsami.0c12688.

[88] X. Zheng, J. Yan, W. You, F. Li, J. Diao, W. He, Y. Yao, De novo Nano-erythrocyte structurally braced by biomimetic Au (I)-peptide skeleton for MDM2/MDMX predation toward augmented pulmonary adenocarcinoma immunotherapy, Small 17 (20) (2021) 2100394, https://doi.org/10.1002/smll.202100394.

[89] M. Fang, H. Zhang, Y. Wang, H. Zhang, D. Zhang, P. Xu, Biomimetic selenium nanosystems for infectious wound healing, Engineered Regeneration 4 (2) (2023) 152–160, https://doi.org/10.1016/j.engreg.2023.01.004.

[90] J.W. Xu, K. Yao, Z.K. Xu, Nanomaterials with a photothermal effect for antibacterial activities: an overview, Nanoscale 11 (18) (2019) 8680–8691, https://doi.org/10.1039/c9nr01833f.

[91] L. Rizzello, P.P. Pompa, Nanosilver-based antibacterial drugs and devices: mechanisms, methodological drawbacks, and guidelines, Chem. Soc. Rev. 43 (5) (2014) 1501–1518, https://doi.org/10.1039/c3cs60218d.

[92] X. Zhang, L.-Y. Xia, X. Chen, Z. Chen, F.-G. Wu, Hydrogel-based phototherapy for fighting cancer and bacterial infection, Sci. China Mater. 60 (6) (2017) 487–503, https://doi.org/10.1007/s40843-017-9025-3.

[93] B. Chen, F. Li, X.K. Zhu, W. Xie, X. Hu, M.H. Zan, X. Li, Q.Y. Li, S.S. Guo, X. Z. Zhao, Y.A. Jiang, Z. Cao, W. Liu, Highly biocompatible and recyclable biomimetic nanoparticles for antibiotic-resistant bacteria infection, Biomater. Sci. 9 (3) (2021) 826–834, https://doi.org/10.1039/d0bm01397h.

[94] S. Hu, X. Wang, Z. Li, D. Zhu, J. Cores, Z. Wang, J. Li, X. Mei, X. Cheng, T. Su, K. Cheng, Platelet membrane and stem cell exosome hybrid enhances cellular uptake and targeting to heart injury, Nano Today 39 (2021), https://doi.org/10.1016/j.nantod.2021.101210.

[95] M. Liu, H. Lutz, D. Zhu, K. Huang, Z. Li, P.C. Dinh, J. Gao, Y. Zhang, K. Cheng, Bispecific antibody inhalation therapy for redirecting stem cells from the lungs to repair heart injury, Adv. Sci. 8 (1) (2020) 2002127, https://doi.org/10.1002/advs.202002127.

[96] C.M. Hu, R.H. Fang, K.C. Wang, B.T. Luk, S. Thamphiwatana, D. Dehaini, P. Nguyen, P. Angsantikul, C.H. Wen, A.V. Kroll, C. Carpenter, M. Ramesh, V. Qu, S.H. Patel, J. Zhu, W. Shi, F.M. Hofman, T.C. Chen, W. Gao, K. Zhang, S. Chien, L. Zhang, Nanoparticle biointerfacing by platelet membrane cloaking, Nature 526 (7571) (2015) 118–121, https://doi.org/10.1038/nature15373.

[97] U. Ozcelik, Y. Ekici, H.Y. Bircan, C. Aydogan, S. Turkoglu, O. Ozen, G. Moray, M. Haberal, Effect of topical platelet-rich plasma on burn healing after partial-thickness burn injury, Med. Sci. Monit. 22 (2016), https://doi.org/10.12659/msm.895395, 1903.

[98] P. Borzini, I. Mazzucco, Platelet-rich plasma (PRP) and platelet derivatives for topical therapy. What is true from the biologic view point? ISBT Sci. Ser. 2 (1) (2007) 272–281, https://doi.org/10.1111/j.1751-2824.2007.00085.x.

[99] N. Pallua, T. Wolter, M. Markowicz, Platelet-rich plasma in burns, Burns 36 (1) (2010) 4–8, https://doi.org/10.1016/j.burns.2009.05.002.

[100] M. Xuan, J. Shao, J. Li, Cell membrane-covered nanoparticles as biomaterials, Natl. Sci. Rev. 6 (3) (2019) 551–561, https://doi.org/10.1093/nsr/nwz037.

[101] Y. Shang, Q. Wang, J. Li, Q. Zhao, X. Huang, H. Dong, H. Liu, R. Gui, X. Nie, Platelet-membrane-camouflaged zirconia nanoparticles inhibit the invasion and metastasis of hela cells, Front. Chem. 8 (2020) 377, https://doi.org/10.3389/fchem.2020.00377.

[102] B. Wang, J. Chen, C. Zhang, Q. Zhang, Z. Zhu, L. Qiu, J. Yan, Z. Li, X. Zhu, Y. Zhang, Y. Jiang, Biomimetic nanoparticles of platelet membranes carrying bFGF and VEGFA genes promote deep burn wound healing, Int.

