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Teaser Cell membrane-coated nanosystems can provide a better solution for a more effective treatment of cardiovascular diseases with better prognoses and minimal adverse effects profiles.

Bio-inspired nanomaterials as novel options for the treatment of cardiovascular disease

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Cardiovascular disease (CVD) and its sequelae have long been the leading causes of death and disability in the developed world. Although mortality associated with CVD has been decreasing, due in large part to novel therapeutic options, the rate of decrease has flattened. Thus, there is a great need to investigate alternate therapeutic strategies that can increase efficacy while decreasing adverse effects. Nanomaterials have been widely investigated and have emerged as promising tools for both therapeutic and diagnostic purposes in oncology; however, the potential of nanomaterials has not been extensively explored for cardiovascular medicine. In this review, we focus on recent developments in the field of nanomedicines targeted for CVDs, with a special emphasis on cell membrane-coated nanoparticles (NPs) and their applications.

Introduction

CVD comprises several distinct diseases that affect the heart and vasculature and include atherosclerosis, myocardial infarction (MI), and stroke [1,2]. Although remarkable progress has been made in CVD treatment, and these advances have enabled a decrease in the prevalence of the disease, heart disease is still the leading cause of death in the USA. Thus, novel therapeutic options are required to enable a more dramatic reduction in the morbidity and mortality associated with CVD. Nanomedicine, or the use of nanocarriers (NCs) to modulate the pharmacokinetics (PK) and biodistribution of drugs, has the potential to revolutionize the treatment of CVD. Over the past 20 years, the utility of nanomaterials for both diagnostic and therapeutic purposes has been extensively explored, particularly in the field of oncology; however, a similar focus in other disease areas, including CVD, has languished. Nanomaterials are starting to gain interest in multiple diseases, including CVD, with the development of NPs featuring coating materials derived from natural sources, including cell membranes and extracellular vesicles, demonstrating exceptional efficacy.

To further push the boundaries of classical nanomaterial performance and functionality, there has been a paradigm shift towards cell-mimetic design approaches. To create next-generation nanomedicines that can successfully navigate and interact with the incredibly complex biological

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Dr. Khanh Ha started his research career at the Favorsky Irkutsk Institute of Chemistry, a Siberian Branch of the Russian Academy of Sciences, as a Favorsky Scholar in 2006. In 2010, he began his graduate studies at the University of Florida under Professor Alan Katritzky, completing his Ph.D. in Chemistry with a minor in Pharmaceutical Science in 2016. Dr. Ha started his postdoctoral research training at the Center for System Biology and Center for Cardiovascular Research of Mass General Hospital and Harvard Medical School. He moved to the Masonic Medical Research Institute in Utica in 2018 to continue his postdoctoral studies with Prof. Jason McCarthy. His research focuses on bench-to-bedside approaches to image and to understand in vivo inflammation and thrombogenesis in vascular disease, including atherosclerosis and venous thrombosis.

Prof. Jason R. McCarthy completed his Ph.D in Inorganic Chemistry at the University of Connecticut under the tutelage of Dr. Christian Brückner in 2003. He subsequently obtained a Ruth L. Kirschstein Institutional National Research Service Award T32 postdoctoral fellowship within the Center for Molecular Imaging Research, at the Massachusetts General Hospital (MGH) in Boston, MA, under the direction of Dr. Ralph Weissleder. In 2006, he was appointed as an Instructor in Radiology at Harvard Medical School (HMS) and moved to the Center for Systems Biology at the MGH in 2007, where he was promoted to Assistant Professor of Radiology in 2010. Currently he is an Associate Professor and Scientific Operation

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systems that exist within the body, researchers are now directly leveraging naturally derived cell membranes as a means of bestowing NPs with enhanced bio-interfacing capabilities, instead of attempting to replicate cell functions via synthetic techniques [3–5]. These cell membrane-coated nanocarriers (CMCNCs) or cell-derived vesicle (CDV)-coated nanocarriers not only confer site-specific natural targeting abilities to NCs and show robust tropism to disease pathologies, response to biological signals, and significantly improved biological interactions, but the insertion of exogenous targeting ligands can also be achieved to elicit advanced targeting capabilities [3–5]. Importantly, the core of each material can be specifically engineered for the desired application, resulting in versatile features, in which multiple drugs or therapeutic agents (e.g., RNAi/DNA) can be incorporated and released in either a sustained or controlled manner [4,6,7]. This naturally targeted combinatorial drug delivery is a potential strategy that provides a synergistic pharmacological effect for efficient CVD treatments.

A variety of CMCNCs have been developed for drug delivery applications using a multitude of cell sources, including non-nucleated [red blood cells (RBCs) and platelets (PTLs)] and nucleated cells (monocytes, macrophages, stem cells, cancer cells, and bacteria) [4,7–10]. The synthesis of CMCNCs has been reported elsewhere [4,7,9,10]; thus, here, we discuss the generation of agents featuring cell-derived materials from relevant sources, including stem cells, PTLs, RBCs, and leukocytes. CMCNCs offer immense translational benefits in CVD therapies (Fig. 2), because they preserve the properties of the cell membrane proteins, thereby improving NC interaction within the physiological environment. Thus, CDVs coated onto the NC surface elicit better stealth and targeting properties. Although cell membrane coating can provide attributes that are complex and difficult to synthetically replicate, additional functionalization might be required to achieve capabilities beyond those naturally imbued. Researchers are currently investigating novel strategies for the inclusion of additional functionality (Fig. 3), including fusion with functionally different CDVs, the incorporation of synthetic proteolipid vesicles, the insertion of targeting moiety or imaging probe-conjugated lipids, and metabolic or genetic engineering to produce modified parent cells. We strongly believe that all these efforts have the potential to increase the functionality of CMCNCs, thereby enhancing the preclinical and later clinical relevance of these materials in CVDs therapies.

Stem cell-derived membranes as coating materials on NCs in CVD therapy

Stem cell therapy (SCT) represents a promising, yet controversial way to address the treatment of ischemic cardiomyopathy and could pose one of the only alternatives to heart transplantation, because it bears the potential to reduce infarct size, lessening the degree of dysfunction [11,12]. Numerous stem cell types have been suggested for use in cardiac regeneration, including bone marrow-derived stem cells (BMSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), cardiac stem cells (CSCs), and skeletal myoblasts. Recently, pluripotent stem cells (PSCs), such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), have emerged as promising sources for cardiac regenerative medicine [11], the latter of which has shown robust potential for repairing injured heart [11]. Over the past two decades, protocols to differentiate human (h)iPSCs into cardiomyocytes (CMs) at a high efficiency have been developed, opening the door for potential clinical testing and application. Studies have further demonstrated the therapeutic effects of hiPSC-CMs in small and large animal models and the underlying mechanisms of cardiac repair [13]. Stem cells secrete several inducible factors (bioactive molecules, such as proteins, lipids, DNA, and RNA) that are released into the intercellular space as free-floating solutes or transported into proteolipid membranous vesicles called stem cell-derived extracellular vesicles (SCDVs). For instance, mRNAs in iPSC-EVs contain reprogramming factors Oct3/4, Nanog, Klf4, and c-Myc. Additionally, cardioprotective miRNAs (miR-1, miR-21, and miR-30) have been shown in exosomes from ESC-CMs and iPSC-derived CMs [14]. The protein–protein interactions between SCDVs and the diseased cells could have an essential role in SCDV-mediated targeting and uptake. There is a wide variety of proteins associated with SCDVs, including transmembrane proteins and adhesion molecules (e.g., tetraspanins and integrins), and membrane receptors, which have a crucial role in homologous and heterologous adhesion [7]. Extensive research has also shown that stem cells have beneficial effects on cardiac regeneration and repair through the SCDVs. For instance, stromal cell-derived factor-1 (SDF-1) and its corresponding receptors, C-X-C chemokine receptor type 4 (CXCR4) and C-X-C chemokine receptor type 7 (CXCR7), have pivotal roles during cardiovascular development, cardiac repair,

