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Novel bioengineering strategies for drug delivery systems

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ABSTRACT

Cellular membrane-derived vesicles (CMVs) have recently attracted attention as a drug delivery system (DDS) because CMVs offer unique advantages, including nanosized particles, superior transcellular cross-communication, excellent biocompatibility, and active targeting ability. However, some challenges remain in the design and production of CMVs, such as their low yield, chemical and mechanical instability, and difficulties in functionalizing membrane surfaces. In this paper, we introduce three strategies to overcome the limitation of CMVs. First, hybrid vesicles combined CMVs from cellular membranes with synthetic liposomes (SLs) offer new engineering solutions to tackle such issues. The membrane fusion of SLs and CMVs can increase their production yield and stability while allowing for the presentation of surface proteins from donor cells. Additional compounds, such as targeted ligands and imaging agents, can be easily integrated into CMVs by using functionalized SLs. Second, core/shell nanostructures composed of synthetic nanoparticles as cores and cell membrane structures as shells can offer unique advantages for improving the stability and preservation of the inherent capabilities of the various nanoparticles in these core/shell nanostructures. Lastly, CMV/scaffold complexes are also a pronounced approach for DDSs because the scaffold structures help CMVs or loaded therapeutic agents to sustained release. The sustainable released system extends the bioavailability of CMVs or loaded therapeutic agents for a long time *in vivo*. Altogether, we suggest a combination strategy of hybrid vesicle-coated nanoparticles or hybrid vesicle/scaffold complex could be a promising drug delivery system.

List of abbreviations

CMV	cellular membrane-derived vesicle
SL	synthetic liposome
DDS	drug delivery system
EPR	enhanced permeability and retention
ICAM-1	intercellular adhesion molecule-1
LFA-1	lymphocyte function-associated antigen 1
NK	natural killer
DOX	doxorubicin
PEGylation	polyethylene glycolylation
MSC	mesenchymal stem cells
SiO_2NP	porous silica nanoparticles
PLGA	poly (lactic-co-glycolic acid)
hASC	human adipose-derived stem cells
UCNPs@SiO_2	mesoporous silica up-conversion nanoparticles
RBC	red blood cells
AuNC	gold nanocapsule
NIR	near-infrared
WBC	white blood cells
MAC-1	macrophage-1 antigen
ES	E-selectin
TRAIL	tumor-specific apoptosis-inducing ligand
LMGNS	leukocyte membrane-coated gallium nano-swimmers
PLT	platelets
CTC	circulating tumor cells
AuNR	gold nanorods
VCAM-1	vascular cell adhesion molecule-1
PAMP	pathogen-associated molecular patterns
IFN-g	interferon-gamma

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IL-17	interleukin-17
IL-4	interleukin-4
FRET	fluorescence resonance energy transfer
ZIKV	Zika virus

1. Introduction

Several studies are being conducted around the world to find a new delivery system, because traditional therapeutic drugs have problems, such as abrupt release, high toxicity levels, non-targeting, rapid degradation, and developed resistance [1]. To overcome these obstacles, drug delivery systems (DDSs) have been developed in various research areas, including chemistry, medicine, and materials science [2]. A DDS is a formulation or device that allows the entrance of a therapeutic material into the body and increases its efficacy and safety by controlling the rate, time, and anatomical location of drug release. To create clinically relevant DDSs, improved pharmacokinetics, avoidance of systemic side effects, degradability *in vivo*, and cost savings by employing lower dosages should be carefully considered. Importantly, DDSs are required to have some form of preventive measure against random oxidation or enzymatic degradation *in vivo* to avoid potential side effects. Many researchers have used nanoparticle-based DDSs (Fig. 1), such as polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticle, nano-scaffold. These nano-scaled particles offer unique advantages, including increases in enhanced permeability and retention (EPR) (i.e., passive targeting) and provision of large surface areas [3–7]. Incorporation of pharmaceuticals, antibiotics, diagnostic and imaging modalities, and/or free medications into nanoparticles can improve drug solubility (loading capability), active targeting ability, and imaging. Drug-loaded nanoparticles can also achieve sustained drug release kinetics, minimize adverse effects, and thereby improve therapeutic efficacy [8–11].

Despite such benefits of drug-loaded nanoparticles, only a few have been successfully translated into the clinic [12,13] due to several unsolved problems: (1) foreign nanoparticles elicit significant immunological responses in live organisms' innate and adaptive immune systems, which can easily eliminate nanoparticles [14,15]; (2) administered nanoparticles are poorly delivered to targeted areas due to physiological barriers, in which the reticuloendothelial system (RES) prevents long circulation of the nanoparticles in the bloodstream [16]; (3) the EPR effect is the sole means of passive targeting for non-targeted nanoparticles, exposing normal cells to the possible danger of non-specific toxicity of drugs without active targeting [17]; and (4) the potential *in vivo* toxicity of synthetic nanomaterials utilized in biomedical applications has always been a major concern [18].