Immunopharmacol. 125 (Pt A) (2023) 111164, https://doi.org/10.1016/j.intimp.2023.111164.
[103] H. Dong, J. Li, X. Huang, H. Liu, R. Gui, Platelet-membrane camouflaged cerium nanoparticle-embedded gelatin methacryloyl hydrogel for accelerated diabetic wound healing, Int. J. Biol. Macromol. 251 (2023) 126393, https://doi.org/10.1016/j.ijbiomac.2023.126393.
[104] S.N. Naidi, M.H. Harunsani, A.L. Tan, M.M. Khan, Green-synthesized CeO(2) nanoparticles for photocatalytic, antimicrobial, antioxidant and cytotoxicity activities, J. Mater. Chem. B 9 (28) (2021) 5599–5620, https://doi.org/10.1039/d1tb00248a.
[105] M. Nadeem, R. Khan, K. Afridi, A. Nadhman, S. Ullah, S. Faisal, Z.U. Mabood, C. Hano, B.H. Abbasi, Green synthesis of cerium oxide nanoparticles (CeO(2) NPs) and their antimicrobial applications: a review, Int. J. Nanomed. 15 (2020) 5951–5961, https://doi.org/10.2147/IJN.S255784.
[106] Y. Wang, C. Li, Y. Wan, M. Qi, Q. Chen, Y. Sun, X. Sun, J. Fang, L. Fu, L. Xu, B. Dong, L. Wang, Quercetin-loaded ceria nanocomposite potentiate dual-directional immunoregulation via macrophage polarization against periodontal inflammation, Small 17 (41) (2021) e2101505, https://doi.org/10.1002/smll.202101505.
[107] L. Zhou, S. Tang, F. Li, Y. Wu, S. Li, L. Cui, J. Luo, L. Yang, Z. Ren, J. Zhang, D. Zhou, J. Jiang, X. Yang, X. Zhou, Y. Wu, Ceria nanoparticles prophylactic used for renal ischemia-reperfusion injury treatment by attenuating oxidative stress and inflammatory response, Biomaterials 287 (2022) 121686, https://doi.org/10.1016/j.biomaterials.2022.121686.
[108] F.P.R. Santana, R.C. da Silva, V. Ponci, A. Pinheiro, C.R. Olivo, L.C. Caperuto, F. M. Arantes-Costa, S.R. Claudio, D.A. Ribeiro, I. Tiberio, L.G. Lima-Neto, J.H. G. Lago, C.M. Prado, Dehydrodieugenol improved lung inflammation in an asthma model by inhibiting the STAT3/SOCS3 and MAPK pathways, Biochem. Pharmacol. 180 (2020) 114175, https://doi.org/10.1016/j.bcp.2020.114175.
[109] Y. Xiong, Y. Xu, F. Zhou, Y. Hu, J. Zhao, Z. Liu, Q. Zhai, S. Qi, Z. Zhang, L. Chen, Bio-functional hydrogel with antibacterial and anti-inflammatory dual properties to combat with burn wound infection, Bioengineering & Translational Medicine 8 (1) (2023) e10373, https://doi.org/10.1002/btm2.10373.
[110] K.S. Smigiel, W.C. Parks, Macrophages, wound healing, and fibrosis: recent insights, Curr. Rheumatol. Rep. 20 (4) (2018) 17, https://doi.org/10.1007/s11926-018-0725-5.
[111] X. Bai, J. Li, L. Li, M. Liu, Y. Liu, M. Cao, K. Tao, S. Xie, D. Hu, Extracellular vesicles from adipose tissue-derived stem cells affect notch-miR148a-3p Axis to regulate polarization of macrophages and alleviate sepsis in mice, Front. Immunol. 11 (2020) 1391, https://doi.org/10.3389/fimmu.2020.01391.
[112] H. Wang, Y. Zhang, Y. Zhang, C. Li, M. Zhang, J. Wang, Y. Zhang, Y. Du, W. Cui, W. Chen, Activating macrophage continual efferocytosis via microenvironment biomimetic short fibers for reversing inflammation in bone repair, Adv. Mater. 36 (30) (2024) e2402968, https://doi.org/10.1002/adma.202402968.
[113] W. Wu, H. Guo, D. Jing, Z. Zhang, Z. Zhang, F. Pu, W. Yang, X. Jin, X. Huang, Z. Shao, Targeted delivery of PD-L1-derived phosphorylation-mimicking peptides by engineered biomimetic nanovesicles to enhance osteosarcoma treatment, Adv. Healthcare Mater. 11 (23) (2022) e2200955, https://doi.org/10.1002/adhm.202200955.
[114] C. Zhao, W. Song, J. Ma, N. Wang, Macrophage-derived hybrid exosome-mimic nanovesicles loaded with black phosphorus for multimodal rheumatoid arthritis therapy, Biomater. Sci. 10 (23) (2022) 6731–6739, https://doi.org/10.1039/d2bm01274j.
[115] J. Lopes, D. Lopes, M. Pereira-Silva, D. Peixoto, F. Veiga, M.R. Hamblin, J. Conde, C. Corbo, E.N. Zare, M. Ashrafizadeh, F.R. Tay, C. Chen, R.F. Donnelly, X. Wang, P. Makvandi, A.C. Paiva-Santos, Macrophage cell membrane-cloaked nanoplatforms for biomedical applications, Small Methods 6 (8) (2022) e2200289, https://doi.org/10.1002/smtd.202200289.