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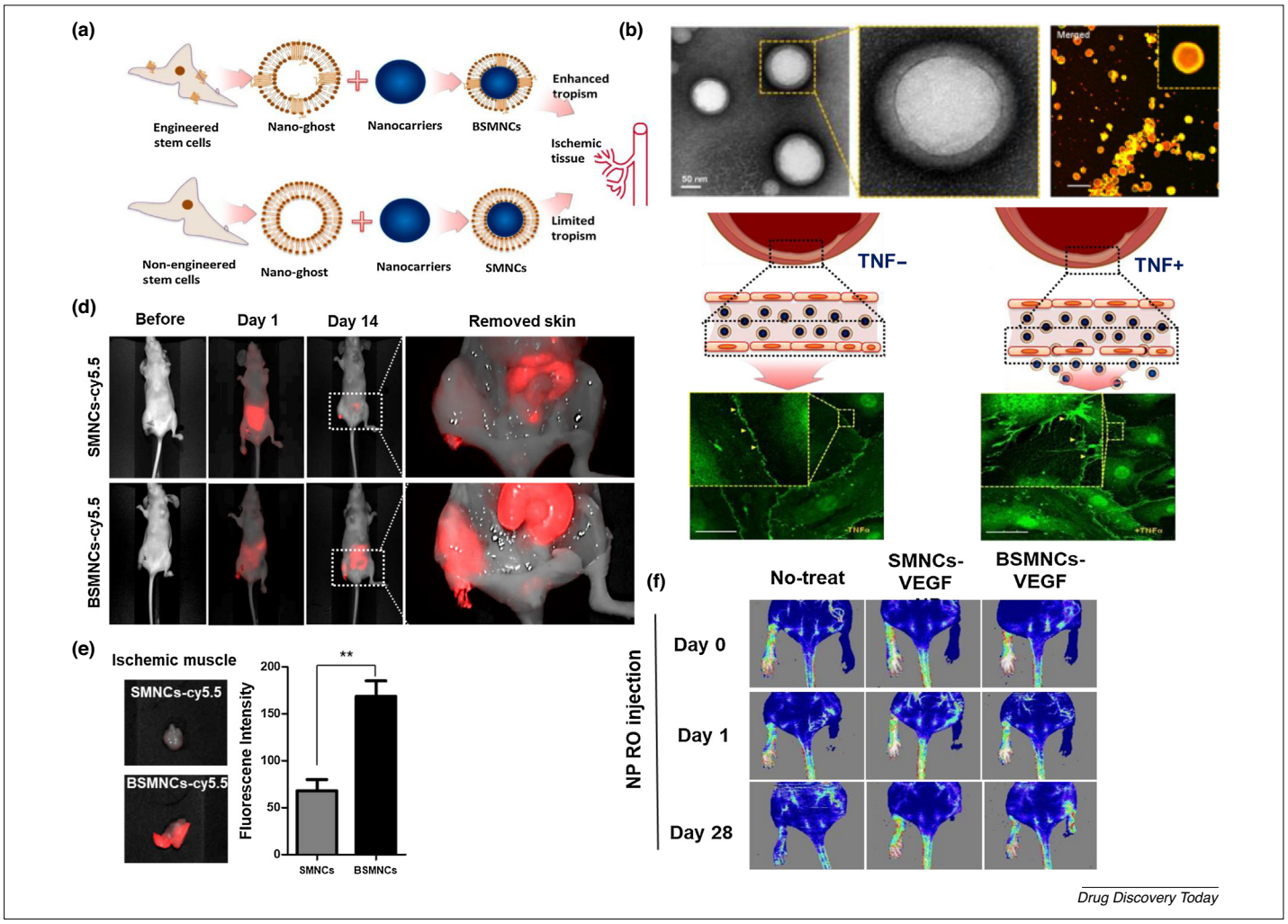

FIGURE 1

Bioengineered stem cell membrane-functionalized nanocarriers for therapeutic targeting of severe hindlimb ischemia. **(a)** Schematic demonstrating the concept and preparation of stem cell membrane nanocarriers (SMNCs) and bioengineered SMNCs (BSMNCs). **(b)** Transmission electron microscopy and confocal microscopy images of SMNCs. **(c)** Bioengineered stem cell membrane coating on NCs enhances transendothelial penetration under inflammatory conditions. Schematic outline and fluorescence images of *in vitro* transendothelial penetration following stimulation with the inflammatory mediator, tumor necrosis factor (TNF)-α. VE-cadherin staining is in green. **(d)** Time-dependent *in vivo* distribution of BSMNCs and SMNCs in murine hindlimb ischemia. **(e)** *Ex vivo* fluorescence intensity of ischemic-induced muscles after intravenous (IV) injection of SMNCs or BSMNCs. **(f)** Revascularization of ischemic limb and reduction of limb loss by SMNCs and vascular endothelial growth factor (VEGF)-BSMNCs in a severe hindlimb ischemic mouse model [3].

and tissue homeostasis after ischemia. Stabilization of the SDF-1/CXCR4$^+$ axis demonstrated enhanced myocardial repair [15]. Also, MSC secretomes have been shown to impact the microenvironment upon cardiac injury, promoting protection, angiogenesis, and tissue repair. The angiogenic potential is of specific interest in the treatment of ischemic cardiac diseases [11]. In a remarkable recent study by Kehl *et al.* comparing the angiogenic potential of hMSC secretomes isolated from adipose tissue (human adipose-derived stem cells; hADSCs), bone marrow (hBMSCs), and umbilical cord Wharton's jelly (hWJSCs), the authors demonstrated that the hWJSC secretome is the most potent hMSC source for inflammation-mediated angiogenesis induction, whereas the potency of the hADSC secretome was lowest [12]. The use of SCDVs, as an alternative to stem cells, confers several advantages, such as an increased safety profile, lower immunogenicity, and the ability to cross biological barriers, and avoids complications that arise from stem cell-induced ectopic tumor formation, entrapment in lung microvasculature, and immune rejection [16]. In addition, SCDVs can be frozen-stored and thawed for instant use in patients with no major loss of functional activity [17]. Several preclinical studies have shown that SCDVs have strong therapeutic potential and are safer for the treatment of CVDs compared with stem cells [18–21]. This tolerance was exemplified by the injection of SCDVs derived from both MSCs and CDCs into clinically relevant pig models of MI [22]. However, significant obstacles to bedside translation still need to be overcome. Several innovative concepts have been proposed to advance the translation of cell-free therapeutics to the clinic [23–25]. For example, Zhang *et al.* fused SCDVs with RAW 264.7 leukocyte membrane vesicles to improve the homing of SCDVs during the treatment of myocardial ischemic–reperfusion injury (I/R) in mice. Through the Mac1/LFA1-ICAM-1 interaction, monocyte mimic-modified SCDVs significantly