To overcome these issues, cellular membrane-derived vesicles (CMVs) would be a great approach. CMVs can avoid immune clearance and low *in vivo* toxicity because they are from cell sources, and have an active targeting ability due to targeting proteins. In this review, we summarize the function of CMVs from different cell lines and three strategies to improve CMV's drawbacks.

2. Cellular membrane-derived vesicles (CMVs)

Bio-inspired materials that resemble biological systems have sparked great interest in biomimetic technologies to address the flaws of synthetic nanoparticles and to design new functional materials by taking advantage of natural biosystems. For example, micro-vesicles, exosomes, and apoptotic bodies are cellular membrane-derived vesicles (CMVs) that can exhibit the characteristics of their donor cells [19]. Because CMVs are directly produced from natural cell sources, they elicit the majority of the surface features and functions of the source cell membranes, enabling biomimetic substances for various biomedical applications [20–23]. For instance, the self-recognition of membrane proteins (e.g., CD47) in cellular membranes can prevent phagocytosis. Also, these membrane proteins can significantly enhance the half-life of

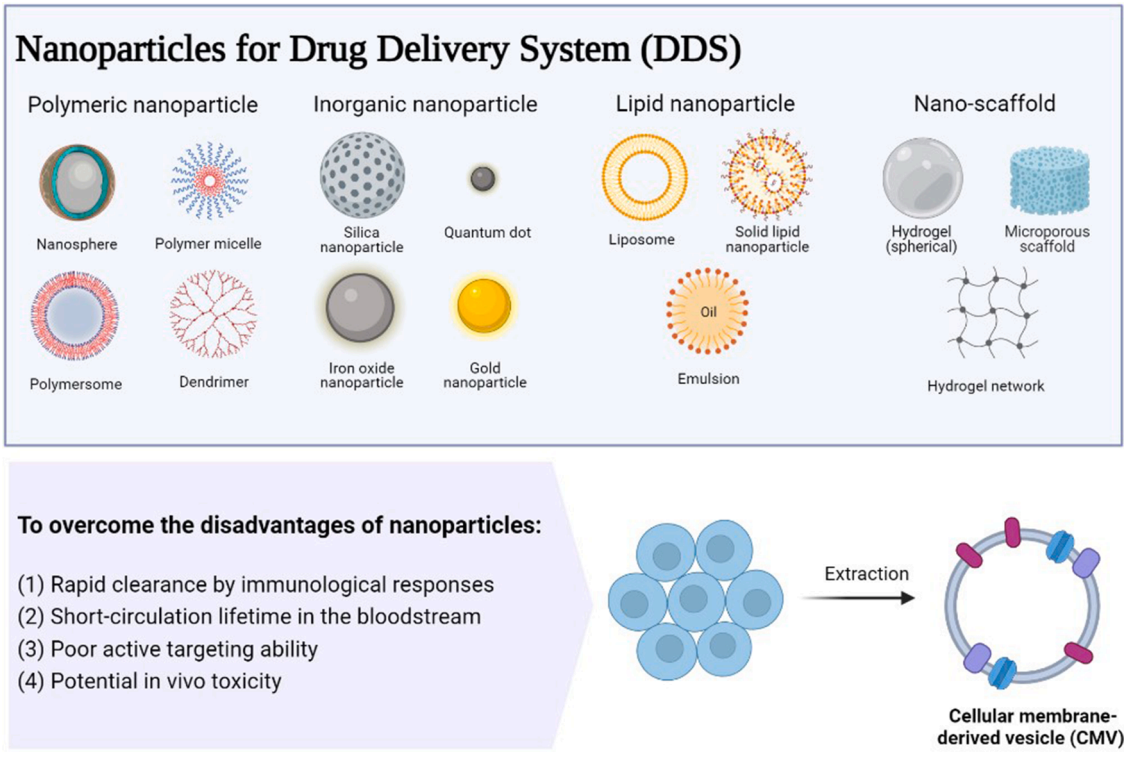

Fig. 1. Illustration of nanoparticle-based drug delivery systems (DDSs) and required characteristics for uses in clinical settings. Various nanoparticle-based nanoparticles, including polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, and nano-scaffold, have been used as DDS because of their distinctive characteristics. However, nanoparticle-based DDSs should overcome some disadvantages for a clinic. To overcome the drawbacks of nanoparticle-based DDSs, the approach using cellular membrane-derived vesicles (CMVs) is a great strategy. Created with BioRender.com.