[116] T. Zhang, Z. Tai, F. Miao, Y. Zhao, W. Wang, Q. Zhu, Z. Chen, Bioinspired nanovesicles derived from macrophage accelerate wound healing by promoting angiogenesis and collagen deposition, J. Mater. Chem. B 12 (47) (2024) 12338–12348, https://doi.org/10.1039/d3tb02158k.
[117] W.R. Francis, Z. Liu, S.E. Owens, X. Wang, H. Xue, A. Lord, V. Kanamarlapudi, Z. Xia, Role of hypoxia inducible factor 1alpha in cobalt nanoparticle induced cytotoxicity of human THP-1 macrophages, Biomaterials Translational 2 (2) (2021) 143–150, https://doi.org/10.12336/biomatertransl.2021.02.004.
[118] R. Zeng, B. Lv, Z. Lin, X. Chu, Y. Xiong, S. Knoedler, F. Cao, C. Lin, L. Chen, C. Yu, J. Liao, W. Zhou, G. Dai, M.A. Shahbazi, B. Mi, G. Liu, Neddylation suppression by a macrophage membrane-coated nanoparticle promotes dual immunomodulatory repair of diabetic wounds, Bioact. Mater. 34 (2024) 366–380, https://doi.org/10.1016/j.bioactmat.2023.12.025.
[119] C. Schwechheimer, NEDD8-its role in the regulation of Cullin-RING ligases, Curr. Opin. Plant Biol. 45 (Pt A) (2018) 112–119, https://doi.org/10.1016/j.pbi.2018.05.017.
[120] X. Xue, H. Liu, S. Wang, Y. Hu, B. Huang, M. Li, J. Gao, X. Wang, J. Su, Neutrophil-erythrocyte hybrid membrane-coated hollow copper sulfide nanoparticles for targeted and photothermal/anti-inflammatory therapy of osteoarthritis, Compos. B Eng. 237 (2022) 109855, https://doi.org/10.1016/j.compositesb.2022.109855.
[121] L.J. O'Neil, M.J. Kaplan, Neutrophils in rheumatoid arthritis: breaking immune tolerance and fueling disease, Trends Mol. Med. 25 (3) (2019) 215–227, https://doi.org/10.1016/j.molmed.2018.12.008.
[122] H.L. Wright, R.J. Moots, S.W. Edwards, The multifactorial role of neutrophils in rheumatoid arthritis, Nat. Rev. Rheumatol. 10 (10) (2014) 593–601, https://doi.org/10.1038/nrrheum.2014.80.
[123] Y. Shao, Z. Guo, Y. Yang, L. Liu, J. Huang, Y. Chen, L. Li, B. Sun, Neutrophil extracellular traps contribute to myofibroblast differentiation and scar hyperplasia through the Toll-like receptor 9/nuclear factor Kappa-B/interleukin-6 pathway, Burns & Trauma 10 (2022), https://doi.org/10.1093/burnst/tkac044 tkac044.
[124] P.X. Liew, P. Kubes, The neutrophil's role during health and disease, Physiol. Rev. 99 (2) (2019) 1223–1248, https://doi.org/10.1152/physrev.00012.2018.
[125] J. Wu, T. Ma, M. Zhu, T. Huang, B. Zhang, J. Gao, N. Lin, Nanotechnology reinforced neutrophil-based therapeutic strategies for inflammatory diseases therapy, Nano Today 46 (2022) 101577, https://doi.org/10.1016/j.nantod.2022.101577.
[126] H. Jin, X. Wen, R. Sun, Y. Yu, Z. Guo, Y. Yang, L. Li, B. Sun, Engineered nanovesicles from activated neutrophils with enriched bactericidal proteins have molecular debridement ability and promote infectious wound healing, Burns & Trauma 12 (2024) tkae018, https://doi.org/10.1093/burnst/tkae018.
[127] S.A. Ragland, A.K. Criss, From bacterial killing to immune modulation: recent insights into the functions of lysozyme, PLoS Pathog. 13 (9) (2017) e1006512, https://doi.org/10.1371/journal.ppat.1006512.
[128] J. Fan, C.S. Lee, S. Kim, C. Chen, T. Aghaloo, M. Lee, Generation of small RNA-modulated exosome mimetics for bone regeneration, ACS Nano 14 (9) (2020) 11973–11984, https://doi.org/10.1021/acsnano.0c05122.
[129] Y. Yu, H. Jin, L. Li, X. Zhang, C. Zheng, X. Gao, Y. Yang, B. Sun, An injectable, activated neutrophil-derived exosome mimetics/extracellular matrix hybrid hydrogel with antibacterial activity and wound healing promotion effect for diabetic wound therapy, J. Nanobiotechnol. 21 (1) (2023) 308, https://doi.org/10.1186/s12951-023-02073-0.
[130] Q. Long, P. Zheng, X. Zheng, W. Li, L. Hua, Z. Yang, W. Huang, Y. Ma, Engineered bacterial membrane vesicles are promising carriers for vaccine design and tumor immunotherapy, Adv. Drug Deliv. Rev. 186 (2022) 114321, https://doi.org/10.1016/j.addr.2022.114321.