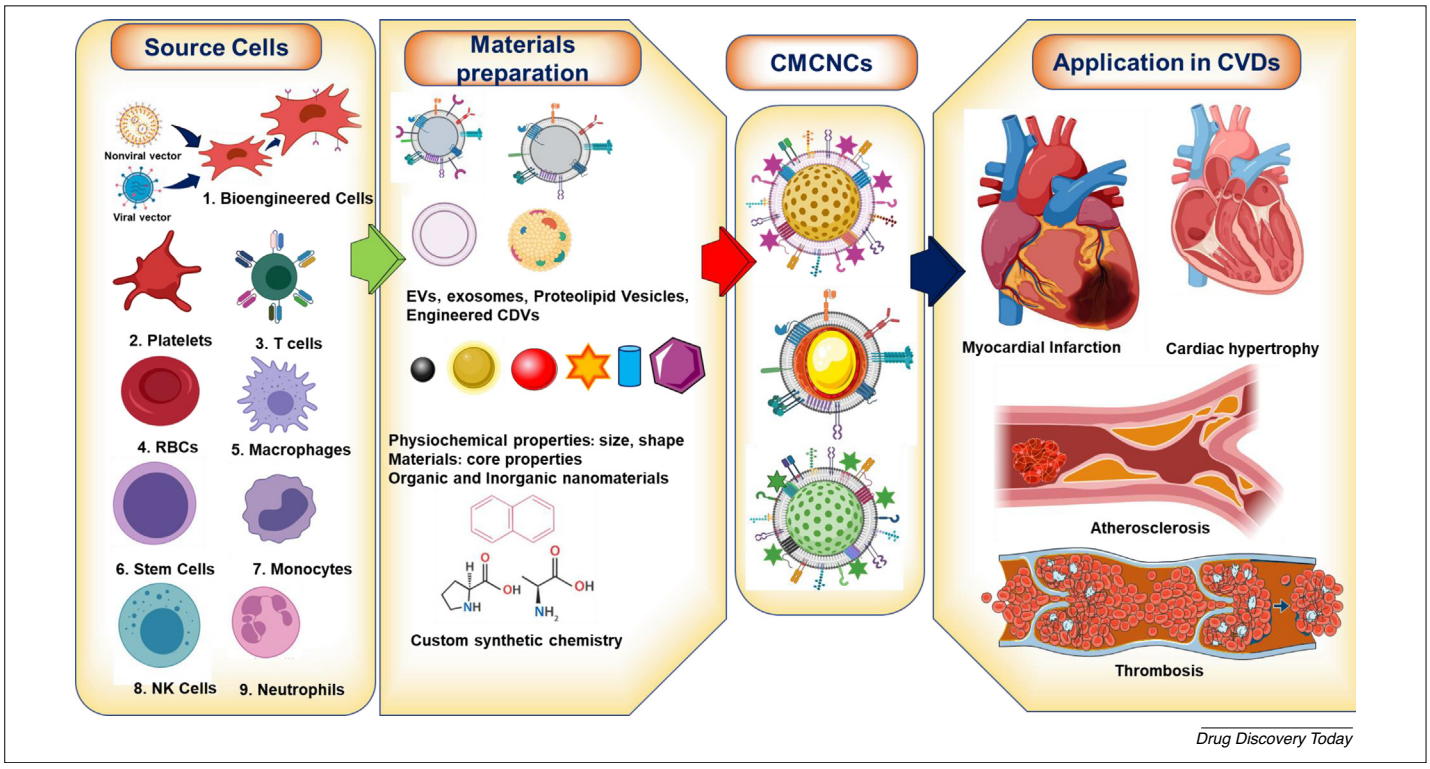

FIGURE 2

Schematic outline depicting the design toolbox concepts for the development and advancement of cell membrane-coated nanocarriers (CMCNCs) in cardiovascular disease (CVD) therapies. Abbreviations: RBC, red blood cell.

accumulated and affected the injured heart, leading to a better therapeutic outcome in murine I/R model [13].

Tang *et al.* proposed using synthetic stem cells, which act like 'mini drug pumps' to promote endogenous myocardial repair. They prepared stem cell-mimicking microparticles (CMMPs) by fusing the cardiac stem cell (CSC) membrane fragments with PLGA MPs preloaded with human CSC conditioned media. In a mouse model of MI, the injection of CMMPs led to the preservation of viable myocardium and augmentation of cardiac functions. Also, they demonstrated that CMMPs prepared from human cells did not stimulate T cell infiltration in immunocompetent mice [14]. Similarly, in another study, Luo *et al.* fabricated synthetic MSCs (synMSCs) using MSC-derived cell membranes and concentrated MSC secretome-encapsulated MPs. They showed that synMSCs share similar human bone marrow-derived MSC properties and are capable of continuously releasing secretory molecules, such as vascular endothelial growth factor (VEGF), SDF-1, and insulin-like growth factor 1 (IGF-1) for up to a week. Furthermore, in a mouse model of acute MI, direct injection of synMSCs into infarcted hearts promoted angiogenesis and significantly reduced infarct size, and maintained a thicker ventricular wall at 14 days, to the same extent as intact MSC-based therapy [15].

Biodegradable scaffold materials penetrated with stem cells have been engineered to perform as cardiac patches for therapeutic myocardial regeneration. However, limitations associated with the long-term viability of natural stem cells remains one of the challenges for these advanced materials. To overcome this problem, Huang *et al.* developed an 'off-the-shelf' artificial cardiac patch comprising a decellularized porcine myocardial extracellular matrix (myoECM) scaffold and synthetic cardiac stromal cells generated by encapsulating secreted factors derived from these cardiac stromal cells into the poly(lactic-co-glycolic acid) (PLGA) MPs. This artificial cardiac patch (artCP) can deliver these factors directly to the site of cardiac injury. In a rat model of acute MI, transplantation of the freezable artCP aided cardiac recovery by reducing scarring, promoting angiomyogenesis, and improving cardiac function. The researchers further confirmed the safety and efficacy of the artCP in a pig model of MI [16]. These preclinical reports are very encouraging in stem cells mimicking CVN development. However, stem cell membranes might not have all the functional proteins required for efficient targeting to diseased tissues, and *in vitro* expansion might affect the natural accumulation of targeting a protein on the stem cell plasma membranes. To mitigate this issue, researchers have developed bioengineering strategies to enhance the functional capability of stem cell membrane-coated NCs.

Bioengineered stem cell membrane-coated nanocarriers (BSMNCs) were designed to improve targeted delivery to ischemic hindlimbs. To take advantage of the unique CXCR4-mediated stem cell tropism, human adipose-derived stem cells (hASCs) were engineered to overexpress CXCR4 on the membrane (CXCR4-hASCs) and were then used as a coating material for the functionalization of VEGF-loaded PLGA-NCs. Systemic injection of BSMNCs loaded with VEGF into mice with hindlimb ischemia resulted in a substantial enhancement of reperfusion, muscle repair, and limb salvage compared with animals treated with control NCs (Fig. 1) [3]. In another study, Wang *et al.* used a molecular cloning and lentivirus packaging method to engineer MSC-derived exosome-enriched lysosome-associated membrane protein 2b (Lamp2b) fused with ischemic myo-