DDSs because the RESs would recognize the DDSs as their materials [24]. The active targeting ability of membrane surface proteins is considered a novel targeting tool for various diseases and can be specialized by using different types of cell sources. [25]. For example, CD63 is responsible for boosting cell adhesion and is also involved in cellular internalization [26]. Théry et al. demonstrated that vesicular ligands play a role in cellular receptor-mediated internalization. For instance, Intercellular adhesion molecule-1 (ICAM-1)-conjugated CMVs from mature dendritic cells are captured by binding to lymphocyte function-associated antigen 1 (LFA-1; ligand of ICAM-1) on the surface of $CD8^+$ dendritic cells and activated T cells, suggesting that this ligand-receptor interaction plays a role in CMV capture [27]. In general, CMVs present good biodistribution and low toxicity *in vivo* because of their similarity in structure to cell membranes [18]. CMVs can be used to carry a wide range of biological molecules in their lipid bilayer structure, which can protect the drugs from plasma or the immune system [28,29]. CMVs can efficiently deliver drug molecules to recipient cells because the drug molecules are intracellularly delivered via fusion or endocytosis mechanisms, which are not interfered with by the medications' natural functionalities [30,31]. Consequently, they offer great potential for usage as an effective nanocarrier for DDSs.

Despite the mentioned advantages of CMVs, it is still challenging to employ the biological benefits inherited from cellular membranes due to the main two reasons. One of the primary challenges in CMV-based DDSs for clinical applications is their low scalability [32]. In addition, CMVs are chemically unstable and mechanically fragile, leading to difficulties in controlling their fate *in vivo* and, thus, long-term delivery and in modifying the surface of CMVs by using engineering and functionalizing for therapeutic potential [33–37]. Because of the poor yield and instability of CMVs, the fabrication of biological membrane-based DDSs in laboratory settings and the encapsulation of foreign chemicals into CMVs is problematic [38,39]. Hence, researchers have tried to develop novel solutions for overcoming these drawbacks (e.g., low scalability and poor stability) until recently.

3. Unique properties of CMVs from different cell lines

Fabrication of CMVs is easy with simple methods like the serial extrusion of cells, and ultracentrifugation. Because immune systems can generally recognize CMVs from cell sources as an autologous material, they can avoid the immune system, resulting in long circulation time in the bloodstream. CMVs have proved their high potential as DDSs because of low cytotoxicity to normal cells, the prevention of cargoes from immune response before reaching targeted tissues or cells. The most critical advantage of CMVs is that they can maintain the unique properties of each cell type. It is extremely difficult to fabricate biomaterials that show similar structures and functions of proteins on cell membranes. However, because CMVs do not need to synthesize such proteins or peptides, they can execute those functions, such as active targeting ability, and immunomodulation. In this chapter, we summarized the unique roles of CMVs from various cell types (Fig. 2, and Table 1).

3.1. Mesenchymal stem cells (MSCs)

MSCs have been extensively explored because of their high therapeutic activities (e.g., immunomodulation, secretion of growth factor, and homing properties). Moreover, MSCs can be easily separated from patients and used as autologous sources, which alleviates immune rejection during post-transplantation [40]. Because MSCs naturally have high tumor affinity [41], they can target cancers and stay in tumors *in vivo*, although the exact process has yet to be established [42]. Hence, MSC CMVs were found to deliver multiple cargoes together and directly home to tumors and deliver therapeutic agents to the target and showed excellent blood circulation and the tumor-targeting ability post intravenous injection [41,43]. Plus, MSCs have the ability to transmigrate across the endothelial barrier and to leave blood vessels after application [44]. For example, CMVs of human adipose-derived stem cells (hASCs) showed better translocation across endothelial cell barriers and reduced absorption by murine and human macrophages [45]. Dental pulp stem cell-derived CMVs (DPSC-CMVs) shrunk the protein expression of IL-1β, IL-6, and TNF-α *in vitro* and *in vivo*, and attributed to the suppression of HMGB1/TLR4/MyD88/NF-κB pathway, resulting in therapeutic effects against cerebral ischemia-reperfusion injury with an extremely poor prognosis [46], because of specific brain-targeting and efficiently penetrating the blood–brain barrier [47].