[131] H. Lu, G. Zhang, Z. Zheng, F. Meng, T. Du, S. He, Bio-conversion of photosynthetic bacteria from non-toxic wastewater to realize wastewater treatment and bioresource recovery: a review, Bioresour. Technol. 278 (2019) 383–399, https://doi.org/10.1016/j.biortech.2019.01.070.
[132] O.Y. Kim, N.T. Dinh, H.T. Park, S.J. Choi, K. Hong, Y.S. Gho, Bacterial protoplast-derived nanovesicles for tumor targeted delivery of chemotherapeutics, Biomaterials 113 (2017) 68–79, https://doi.org/10.1016/j.biomaterials.2016.10.037.
[133] T. Xiao, Y. Ma, Z. Zhang, Y. Zhang, Y. Zhao, X. Zhou, X. Wang, K. Ge, J. Guo, J. Zhang, Z. Li, H. Liu, Tailoring therapeutics via a systematic beneficial elements comparison between photosynthetic bacteria-derived OMVs and extruded nanovesicles, Bioact. Mater. 36 (2024) 48–61, https://doi.org/10.1016/j.bioactmat.2024.02.025.
[134] P. Liu, W. Zhu, C. Chen, B. Yan, L. Zhu, X. Chen, C. Peng, The mechanisms of lysophosphatidylcholine in the development of diseases, Life Sci. 247 (2020) 117443, https://doi.org/10.1016/j.lfs.2020.117443.
[135] J. Bi, T.A. Ichu, C. Zanca, H. Yang, W. Zhang, Y. Gu, S. Chowdhry, A. Reed, S. Ikegami, K.M. Turner, W. Zhang, G.R. Villa, S. Wu, O. Quehenberger, W. H. Yong, H.I. Kornblum, J.N. Rich, T.F. Cloughesy, W.K. Cavenee, F.B. Furnari, B. F. Cravatt, P.S. Mischel, Oncogene amplification in growth factor signaling pathways renders cancers dependent on membrane lipid remodeling, Cell Metab. 30 (3) (2019) 525–538, https://doi.org/10.1016/j.cmet.2019.06.014, e8.
[136] Y. Morita, T. Sakaguchi, K. Ikegami, N. Goto-Inoue, T. Hayasaka, V.T. Hang, H. Tanaka, T. Harada, Y. Shibasaki, A. Suzuki, K. Fukumoto, K. Inaba, M. Murakami, M. Setou, H. Konno, Lysophosphatidylcholine acyltransferase 1 altered phospholipid composition and regulated hepatoma progression, J. Hepatol. 59 (2) (2013) 292–299, https://doi.org/10.1016/j.jhep.2013.02.030.
[137] J. Sun, H. Zhao, C. Shen, S. Li, W. Zhang, J. Ma, Z. Li, M. Zhang, J. Yang, Tideglusib promotes wound healing in aged skin by activating PI3K/Akt pathway, Stem Cell Res. Ther. 13 (1) (2022) 269, https://doi.org/10.1186/s13287-022-02949-2.
[138] L. Rao, B. Cai, L.L. Bu, Q.Q. Liao, S.S. Guo, X.Z. Zhao, W.F. Dong, W. Liu, Microfluidic electroporation-facilitated synthesis of erythrocyte membrane-coated magnetic nanoparticles for enhanced imaging-guided cancer therapy, ACS Nano 11 (4) (2017) 3496–3505, https://doi.org/10.1021/acsnano.7b00133.
[139] C. Ducrot, S. Loiseau, C. Wong, E. Madec, J. Volatron, M. Piffoux, Hybrid extracellular vesicles for drug delivery, Cancer Lett. 558 (2023) 216107, https://doi.org/10.1016/j.canlet.2023.216107.
[140] M. Sun, J. Yang, Y. Fan, Y. Zhang, J. Sun, M. Hu, K. Sun, J. Zhang, Beyond extracellular vesicles: hybrid membrane nanovesicles as emerging advanced tools for biomedical applications, Adv. Sci. 10 (32) (2023) e2303617, https://doi.org/10.1002/advs.202303617.
[141] L. Wang, W. Su, W. Du, Y. Xu, L. Wang, D. Kong, Z. Han, G. Zheng, Z. Li, Gene and MicroRNA profiling of human induced pluripotent stem cell-derived endothelial cells, Stem Cell Rev. 11 (2) (2015) 219–227, https://doi.org/10.1007/s12015-014-9582-4.
[142] W. Zhang, X. Yang, X. Huang, L. Chen, Bioinspired nanovesicles released from injectable hydrogels facilitate diabetic wound healing by regulating macrophage polarization and endothelial cell dysfunction, J. Nanobiotechnol. 21 (1) (2023) 358, https://doi.org/10.1186/s12951-023-02119-3.
[143] N. Filipczak, J. Pan, S.S.K. Yalamarty, V.P. Torchilin, Recent advancements in liposome technology, Adv. Drug Deliv. Rev. 156 (2020) 4–22, https://doi.org/10.1016/j.addr.2020.06.022.
[144] S. Hong, V.P. Dia, Q. Zhong, Synergistic anti-inflammatory activity of apigenin and curcumin co-encapsulated in caseins assessed with lipopolysaccharide-