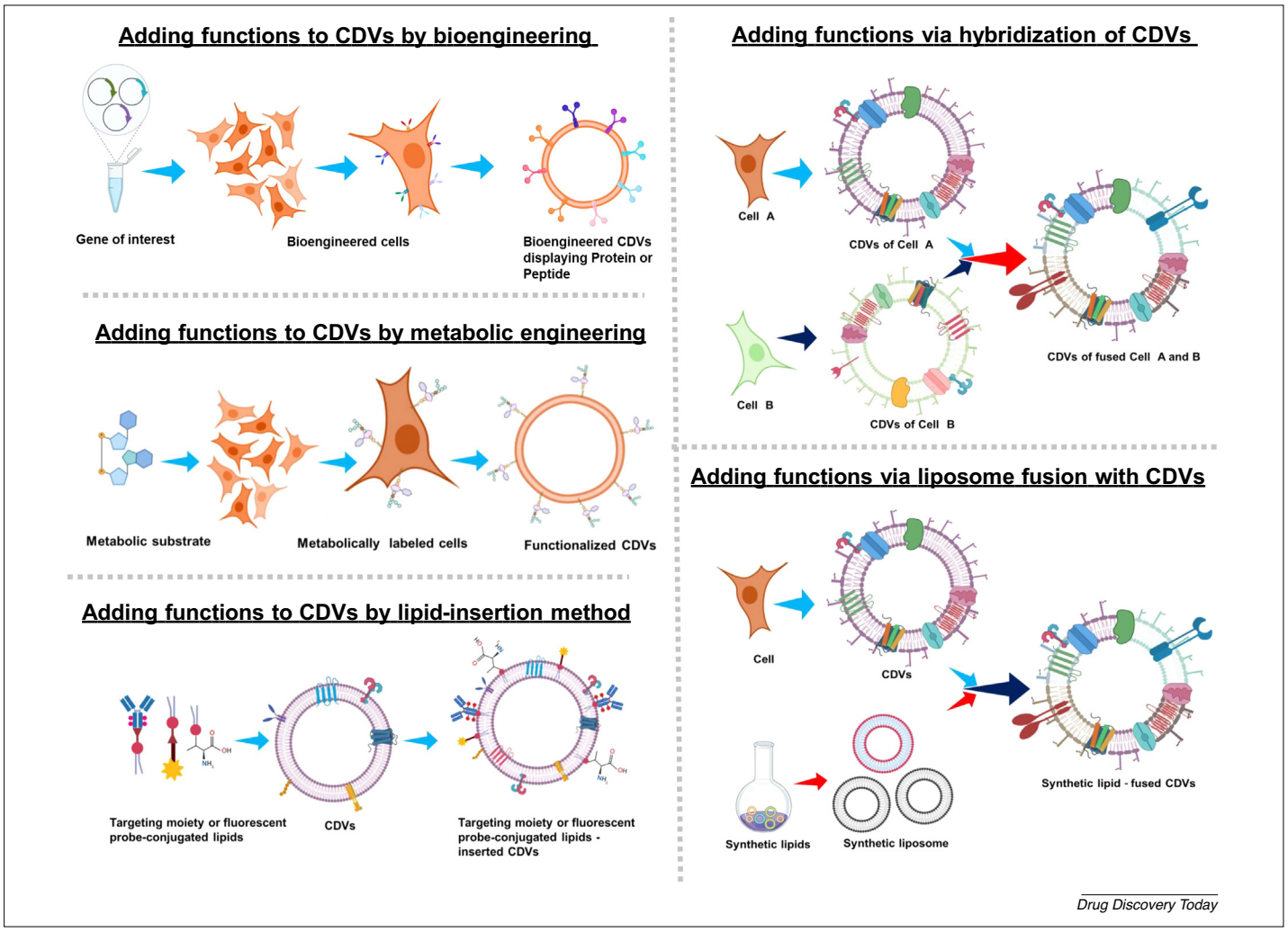

FIGURE 3

Schematic diagram showing the multitude of methods available for the addition of functionality to cell-derived vesicles (CDVs).

cardium-targeting peptide CSTSMLKAC (IMTP). The *in vitro* and *in vivo* results showed that IMTP-exosome treatment decreased inflammation and apoptosis, diminished fibrosis, and enhanced angiogenesis in the ischemic heart [17].

Anucleate cell-derived membranes as coating materials on NCs in CVD therapy

The human body contains certain unique non-nucleated cells, such as mature RBCs, PTLs, and cornified cells in the skin, hair, and nails. Among these cells, RBCs are like autologous immune cells, in that they are not cleared by the immune system until they are damaged or dead. Therefore, RBCs can circulate in the blood for up to 120 days [9,18]. As part of the maturation process, human RBCs extinguish their cell nuclei to carry as much oxygen as possible and still stay small enough to fit through narrow capillaries. The external membrane of the RBC contains numerous proteins that either traverse the lipid bilayer one or more times or are anchored to it through a lipid tail [9]. They are loosely divided into four categories based on their functions: membrane transporters; adhesion molecules and receptors; enzymes; and structural proteins that link the membrane with the membrane skeleton [18]. In particular, the immunoglobulin superfamily (IgSF) is a large group of glycoprotein receptors and adhesion molecules that are involved in signal transduction, which includes the Lutheran (Lu) glycoproteins, intercellular adhesion molecule 4 (ICAM4), erythroblast membrane-associated protein (ERMAP, the JMH protein), Scianna antigen, basigin (Ok antigen), and CD47. ICAM4 and CD47 are part of the band 3/Rh macro complex [18]. CD47 has been identified on the RBC surface as a self-marker that inhibits macrophage phagocytosis through interactions with the signal regulatory protein-alpha (SIRP-α) receptor [19]. Similarly, membrane proteins, C8-binding protein (C8bp), homologous restriction protein (HRP), decay-accelerating factor (DAF), membrane cofactor protein (MCP), complement receptor 1 (CR1), and CD59 prevent attack by complement complexes [20,21]. Bridging this complex surface biochemistry of RBCs with the versatile cargo-carrying capacity of polymeric NPs, an RBC membrane-cloaked NP (RBC-NP) platform represents a new class of bio-inspired nanocarriers with long-circulating capability [9]. Studies have shown that RBC membranes with abundant self-markers can help the NCs to evade recognition by the immune system, substantially extending the circulation half-life of NCs from a few hours to approximately 40 h [9].

Valvular heart disease (VHD) is caused by the damage or dysfunction of one or more valves in the heart and can require replacement of the damaged valve with an artificial biological heart valve (BHV) to recover function. Clinical data demonstrate that interventional artificial heart valve products have a higher risk of subclinical valve thrombosis within 1 year after implantation, with an incidence of 15–40% [22,23]. In addition, BHVs also have additional disadvantages, including increased immune response, thrombosis and calcification risks, and an overall shorter lifespan. Interestingly, Hu *et al.* designed a BHV that was cross-linked with RBC-NCs loaded with rapamycin and atorvastatin. The incorporation of drug-loaded RBC-NCs preserved the structural stability and mechanical properties of the glutaraldehyde-treated BHVs and demonstrated excellent anticoagulation, endothelialization, and anticalcification by inhibition of the inflammatory response both *in vitro* and *in vivo* in a rat model of disease [24].

In addition to RBC membrane-derived mimetics, the physical properties of the NCs have a crucial role in tissue distribution and physiological interaction [25]. For instance, the anisotropic design of RBC-mimetic NCs showed significance in terms of physiological interactions compared with those featuring conventional spherical isotropy [25,26]. They had a higher resistance to nonspecific cellular elimination upon systemic administration compared with spherical particles, which would augment the stealth nature of membrane-coated NCs [26]. Anisotropic NCs also have increased targeted interactions with cells because of a higher surface area: volume ratio. Cell membranes have the ability to undergo structural remodeling, frequently display anisotropic shapes and varying degrees of curvature. Akiva *et al.* identified that the combination of shape and RBC-mimicking features attains an enhanced drug delivery efficacy that neither parameter can accomplish on its own [26]. RBC membrane-coated NCs have the advantages related to not only the functional diversity of natural RBCs membranes, but also the physicochemical customization of the synthetic polymeric core for customized cargo loading and release [27]. In the context of CVD, Wang *et al.* developed rapamycin-loaded RBC-mimetic NPs for effective treatment of atherosclerosis [28]. These RBC-mimetic NPs showed favorable properties, including controllable size, negative charge, sustained drug-release kinetics, effective inhibition of macrophage proliferation *in vitro*, and prolonged blood circulation *in vivo*. Importantly, they accumulated and significantly delayed the progression of atherosclerosis in established atherosclerotic plaques in the atherosclerosis-prone apolipoprotein E-deficient ($ApoE^{-/-}$) mouse model [28].

PTLs are another unique anucleate cell produced from megakaryocytes in the bone marrow that are also small in size (2–3 mm) [29]. In circulation, PTLs can rapidly adhere to, and aggregate at, sites of vascular injury, forming a hemostatic plug. Activated PTLs provide a negatively charged phosphatidylserine-rich membrane surface that enhances cell-based thrombin generation, which enables coagulation. Thus, PTLs have a vital role in hemostasis. Yet, under pathological conditions, excessive clotting can induce an ischemic insult, such as a MI or stroke, as can occur as a result of the rupture of atherosclerotic lesions [30]. At disease or vascular injury sites, subendothelial matrix proteins, such as collagens, are exposed to the blood components. Plasma von Willebrand Factor (vWF), originating from endothelial cells (ECs), megakaryocytes, and PTLs, can then anchor onto the collagen. The vWF receptor on PTLs (glycoprotein GP-Ibα), via interaction with the immobilized vWF, subsequently initiates PTL tethering to the site of injury, triggers their activation and the formation of a hemostatic plug. Aside from GP-Ibα, several collagen receptors have been identified on PTLs, most notably integrin alpha2beta1(α2β1) and immunoglobulin (Ig) superfamily member GP-VI [31].

In addition to this immunomodulatory protein, a cluster of differentiation 47 (CD47), CD55, and CD59, other integrin components (α2, α5, α6, β1, and β3), and other transmembrane glycoproteins (GP-IV, GP-V, GP-VI, and GPIX), and C-type lectin-like type II transmembrane receptor (CLEC-2) have been reported for their biological activity [32]. Cell mimetics prepared from PTLs have several advantages, including a long circulation time attributed to the CD47 protein in PTLs, which sends 'don't eat me' signals to macrophages, inherent disease-targeting ability owing to the cell surface adhesion molecules, (P-selectin), and large volumes and surface area for cargo loading.

Given the crucial role of PTLs in CVD and their natural interactions with the associated disease substrates, several researchers have developed PTL mimetics for the targeted delivery of therapeutics [32]. In earlier studies, Anselmo *et al.* designed PTL-NPs (PLNs) that mimic four main attributes of natural PTLs: (i) discoidal morphology; (ii) mechanical flexibility; (iii) biophysically and biochemically mediated aggregation; and (iv) hetero-multivalent presentation of ligands that mediate adhesion to both vWF and collagen, as well as precise clustering to activated PTLs [33]. PLNs display enhanced surface-binding, site-specific adhesive, and PTL-aggregatory properties compared with spherical and rigid discoidal counterparts under *in vitro* flow conditions [33]. Additionally, in a mouse model, they further demonstrated the enhanced accumulation of PLNs and subsequently an ~65% bleeding time reduction at the wound site [33]. Similarly, Hu *et al.* reported a multifaceted bio-interfacing strategy using the entire PTL membrane on drug-loaded PLGA NCs. These PTL membrane-cloaked PLGA NCs exhibited selective adhesion to damaged human and rodent vessels as well as enhanced binding to PTL-adhering pathogens. Furthermore, docetaxel and vancomycin-loaded PLGA NCs showed higher therapeutic efficacy in rat coronary restenosis and a mouse model of systemic bacterial infection, respectively [34]. Tang *et al.* utilized the natural injury-targeting capability of PTLs to enhance the vascular delivery and therapeutic efficacy of CSCs. They showed that attaching PTL-derived nanovesicles (PNVs) to the surface of CSCs increased retention in the heart and reduced infarct size in endothelium-denuded rat aortas, and rat and porcine models of acute MI [35]. Similarly, Cheng *et al.* designed biomimicking PTL-like proteoliposomes (PLPs) comprising PTL-derived proteins and synthetic lipid vesicles. The PLPs showed a robust binding affinity for monocytes but not for ECs *in vitro*, mimicking normal PTL activity. Using intravital multiphoton imaging, the authors demonstrated that, compared with plain liposomes, PLPs aggregate at the diseased site 72 h post infarction and were able to deliver an anti-inflammatory drug, cobalt protoporphyrin, in a murine model of I/R injury [36].

Prostaglandin (PGE2) is a lipid-signaling molecule that activates endogenous stem/progenitor cells for cardiac repair post ischemic injury. PGE2 exerts pharmacological effects via G-protein-coupled EP receptors subtypes (i.e., EP1, EP2, EP3, and EP4). Among these

EP receptors, recent studies identified that EP2, EP3, and EP4 are overexpressed on the surface of CMs following I/R injury. To take advantage of the overexpression of PGE2 receptors (EPs), Su *et al.* designed a PTL-inspired nano cell (PINC) that incorporates both prostaglandin E2 (PGE2)-modified PTL membrane and cardiac stromal cell-secreted factors to target the heart after I/R injury [37]. Intravenous injection of PINCs resulted in augmented cardiac function and mitigated maladaptive heart remodeling, accompanied by increases in cycling CMs, activation of endogenous stem/progenitor cells, and promotion of angiogenesis in a mouse model of myocardial I/R injury [37].