stimulated RAW 264.7 macrophages, Int. J. Biol. Macromol. 193 (Pt A) (2021) 702–712, https://doi.org/10.1016/j.ijbiomac.2021.10.153.
[145] P. Anand, A.B. Kunnumakkara, R.A. Newman, B.B. Aggarwal, Bioavailability of curcumin: problems and promises, Mol. Pharm. 4 (6) (2007) 807–818, https://doi.org/10.1021/mp700113r.
[146] J. Ren, M. Yang, J. Chen, S. Ma, N. Wang, Anti-inflammatory and wound healing potential of kirenol in diabetic rats through the suppression of inflammatory markers and matrix metalloproteinase expressions, Biomed. Pharmacother. 129 (2020) 110475, https://doi.org/10.1016/j.biopha.2020.110475.
[147] Q. Tang, M. Dong, Z. Xu, N. Xue, R. Jiang, X. Wei, J. Gu, Y. Li, R. Xin, J. Wang, X. Xiao, X. Zhou, S. Yin, Y. Wang, J. Chen, Red blood cell-mimicking liposomes loading curcumin promote diabetic wound healing, J. Contr. Release 361 (2023) 871–884, https://doi.org/10.1016/j.jconrel.2023.07.049.
[148] J. Che, X. Wu, Y. Shi, C. Song, Y. Zhao, L. Sun, Bioinspired hierarchical delivery system with macrophage-like nanovesicles encapsulation for diabetic wound healing, Chem. Eng. J. 456 (2023) 141111, https://doi.org/10.1016/j.cej.2022.141111.
[149] G. Jiang, J. Guo, C. Yan, Y. He, J. Chen, M. Zhang, K. Xiang, X. Xiang, C. Zhang, Y. Wang, S. Liu, P. Nie, T. Jiang, Y. Kang, C. Wang, X. Xu, X. Yang, Z. Chen, Biomimetic hybrid nanovesicles improve infected diabetic wound via enhanced targeted delivery, J. Contr. Release 365 (2024) 193–207, https://doi.org/10.1016/j.jconrel.2023.11.019.
[150] C. Cheng, Z. Wu, D.J. McClements, L. Zou, S. Peng, W. Zhou, W. Liu, Improvement on stability, loading capacity and sustained release of rhamnolipids modified curcumin liposomes, Colloids Surf. B Biointerfaces 183 (2019) 110460, https://doi.org/10.1016/j.colsurfb.2019.110460.
[151] L.C. Radlinski, S.E. Rowe, R. Brzozowski, A.D. Wilkinson, R. Huang, P. Eswara, B. P. Conlon, Chemical induction of aminoglycoside uptake overcomes antibiotic tolerance and resistance in Staphylococcus aureus, Cell Chem. Biol. 26 (10) (2019) 1355–1364, https://doi.org/10.1016/j.chembiol.2019.07.009, e4.
[152] B. Kaskatepe, S. Ozturk, Assessment of synergistic activity of rhamnolipid and linezolid against methicillin-resistant Staphylococcus aureus in-vitro and in-vivo with Galleria mellonella larvae model, Microb. Pathog. 174 (2023) 105945, https://doi.org/10.1016/j.micpath.2022.105945.
[153] C.M. Hu, L. Zhang, S. Aryal, C. Cheung, R.H. Fang, L. Zhang, Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform, Proceedings of the National Academy of Sciences of the United States of America 108 (27) (2011) 10980–10985, https://doi.org/10.1073/pnas.1106634108.
[154] C. Zhao, Y. Pan, G. Yu, X.Z. Zhao, X. Chen, L. Rao, Vesicular antibodies: shedding light on antibody therapeutics with cell membrane nanotechnology, Adv. Mater. 35 (12) (2023) e2207875, https://doi.org/10.1002/adma.202207875.
[155] Q. Cheng, Y. Kang, B. Yao, J. Dong, Y. Zhu, Y. He, X. Ji, Genetically engineered-cell-membrane nanovesicles for cancer immunotherapy, Adv. Sci. 10 (26) (2023) e2302131, https://doi.org/10.1002/advs.202302131.
[156] H. Yan, D. Shao, Y.H. Lao, M. Li, H. Hu, K.W. Leong, Engineering cell membrane-based nanotherapeutics to target inflammation, Adv. Sci. 6 (15) (2019) 1900605, https://doi.org/10.1002/advs.201900605.
[157] Y. Deng, M. Ren, P. He, F. Liu, X. Wang, C. Zhou, Y. Li, S. Yang, Genetically engineered cell membrane-coated nanoparticles for antibacterial and immunoregulatory dual-function treatment of ligature-induced periodontitis, Front. Bioeng. Biotechnol. 11 (2023) 1113367, https://doi.org/10.3389/fbioe.2023.1113367.
[158] E. Ren, C. Liu, P. Lv, J. Wang, G. Liu, Genetically engineered cellular membrane vesicles as tailorable shells for therapeutics, Adv. Sci. 8 (21) (2021) e2100460, https://doi.org/10.1002/advs.202100460.
[159] Y. Yu, Q. Cheng, X. Ji, H. Chen, W. Zeng, X. Zeng, Y. Zhao, L. Mei, Engineered drug-loaded cellular membrane nanovesicles for efficient treatment of postsurgical cancer recurrence and metastasis, Sci. Adv. 8 (49) (2022) eadd3599, https://doi.org/10.1126/sciadv.add3599.
[160] L. Xi, L. Wang, M. Zhang, C. He, X. Yang, Y. Pang, H. Chen, F. Cheng, TNF-R1 cellular nanovesicles loaded on the thermosensitive F-127 hydrogel enhance the repair of scalded skin, ACS Biomater. Sci. Eng. 9 (10) (2023) 5843–5854, https://doi.org/10.1021/acsbiomaterials.2c01257.
[161] J. Liu, Y. Sun, X. Zeng, Y. Liu, C. Liu, Y. Zhou, Y. Liu, G. Sun, M. Guo, Engineering and characterization of an artificial drug-carrying vesicles nanoplatform for enhanced specifically targeted therapy of glioblastoma, Adv. Mater. 35 (41) (2023) e2303660, https://doi.org/10.1002/adma.202303660.
[162] R.F. Service, Synthetic biology. Synthetic biologists design 'living materials' that build themselves, Science 343 (6178) (2014) 1421, https://doi.org/10.1126/science.343.6178.1421.
[163] S. Roy, J.N. Cha, A.P. Goodwin, Nongenetic bioconjugation strategies for modifying cell membranes and membrane proteins: a review, Bioconjug. Chem. 31 (11) (2020) 2465–2475, https://doi.org/10.1021/acs.bioconjchem.0c00529.
[164] M. Rahmati, E.A. Silva, J.E. Reseland, A.H. C, H.J. Haugen, Biological responses to physicochemical properties of biomaterial surface, Chem. Soc. Rev. 49 (15) (2020) 5178–5224, https://doi.org/10.1039/d0cs00103a.
[165] H. Zhou, Z. Fan, P.K. Lemons, H. Cheng, A facile approach to functionalize cell membrane-coated nanoparticles, Theranostics 6 (7) (2016) 1012–1022, https://doi.org/10.7150/thno.15095.
[166] Q. Hu, Y. Bu, R. Cao, G. Zhang, X. Xie, S. Wang, Stability designs of cell membrane cloaked magnetic carbon nanotubes for improved life span in screening drug leads, Anal. Chem. 91 (20) (2019) 13062–13070, https://doi.org/10.1021/acs.analchem.9b03268.