PTLs also have a significant role in the initiation and development of atherosclerosis, especially during the erosion or rupture of a vulnerable plaque. Local inflammation of atherosclerosis leads to endothelial activation and stimulates PTL attachment and aggregation. PTLs adhering to collagen or ECs serve as a bridge, directing inflammation cells to sites of atherosclerosis by PTL-monocyte complex formation and PTL–$CD4^+$ T cell crosstalk; thus, mimicking the inherent adhesive function of PTLs can be a powerful approach for targeting plaques. Song *et al.* demonstrated the efficacy and proresolving potential of PTL membrane-coated NPs (PNP) loaded with rapamycin as a targeted drug delivery platform for atherosclerosis treatment. These PNPs displayed 4.98-fold greater efficiency than control NPs in atherosclerotic arterial trees, representing their targeting efficacy to atherosclerotic plaques in a $ApoE^{-/-}$ atherosclerosis mouse model. Moreover, PNP significantly attenuated the progression of atherosclerosis and stabilized atherosclerotic plaques [36]. In another study, Wei *et al.* developed PTL-mimicking nanocarriers capable of interacting with the activated endothelium, foam cells, and collagen, which can also target subclinical regions of arteries susceptible to plaque formation [39]. Should an inflamed atherosclerotic lesion rupture, it might result in an acute MI or stroke. Front-line therapies have included the administration of anticoagulant, antiplatelet, and fibrinolytic agents, such as tissue plasminogen activators (tPA), streptokinase (SK), and urokinase (UK)-type plasminogen activators (uPA). Although these drugs have the potential to significantly reduce early mortality and morbidity, significant issues arise, including short circulation half-lives and systemic off-target effects that affect hemostatic capabilities and cause substantial hemorrhagic risks. PTLs have a pivotal role in thrombosis, and the most abundant receptor expressed on the PTL surface is the GP-IIb/IIIa complex, also known as integrin αIIbβ3 (CD41/CD61), which is the primary fibrinogen/fibrin receptor mediating PTL aggregation. Therefore, researchers have designed PTL-mimicking NCs that offer biocompatibility, and protect the encapsulated thrombolytic drugs while in circulation, preventing off-target uptake and action, and actively anchoring the materials onto thrombus via natural homing mechanisms. For instance, Pawlowski *et al.* utilized the liposomal version of PTL MP (PMP)-inspired nanovesicles (PMINs), which can protect entrapped thrombolytics in blood circulation to prevent off-target uptake and action, anchor actively onto thrombus through PMP-relevant molecular machineries, and allow drug release via a thrombus-relevant enzymatic trigger. PMINs anchor onto thrombi via heteromultivalent ligand-mediated binding to active PTL integrin GPIIb-IIIa and P-selectin; they then release the thrombolytic drug owing to vesicle destabilization triggered by clot-relevant enzyme phospholipase-A_2 for targeted fibrinolytic action while minimizing off-target systemic adverse effects [34]. Similarly, Li *et al.* used the intrinsic properties of PLTs in binding to injured vasculature to design PTL mimetic nanobubbles (PNB) for timely perfusion intervention and ultrasound imaging of acute ischemic stroke [33]. Xu *et al.* designed a PTL membrane-coated nano agent for the targeted delivery of recombinant rtPA [40]. These customized nanoplatelets showed higher targeting efficiency to thrombi in pulmonary embolism and mesenteric arterial thrombosis model mice, producing a superior thrombolytic activity compared with free rtPA [40]. In another study, Chen *et al.* reported the construction of blood cell membrane-cloaked mesoporous silica NPs for the delivery of fullerenols, ultimately showing that the RBC membrane coating on fullerenols displayed rapid and efficient thrombolysis activity with less bleeding risk compared with the clinical drug UK [41].

When a clot blocks the coronary arteries of the heart, MI occurs, potentially resulting in myocardial necrosis. This large volume of myocardial cell death triggers an inflammatory response that contributes to adverse left ventricular (LV) remodeling and heart failure. Therefore, modulation of the inflammatory response might serve as a potent strategy for the prevention of adverse cardiac remodeling and eventual heart failure. Li *et al.* fabricated PMPs coated with anti-interleukin (IL)-1β antibodies to neutralize IL-1β after acute MI. Their results indicate that the anti-IL-1β PTL PMs (IL1-PMs) protected CMs from apoptosis by neutralizing IL-1β and decreasing IL-1β-driven caspase-3 activity [42]. Similarly, Zhuang *et al.* developed a PTL cell membrane-coated metal-organic framework (MOF) nanodelivery platform for the targeted delivery of siRNA *in vivo*. The MOF core is capable of high loading yields, and its pH sensitivity enables endosomal disruption upon cellular uptake. The developed NCs showed high silencing efficiency *in vitro* against multiple target genes and significant targeting and therapeutic efficacy in a murine xenograft model [43].

PTL-derived materials have also been investigated for the prevention of restenosis after drug-eluting stent (DES) implantation. DES has increasingly become a standard procedure in the clinic and is used to control postangioplasty restenosis in the treatment of atherosclerosis. However, DES has been associated with endothelium damage that can further neointimal hyperplasia. To resolve this issue, Wang *et al.* developed an epigenetic inhibitor (JQ1)-loaded PTL-mimicking polyamidoamine polyvalerolactone (PAMAM-PVL) nanocluster as an endothelium-protective, nonthrombogenic, stent-free antirestenotic nanosystem. They compared the antirestenotic effects of biomimetic nanoclusters loaded with rapamycin and JQ1 or their respective drug-only controls in a rat carotid artery balloon injury model [44]. Their results showed biomimetic nanoclusters containing JQ1 resulted in robust targeting to balloon-injured areas in arteries and reduced neointimal hyperplasia (>60%), preserving endothelial recovery, whereas the rapamycin formulation impaired endothelial recoverage [44].

Traditional NCs have their limitations in thrombolysis therapy because their mobility in biological media cannot be controlled externally, which is a desirable feature required to improve the thrombolytic effect [45]. To overcome these obstacles, the micro/nanomotor technology and its self-driven mobility have brought more opportunities for using nanomaterials in thrombolysis therapy [45]. For instance, Shao *et al.* showed the construction of erythrocyte membrane-cloaked Janus polymeric micromotors propelled

by near-infrared (NIR) irradiation and applied in thrombus ablation [46]. The thrombolytic effect was achieved by using heparin (Hep) and photothermal effects. Alternatively, Wan *et al.* used PTL membranes as cell-mimetic sources for the targeting functionalization of mesoporous/macroporous silica/platinum nanomotors (PM/MMNMs). The surface proteins on the PMs assist in the targeting of the nanomotors to the thrombus, where the PTL membrane can then be burst under NIR irradiation to accomplish desirable sequential drug release, including the rapid release of UK (3 h) and slow release of the anticoagulant heparin (>20 days) [47]. In another study, Huang *et al.* synthesized PTL membrane-coated Janus-aminated mesoporous silica balloons loaded with the antiproliferative drug paclitaxel (JAMS/PTX) modified with the antivascular cell adhesion molecule-1 antibody) anti-VCAM-1 (MJAMS/PTX/aV). *In vivo*, these materials demonstrated that the nanomotor effectively decreased vascular proliferation through the combination of both photothermal treatment and drug therapy [48].

Staphylococcus aureus is a highly pathogenic facultative anaerobe that, in some instances, resides as an intracellular bacterium within phagocytic and nonphagocytic cells. This pathogen can establish secondary infection foci, resulting in recurrent systemic infections that are difficult to treat using systemic antibiotics. In the context of CVD, *S. aureus* is the leading cause of bacterial infective endocarditis (IE) in most of the world, present in ~31% of cases, followed by the viridans group streptococci at 17% and *Enterococcus* spp. Vancomycin is the treatment of choice for native valve IE because of methicillin-resistant *S. aureus* (MRSA). However, because of intracellular survival, *S. aureus* is often resistant to vancomycin. *S. aureus* and other pathogenic bacteria rely on the binding interactions with PTLs and RBCs to promote their colonization and evade the host immune response. The bacteria can bind directly with cell membrane proteins or indirectly through an extracellular matrix that links bacterial and cell surface receptors. Such common and diverse PTLs and RBC–bacterium binding interactions have motivated the use of cell-mimetic NCs for pathogen-targeted vancomycin delivery. In addition to binding with PTL to invade the host, pathogenic bacteria also release virulent toxins to attack PTLs and promote infection. For example, MRSA releases α-toxin to induce PTL aggression, which aids bacterial colonization and immune evasion. The mechanism is likely to embed the bacteria inside the thrombi and, therefore, escape the immune surveillance. Some strains of *Escherichia coli* secrete Shiga toxin and lipopolysaccharide (LPS), which bind to glycosphingolipid receptors on the PTL. Such connections activate PTL and induce PTL aggregation, leading to ischemic damage. Instead, *Bacillus anthracis* secretes lethal toxins (LeTx) and edema toxins (ETx) that inhibit PTL aggregation and, therefore, promote hemorrhages essential for the infection. Inclusive, these observations showed that PTLs and RBCs are popular virulence targets in various pathogenic bacterial infections, and motivating researchers to apply cell-derived materials such as exosomes, artificial liposomes, and CMCNCs as a nanodecoy to intercept and neutralize incoming toxins for antibacterial efficacy.

Similarly, the ongoing Coronavirus 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to wreak havoc worldwide, causing the death of nearly 2 million people as of the mid-end of January 2020 [49]. Whereas the primary organ system affected by the virus is the lungs, >20% of hospitalized patients present with significant myocardial injuries, including infection-related myocarditis with reduced systolic function and arrhythmias [49]. Recently approved drugs and preventive vaccines are in the process of reducing the health burden caused by SARS-CoV-2 [50]. Now it is well known that one of the primary mechanisms through which SARS-CoV-2 enters cells to facilitate viral replication is by binding to the angiotensin-converting enzyme 2 (ACE2) [50]. The recent studies suggested a direct role of ACE2 in the heart and its relation to SARS-CoV-2 virus-mediated cardiac complications [50,51]. Soluble recombinant ACE2 neutralizes SARS-CoV-2 by binding the S protein and has proven to reduce the entry of SARS-CoV-2 in Vero-E6 cells and engineered human organoids [52]. Alternatively, a promising treatment strategy is to use cell-mimetic nanodecoys (CMND) as nanosponges to trap and detain SARS-CoV-2. For instance, recently, Zhang *et al.* developed two kinds of CMNDs comprising the plasma membranes of human lung epithelial type II cells or human macrophages. These CMNDs trap SARS-CoV-2 by displaying the same protein receptors, both identified and unidentified, required for SARS-CoV-2 cellular binding and entry. Following incubation with the CMND, SARS-CoV-2 was neutralized and unable to infect cells. Importantly, the CMNDs act agnostic to viral mutations and potentially viral species [53,54]. Additionally, Rao *et al.* further advanced CMNDs acting against SARS-CoV-2. They constructed CMNDs by fusing cell membrane nanovesicles derived from genetically engineered human embryonic kidney 293 T cells, which stably express SARS-CoV-2 receptor ACE2, and human monocytes (THP-1), which display plentiful cytokine receptors. By competing with host cells, these CMNDs proficiently trapped the virus and inflammatory cytokines, such as IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF). These two functionalities allow effective interference of viral infection and its associated immune disorder, presenting a promising therapeutic strategy for COVID-19 and its related co-infections [55]. By contrast, engineered cell-secreting vesicles that display ACE-2 are also suggested as a viable option to trap and detain SARS-CoV-2 [56,57].

Immune cell membranes as coating materials on NC in cardiovascular disease therapy

The mammalian heart comprises several cell types, including CMs, fibroblasts (FBs), ECs, and perivascular cells. Non-myocyte cell types occupy a relatively small volume fraction, but are essential for healthy heart homeostasis, providing the extracellular matrix, intercellular communication, and vascular supply needed for efficient CM contraction and long-term survival [58]. Studies show that resident and recruited immune cells have a pivotal role in not only modulating CM function, but also regulating injury responses involving scar formation, and cardiac remodeling. At rest, the heart comprises a small fraction of resident immune cells, mainly macrophages, which are maintained through local proliferation [59,60]. Following injury, there is a significant infiltration of immune cells into the heart tissue, including macrophages, mast cells, monocytes, neutrophils, eosinophils, B cells, and T cells [59]. Activation of leukocytes via inflammatory mediators, such as chemokines, cytokines, and adhesion molecules, is instrumental in these processes [61].

Leukocyte infiltration in the ischemic area is a hallmark of the acute inflammatory response after MI or I/R injury and monocytes are the dominant cell type that infiltrates injured myocardium from circulation [13]. Within 30 min post MI, inflammatory monocytes are abundantly recruited to the wounded heart, peaking at approximately 24–72 h. After being recruited to the site of injury, monocytes differentiate into macrophages, [13,14], and have essential roles in removing dead cell debris and cardiac repair [15,16]. This migration of monocytes happens in a highly controlled and precise manner and depends on adhesive molecules [17,18], such as macrophage receptor 1 (Mac1; also known as integrin αMβ2), lymphocyte function-associated antigen 1 (LFA1; also known as αLβ2 integrin), P-selectin glycoprotein ligand 1 (PSGL1), very late antigen 4 (VLA4; also known as integrin α4β1) and C-C motif chemokine receptor 2 (CCR2). Chemokine-induced leukocyte migration into the vessel wall is an early pathological event in the progression of atherosclerosis, the underlying cause of MI [61].

Cardiac macrophages constitute 10% of noncardiomyocytes in the heart and maintain homeostasis by removing dying senescent cells and promoting angiogenesis [62]. These cells express a remarkable variety of receptor glycoproteins on their surface implicated in the recognition and uptake of self and foreign antigens. CCR2 is one such well-characterized receptor that specifically mediates monocyte/macrophage chemotaxis. The human myocardium contains distinct subsets of CCR2– and $CCR2^+$ macrophages. CCR2– macrophages are a cardiac tissue-resident population exclusively replenished through local proliferation, whereas $CCR2^+$ macrophages are maintained through monocyte recruitment and proliferation. CCR2– and $CCR2^+$ macrophages in humans have distinct functional properties, analogous to reparative CCR2– and inflammatory $CCR2^+$ macrophages found in the mouse heart [63]. Clinically, $CCR2^+$ macrophage abundance is associated with pathological left ventricular and systolic dysfunction in patients with heart failure [63]. Upon injury, $CCR2^+$ macrophages also secrete multiple proinflammatory cytokines, such as IL-6 and tumor necrosis factor-α (TNF-α), which promote local inflammation and cell death. Similarly, macrophages also constitute one of the defining cells present in an atherosclerotic lesion in addition to the macrophage-derived foam cell, an enlarged macrophage characterized by the accumulation of oxidized low-density lipoprotein (oxLDL) and cholesterol crystals [64]. To utilize the natural ability of macrophages to specifically localize to myocardial infarcts and atherosclerotic lesions, researchers functionalized NCs with macrophage membranes [65,66]. The biological features of the outer membranes of macrophages provide advantageous biocompatibility and reticuloendothelial system (RES) evasion in systemic circulation for the NCs. Additional functionalization with peptides can synergistically enhance the targeting of the function of macrophage membrane-coated NCs [67]. Recently, Gao *et al.* established macrophage cell-mimicking reactive oxygen species (ROS)-responsive NCs. These macrophage cell-mimicking NCs not only evade the clearance of NCs by the RES, but also provide tropism toward the inflammatory site, where the ROS responsiveness of NCs allows precise drug release. Furthermore, these NCs sequester proinflammatory cytokines to suppress local inflammation in atherosclerosis [68]. Parodi *et al.* demonstrated the functionalization of silicon NCs with cellular membranes derived from leukocytes (J774, THP-1, and Jurkat cells). Dubbed 'leukolike vectors' (LLVs), the authors successfully embedded over 300 proteins on the NCs surface [69]. Among them, they identified proteins that promote reduced mononuclear phagocytic system (MPS) uptake (i.e., clusterin), immune tolerance (i.e., CD47 and CD45), and endothelium targeting [i.e., lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1)]. Additionally, the same research group designed leukocyte protein-rich liposomal vesicles called leukosomes for targeting activated endothelium [70]. This proteolipid vesicle successfully incorporated >340 distinct proteins, with most being associated with plasma membrane adhesion proteins (such as LFA-1 and Mac-1), resulting in significant accumulation of NCs at the activated endothelium [70]. Using an inflamed ear murine model, leukosomes were shown to display a sevenfold increase in accumulation compared with bare liposome particles. This strategy demonstrated that functionalizing NCs with leukocyte cell-derived vesicles resulted in increased association with the inflamed vessel area, whereas bare NCs tended to diffuse from blood vasculature into the interstitial space, indicating poor adhesion with inflamed vasculature [70,71]. Similar strategies have also been used with peripheral blood mononuclear cells (PBMCs) as a promising source of cell membranes for NC functionalization. Compared with conventional NCs, PBMC-derived biomimetic NCs are endowed with leukocyte properties, such as immune evasion, prolonged blood circulation, and diseased tissue recognition and targeting.