[167] Y. Han, H. Pan, W. Li, Z. Chen, A. Ma, T. Yin, R. Liang, F. Chen, Y. Ma, Y. Jin, M. Zheng, B. Li, L. Cai, T cell membrane mimicking nanoparticles with bioorthogonal targeting and immune recognition for enhanced photothermal therapy, Adv. Sci. 6 (15) (2019) 1900251, https://doi.org/10.1002/advs.201900251.
[168] R.B. Patel, M. Ye, P.M. Carlson, A. Jaquish, L. Zangl, B. Ma, Y. Wang, I. Arthur, R. Xie, R.J. Brown, X. Wang, R. Sriramaneni, K. Kim, S. Gong, Z.S. Morris, Development of an in situ cancer vaccine via combinational radiation and bacterial-membrane-coated nanoparticles, Adv. Mater. 31 (43) (2019) e1902626, https://doi.org/10.1002/adma.201902626.
[169] S.W. Kang, S. Lee, J.H. Na, H.I. Yoon, D.E. Lee, H. Koo, Y.W. Cho, S.H. Kim, S. Y. Jeong, I.C. Kwon, K. Choi, K. Kim, Cell labeling and tracking method without distorted signals by phagocytosis of macrophages, Theranostics 4 (4) (2014) 420–431, https://doi.org/10.7150/thno.7265.
[170] S. Park, J. Lim, S. Kim, M. Jeon, H. Baek, W. Park, J. Park, S.N. Kim, N.-G. Kang, C.G. Park, Anti-inflammatory artificial extracellular vesicles with notable inhibition of particulate matter-induced skin inflammation and barrier function impairment, ACS Appl. Mater. Interfaces 15 (51) (2023) 59199–59208, https://doi.org/10.1021/acsami.3c14377.
[171] J.R. Lee, W.S. Sim, H.J. Park, B.W. Park, Y.K. Joung, Targeted delivery of apoptotic cell-derived nanovesicles prevents cardiac remodeling and attenuates cardiac function exacerbation, Adv. Funct. Mater. 33 (23) (2023) 2210864, https://doi.org/10.1002/adfm.202210864.
[172] B. Liu, Y. Yang, Y. Chao, Z. Xiao, J. Xu, C. Wang, Z. Dong, L. Hou, Q. Li, Z. Liu, Equipping cancer cell membrane vesicles with functional DNA as a targeted vaccine for cancer immunotherapy, Nano Lett. 21 (22) (2021) 9410–9418, https://doi.org/10.1021/acs.nanolett.1c02582.
[173] X. Huang, L. Wang, H. Guo, W. Zhang, Macrophage membrane-coated nanovesicles for dual-targeted drug delivery to inhibit tumor and induce macrophage polarization, Bioact. Mater. 23 (2023) 69–79, https://doi.org/10.1016/j.bioactmat.2022.09.027.
[174] B. Zheng, Z. Liu, H. Wang, L. Sun, W.F. Lai, H. Zhang, J. Wang, Y. Liu, X. Qin, X. Qi, S. Wang, Y. Shen, P. Zhang, D. Zhang, R11 modified tumor cell membrane nanovesicle-camouflaged nanoparticles with enhanced targeting and mucus-penetrating efficiency for intravesical chemotherapy for bladder cancer, J. Contr. Release 351 (2022) 834–846, https://doi.org/10.1016/j.jconrel.2022.09.055.
[175] R.J. Bose, S.H. Lee, H. Park, Biofunctionalized nanoparticles: an emerging drug delivery platform for various disease treatments, Drug Discov. Today 21 (8) (2016) 1303–1312, https://doi.org/10.1016/j.drudis.2016.06.005.
[176] S. Tan, T. Wu, D. Zhang, Z. Zhang, Cell or cell membrane-based drug delivery systems, Theranostics 5 (8) (2015) 863–881, https://doi.org/10.7150/thno.11852.
[177] L. Rao, L.L. Bu, J.H. Xu, B. Cai, G.T. Yu, X. Yu, Z. He, Q. Huang, A. Li, S.S. Guo, W. F. Zhang, W. Liu, Z.J. Sun, H. Wang, T.H. Wang, X.Z. Zhao, Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance, Small 11 (46) (2015) 6225–6236, https://doi.org/10.1002/smll.201502388.
[178] R.H. Fang, C.M. Hu, B.T. Luk, W. Gao, J.A. Copp, Y. Tai, D.E. O'Connor, L. Zhang, Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery, Nano Lett. 14 (4) (2014) 2181–2188, https://doi.org/10.1021/nl500618u.
[179] R.J. Bose, S.-H. Lee, H. Park, Lipid polymer hybrid nanospheres encapsulating antiproliferative agents for stent applications, J. Ind. Eng. Chem. 36 (2016) 284–292, https://doi.org/10.1016/j.jiec.2016.02.015.
[180] S.C. Tao, B.Y. Rui, Q.Y. Wang, D. Zhou, Y. Zhang, S.C. Guo, Extracellular vesicle-mimetic nanovesicles transport LncRNA-H19 as competing endogenous RNA for the treatment of diabetic wounds, Drug Deliv. 25 (1) (2018) 241–255, https://doi.org/10.1080/10717544.2018.1425774.
[181] W. Ma, X. Zhang, Y. Liu, L. Fan, J. Gan, W. Liu, Y. Zhao, L. Sun, Polydopamine decorated microneedles with Fe-MSC-Derived nanovesicles encapsulation for wound healing, Adv. Sci. 9 (13) (2022) e2103317, https://doi.org/10.1002/advs.202103317.
[182] J. Liao, L. Gong, Q. Xu, J. Wang, Y. Yang, S. Zhang, J. Dong, K. Lin, Z. Liang, Y. Sun, Y. Mu, Z. Chen, Y. Lu, Q. Zhang, Z. Lin, Revolutionizing Neurocare, Biomimetic nanodelivery via cell membranes, Adv. Mater. 36 (26) (2024) e2402445, https://doi.org/10.1002/adma.202402445.
[183] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca-Cancer J. Clin. 71 (3) (2021) 209–249, https://doi.org/10.3322/caac.21660.
[184] R. Vankayala, K.C. Hwang, Near-infrared-light-activatable nanomaterial-mediated phototheranostic nanomedicines: an emerging paradigm for cancer treatment, Adv. Mater. 30 (23) (2018) e1706320, https://doi.org/10.1002/adma.201706320.
[185] J. Sun, Y. Liu, Y. Zhao, W. Yin, Z. Yang, J. Chang, L. Huang, S. Chen, H. Zhi, L. Xue, Erythrocyte-derived bioactive nanovesicles reverse the immunosuppressive function of adenosine for tumor photoimmunotherapy, Adv. Funct. Mater. (2024) 2400114, https://doi.org/10.1002/adfm.202400114.
[186] Y. Ding, Y. Wang, Q. Hu, Recent advances in overcoming barriers to cell-based delivery systems for cancer immunotherapy, Exploration 2 (3) (2022) 20210106, https://doi.org/10.1002/EXP.20210106.
[187] K. Lin, Y. Cao, D. Zheng, Q. Li, H. Liu, P. Yu, J. Li, Y. Xue, M. Wu, Facile phase transfer of hydrophobic Fe(3)O(4)@Cu(2-x)S nanoparticles by red blood cell membrane for MRI and phototherapy in the second near-infrared window, J. Mater. Chem. B 8 (6) (2020) 1202–1211, https://doi.org/10.1039/c9tb02766a.
[188] Z. Chen, P. Zhao, Z. Luo, M. Zheng, H. Tian, P. Gong, G. Gao, H. Pan, L. Liu, A. Ma, H. Cui, Y. Ma, L. Cai, Cancer cell membrane-biomimetic nanoparticles for