Neutrophils are one of the first immune cells to be recruited to an inflammatory site [61]. They are short-lived, undergo apoptosis, and shed the IL-6 receptor, which modulates the outcome of the inflammatory response by activating ECs to recruit additional and a wider variety of leukocytes [72]. Many studies show the involvement of neutrophils in the progression of CVD, including atherosclerosis and thrombosis. In ischemic cardiomyopathy, neutrophils infiltrate the infarcted myocardium and mediate tissue damage [73]. Recently, Zhang *et al.* prepared neutrophil membrane-coated polymeric NCs that inherit the antigenic exterior and associated membrane functions of the neutrophils, which makes them ideal decoys of neutrophil-targeted biological molecules. These neutrophil-mimicking NCs could neutralize proinflammatory cytokines, suppressing the inflammation [74]. Similarly, Dong *et al.* showed functional benefits of neutrophil membrane-coated NCs loaded with coenzyme Q (N-NPCoQ10) in a I/R injury mouse model [75].

Concluding remarks and outlook

CMCNCs have emerged as a potential strategy to overcome obstacles associated with conventional NCs. The proteins retained in the cell membranes can serve to improve blood circulation and increase targeting and retention at sites of interest. In general, cell sources utilized for these materials should be readily available in large numbers to transfer the innate properties of the cells to synthetic materials. In this context, iPSCs, iPSC-derived CMs (iPSC-CMs), and MSCs are some of the most attractive cells because they can serve as an unlimited source and have the most flexibility. Additionally, these cell types can be expandable and stable over many cell passages. After stem cells, blood cells, such as RBCs and leukocytes, would be good choices because they can be acquired from patients with little risk, and are constantly regenerated through hematopoiesis. There is also the capability to optimize

TABLE 1

Preclinical examples of the application of CMCNCs in CVD therapy

Source cell	Material core	Active agents	Functions	Refs
Bioengineered hADMSCs expressing CXCR4	PLGA NCs	VEGF	Angiogenesis	[3]
Monocyte membranes	MSC-EV: stem cell-derived EVs	–	Regenerative therapeutics for ischemic heart	[13]
CSC-derived membranes	PLGA MPs	Conditioned media, hCSCs	Therapeutic cardiac regeneration	[14]
Decellularized porcine myocardium	PLGA MPs	Conditioned media, hCSCs	Therapeutic cardiac regeneration	[16]
hBMSC-derived membranes	PLGA MPs	Secreted factors of hBMSCs	Treatment of acute MI	[15]
Mouse BMSC-derived exosome: display CSTSMLKAC	–	–	Treatment of acute MI	[17]
Reconstructed apoptotic vesicles	–	Vancomycin	Treatment of intracellular infection	[4]
RBC membranes	Bio-heart valve	Rapamycin and Atorvastatin	Treatment of VHD	[24]
	Anisotropic PLGA NPs	–	Shape-dependent targeting; RBC membrane mediated-toxin removal	[26]
	Silica-NPs	Fullerenol	Thrombolysis	[41]
	Heparin and chitosan Janus-type micromotors (JTMs)	Partially coated gold layer on JTMs	Ablation of thrombus through photothermal therapy	[46]
Prostaglandin E2 (PGE2)-functionalized PLT cell membranes	PLGA NCs	Secretome from CSCs	Therapeutic cardiac regeneration	[35]
PLT cell membranes	CSCs	–	Treatment of acute MI	[33]
	Mesoporous/microporous silica/platinum nanomotors	Thrombolytic drug (UK) and anticoagulant drug (Heparin)	Thrombus therapy	[47]
	Janus-aminated mesoporous silica	Paclitaxel	Treatment of atherosclerosis	[48]
Gevokizumab-armed PMPs	–	Anti-IL-1β antibodies; gevokizumab	Cardiac detoxification and repair via blocking IL-1β activity	[42]
Macrophage membranes	Reactive oxidation-sensitive chitosan oligosaccharide NPs	Atorvastatin	Treatment of atherosclerosis	[68]
Hybrid liposome: macrophage membrane proteins with synthetic lipids	–	Rapamycin	Treatment of atherosclerosis	[70]
Engineered 293 T-expressing ACE-2 membranes	THP-cell membranes	–	Nano decoys to adsorb COVID-2 virus and inflammatory cytokines (IL-6 and GM-CSF)	

coating properties through the combination of membranes from different cell sources, or through genetic engineering to add or enhance proteins of interest.

The preclinical results obtained thus far have been encouraging and wider application of the CMCNC concept can be expected in the future as the technology matures. Yet, long-term safety and materials associated with toxicity and stability will need to be taken into consideration for any of these materials to enter translational studies. The engineering aspects of these materials are also vital, because many of the technologies that are used for the isolation of the cell-based materials and coating of NCs are inefficient and time-consuming, which can result in batch-to-batch variability and challenges in scaling up to clinical-level doses. Novel concepts that do not only rely on separation via centrifugation will need to be identified and combined with efficient NC-coating and storage procedures. Advances in nanoengineering methods can be applied to enhance the targeting capabilities of CMCNCs.

Additionally, the flexibility of a material core in the CMCNC system can result in versatile carrier features for the delivery and monitoring of therapeutics, in which one or more drugs or imaging moieties can be incorporated and released in a tailored manner. For instance, the advancement of microfluidics, particle replication in non-wetting templates (PRINT), and 3D printing technology could overcome the challenges associated with the manufacturing of CMCNCs [76,77]. Microfluidic technology can provide full control over the production processes of CMCNCs owing to the miniaturization of the fluidic environment. Compared with conventional lab-scale batch methods, the microfluidic set-up provides a range of advantages, including the improved controllability of material characteristics, as well as the precisely controlled release profiles of payloads [78]. Similarly, recent advances in PRINT technology-based particle engineering enable the precise production of highly uniform biodegradable material cores with independent control over their size, shape, and chemical composition. These technologies have the potential to imbue desirable therapeutic benefits into product candidates, including the modulation of PK or biodistribution, increased therapeutic entrapment, more convenient routes of administration, the ability to generate novel combination products, enhanced storage and stability, and the potential to reduce adverse effects.

Diverse nanomaterial-based strategies have been utilized to provide novel approaches for the treatment of CVD. In this review, we have touched upon the generation of agents featuring cell-derived materials from relevant sources, including stem cells, PTLs, RBCs, and leukocytes. CMCNCs offer immense translational ben-

efits as CVD therapies (Fig. 2 and Table 1), because they preserve the properties of the cell membrane proteins, thereby improving NC interactions within the physiological environment. Thus, CDVs coated onto the NC surface elicit better stealth and targeting properties. Researchers are currently examining innovative strategies for the inclusion of additional functionality (Fig. 3 and Table 1), including fusion with functionally different CDVs, integration of synthetic proteolipid vesicles, insertion of targeting or imaging agent-conjugated lipids, and metabolic or genetic engineering to produce modified source cells. We strongly believe that all of these efforts have the potential to increase the functionality of CMCNCs, thereby enhancing the preclinical and later clinical relevance of these materials as CVD therapies.

Declaration of interests

The authors declare no competing financial interest.

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