homologous-targeting dual-modal imaging and photothermal therapy, ACS Nano 10 (11) (2016) 10049–10057, https://doi.org/10.1021/acsnano.6b04695.
[189] L. Qiang, Z. Cai, W. Jiang, J. Liu, Z. Tai, G. Li, C. Gong, S. Gao, Y. Gao, A novel macrophage-mediated biomimetic delivery system with NIR-triggered release for prostate cancer therapy, J. Nanobiotechnol. 17 (1) (2019) 83, https://doi.org/10.1186/s12951-019-0513-z.
[190] L. Rao, L.L. Bu, Q.F. Meng, B. Cai, W.W. Deng, A. Li, K. Li, S.S. Guo, W.F. Zhang, W. Liu, Antitumor platelet-mimicking magnetic nanoparticles, Adv. Funct. Mater. 27 (9) (2017) 1604774, https://doi.org/10.1002/adfm.201604774.
[191] D. Wang, H. Dong, M. Li, Y. Cao, F. Yang, K. Zhang, W. Dai, C. Wang, X. Zhang, Erythrocyte-cancer hybrid membrane camouflaged hollow copper sulfide nanoparticles for prolonged circulation life and homotypic-targeting photothermal/chemotherapy of melanoma, ACS Nano 12 (6) (2018) 5241–5252, https://doi.org/10.1021/acsnano.7b08355.
[192] T. Yin, Q. Fan, F. Hu, X. Ma, Y. Yin, B. Wang, L. Kuang, X. Hu, B. Xu, Y. Wang, Engineered macrophage-membrane-coated nanoparticles with enhanced PD-1 expression induce immunomodulation for a synergistic and targeted antiglioblastoma activity, Nano Lett. 22 (16) (2022) 6606–6614, https://doi.org/10.1021/acs.nanolett.2c01863.
[193] C.H. Xu, P.J. Ye, Y.C. Zhou, D.X. He, H. Wei, C.Y. Yu, Cell membrane-camouflaged nanoparticles as drug carriers for cancer therapy, Acta Biomater. 105 (2020) 1–14, https://doi.org/10.1016/j.actbio.2020.01.036.
[194] R. Yang, J. Xu, L. Xu, X. Sun, Q. Chen, Y. Zhao, R. Peng, Z. Liu, Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination, ACS Nano 12 (6) (2018) 5121–5129, https://doi.org/10.1021/acsnano.7b09041.
[195] Y. Wan, L. Wang, C. Zhu, Q. Zheng, G. Wang, J. Tong, Y. Fang, Y. Xia, G. Cheng, X. He, Aptamer-conjugated extracellular nanovesicles for targeted drug delivery, Cancer Res. 78 (3) (2018) 798–808, https://doi.org/10.1158/0008-5472.CAN-17-2880.
[196] L. Pang, H. Jin, Z. Lu, F. Xie, H. Shen, X. Li, X. Zhang, X. Jiang, L. Wu, M. Zhang, Treatment with mesenchymal stem cell-derived nanovesicle-containing gelatin methacryloyl hydrogels alleviates osteoarthritis by modulating chondrogenesis and macrophage polarization, Adv. Healthcare Mater. 12 (17) (2023) 2300315, https://doi.org/10.1002/adhm.202300315.
[197] J.-Y. Wu, A.-L. Ji, Z.-x. Wang, G.-H. Qiang, Z. Qu, J.-H. Wu, C.-P. Jiang, Exosome-Mimetic Nanovesicles from Hepatocytes promote hepatocyte proliferation in vitro and liver regeneration in vivo, Sci. Rep. 8 (1) (2018) 2471, https://doi.org/10.1038/s41598-018-20505-y.
[198] K. Oh, S.R. Kim, D.-K. Kim, M.W. Seo, C. Lee, H.M. Lee, J.-E. Oh, E.Y. Choi, D.-S. Lee, Y.S. Gho, In vivo differentiation of therapeutic insulin-producing cells from bone marrow cells via extracellular vesicle-mimetic nanovesicles, ACS Nano 9 (12) (2015) 11718–11727, https://doi.org/10.1021/acsnano.5b02997.
[199] Z. Yang, Z. Zhang, L. Li, Z. Jing, Y. Ma, T. Lan, Y. Li, Z. Lin, W. Fang, J. Zhang, J. Zhang, X. Liang, B. Wu, Y. Zheng, X. Zhang, Bioengineered artificial extracellular vesicles presenting PD-L1 and gal-9 ameliorate new-onset type 1 diabetes, Diabetes 73 (8) (2024) 1325–1335, https://doi.org/10.2337/db23-0987.
[200] X. Li, Y. Wei, Z. Zhang, X. Zhang, Harnessing genetically engineered cell membrane-derived vesicles as biotherapeutics, Extracellular Vesicles and Circulating Nucleic, Acids 5 (1) (2024) 44, https://doi.org/10.20517/evcna.2023.58.
[201] R. Chen, L. Li, L. Feng, Y. Luo, M. Xu, K.W. Leong, R. Yao, Biomaterial-assisted scalable cell production for cell therapy, Biomaterials 230 (2020) 119627, https://doi.org/10.1016/j.biomaterials.2019.119627.
[202] Y. Liu, J. Luo, X. Chen, W. Liu, T. Chen, Cell membrane coating technology: a promising strategy for biomedical applications, Nano-Micro Lett. 11 (1) (2019) 100, https://doi.org/10.1007/s40820-019-0330-9.
[203] C. Dias, J. Nylandsted, Plasma membrane integrity in health and disease: significance and therapeutic potential, Cell Death Discovery 7 (1) (2021) 4, https://doi.org/10.1038/s41421-020-00233-2.
[204] E. Mass, N. Lachmann, From macrophage biology to macrophage-based cellular immunotherapies, Gene Ther. 28 (9) (2021) 473–476, https://doi.org/10.1038/s41434-021-00221-5.
[205] A. Fernandez-Borbolla, L. Garcia-Hevia, M.L. Fanarraga, Cell membrane-coated nanoparticles for precision medicine: a comprehensive review of coating techniques for tissue-specific therapeutics, Int. J. Mol. Sci. 25 (4) (2024), https://doi.org/10.3390/ijms25042071.
[206] Q.V. Le, J. Lee, H. Lee, G. Shim, Y.K. Oh, Cell membrane-derived vesicles for delivery of therapeutic agents, Acta Pharm. Sin. B 11 (8) (2021) 2096–2113, https://doi.org/10.1016/j.apsb.2021.01.020.
[207] L.E. Contreras-Llano, C. Meyer, Y. Liu, M. Sarker, S. Lim, M.L. Longo, C. Tan, Holistic engineering of cell-free systems through proteome-reprogramming synthetic circuits, Nat. Commun. 11 (1) (2020) 3138, https://doi.org/10.1038/s41467-020-16900-7.
[208] X. Ai, S. Wang, Y. Duan, Q. Zhang, M.S. Chen, W. Gao, L. Zhang, Emerging approaches to functionalizing cell membrane-coated nanoparticles, Biochemistry 60 (13) (2021) 941–955, https://doi.org/10.1021/acs.biochem.0c00343.
[209] J.A. Peruzzi, T.F. Gunnels, H.I. Edelstein, P. Lu, D. Baker, J.N. Leonard, N. P. Kamat, Enhancing extracellular vesicle cargo loading and functional delivery by engineering protein-lipid interactions, Nat. Commun. 15 (1) (2024) 5618, https://doi.org/10.1038/s41467-024-49678-z.
[210] R. Raju, S.J. Bryant, B.L. Wilkinson, G. Bryant, The need for novel cryoprotectants and cryopreservation protocols: insights into the importance of biophysical investigation and cell permeability, Biochimica et Biophysica Acta - General Subjects 1865 (1) (2021) 129749, https://doi.org/10.1016/j.bbagen.2020.129749.
[211] S. Lou, W. Hu, P. Wei, D. He, P. Fu, K. Ding, Z. Chen, Z. Dong, J. Zheng, K. Wang, Artificial nanovesicles derived from cells: a promising alternative to extracellular vesicles, ACS Appl. Mater. Interfaces 17 (1) (2025) 22–41, https://doi.org/10.1021/acsami.4c12567.
[212] Y.J. Li, J.Y. Wu, J. Liu, W. Xu, X. Qiu, S. Huang, X.B. Hu, D.X. Xiang, Artificial exosomes for translational nanomedicine, J. Nanobiotechnol. 19 (1) (2021) 242, https://doi.org/10.1186/s12951-021-00986-2.
[213] Y. Zou, S. Ito, M. Fujiwara, N. Komatsu, Probing the role of charged functional groups on nanoparticles grafted with polyglycerol in protein adsorption and cellular uptake, Adv. Funct. Mater. 32 (22) (2022), https://doi.org/10.1002/adfm.202111077.
[214] V. Chugh, K. Vijaya Krishna, A. Pandit, Cell membrane-coated mimics: a methodological approach for fabrication, characterization for therapeutic applications, and challenges for clinical translation, ACS Nano 15 (11) (2021) 17080–17123, https://doi.org/10.1021/acsnano.1c03800.
[215] Y. Ma, S. Dong, A.J. Grippin, L. Teng, A.S. Lee, B.Y.S. Kim, W. Jiang, Engineering therapeutical extracellular vesicles for clinical translation, Trends Biotechnol. 43 (1) (2025) 61–82, https://doi.org/10.1016/j.tibtech.2024.08.007.
[216] Y. Wu, M. Su, S. Zhang, L. Xiao, Y. Xiao, M. Zhang, Y. Bei, M. Li, F. Zhang, Q. Yuan, S. Wu, J. Liu, H. Li, X. Yuan, M. Li, Y. Li, J. Gao, A mesenchymal stem cell-derived nanovesicle-biopotentiated bovine serum albumin-bridged gelatin hydrogel for enhanced diabetic wound therapy, Mater. Des. 230 (2023) 111960, https://doi.org/10.1016/j.matdes.2023.111960.
[217] X. Wang, X. Sun, Y. Zeng, S. Liu, Q. Yi, Y. Wu, Membrane fusion strategy boosts immune homeostasis, mobilizing macrophages to eliminate bacteria and accelerate skin regeneration in infected burn wound, Adv. Funct. Mater. (2024), https://doi.org/10.1002/adfm.202416791.