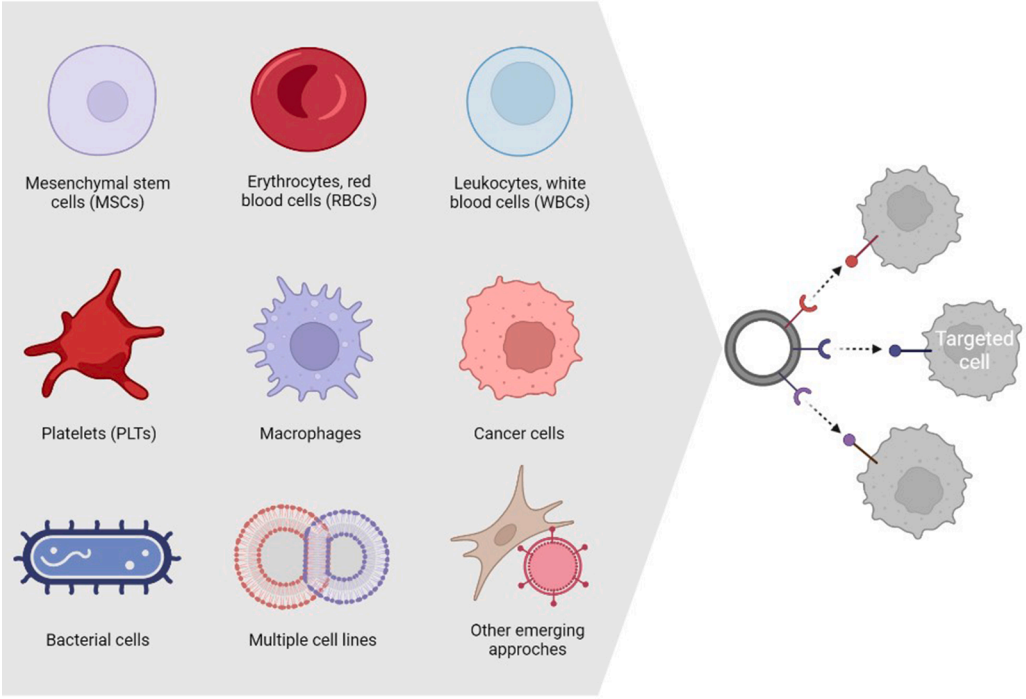

Fig. 2. Cellular membrane-derived vesicles (CMVs) can be extracted from various cells via simple methods such as extrusion. Because CMVs are recognized as an autologous material, they can avoid the immune system, leading to a long circulation lifetime in the bloodstream. Plus, CMVs exhibit low cytotoxicity to normal cells since they have an active targeting ability with membrane proteins. Above all, CMVs maintain their unique properties from each cell line. Created with BioRender.com.

Table 1
Unique properties of CMVs from various cell lines.

Cell line	CMV's properties	Refs.
Mesenchymal stem cells (MSCs)	- Easy isolation from patients - Immunomodulation - Secretion of growth factor - Homing properties - Autologous sources - High tumor affinity - Better translocation across endothelial cell barriers - Reduced absorption by macrophages - Long circulation time in the bloodstream - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	[40–45]
Erythrocytes, red blood cells (RBCs)	- Transition through vascular barriers - Immune evasion after both the first and second doses - Resisting cellular uptake - Autologous sources - Long circulation time in the bloodstream - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	[14,18, 48–52]
Leukocytes, white blood cells (WBCs)	- Detection of inflammation or diseased regions - Migration through tissues - Avoidance of opsonization and phagocytosis clearance - Transition through vascular barriers - Tumor-tropic targeting capacity and induction of apoptosis - Improved permeability across the endothelium - Autologous sources - Long circulation time in the bloodstream - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	[53–58]
Platelets (PLTs)	- Avoidance phagocytosis clearance - Immune evasion - Reduced absorption by macrophages - Targeting to damaged vasculatures, tumor tissues, circulating tumor cells (CTCs) - Causing apoptosis of cancer cells by interactions with tumor-specific apoptosis-inducing ligands (TRAIL) - Long circulation time in the bloodstream - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	[59–62]
Macrophages	- Actively targeting multiple cells - Adherence to metastatic cancer cells in lung metastases - Tumor-tropic targeting capacity - Reduced RES organ accumulation in macrophages - Immunopotentiator for a cancer immunotherapy - Autologous sources - Long circulation time in the bloodstream - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	[65–73, 76]
Cancer cells	- Homologous cancer-targeting capacity - Targeting capacity to different tissues or cells - Targeting capacity to professional antigen-presenting cells - Avoidance of the immune system - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	[77–83]
Bacterial cells	- Targeting capacity to mammalian cells - Targeting capacity to macrophages - Long-distance transport - Avoidance of the host immune system - Activation and maturation of dendritic cells - Activation of both innate and adaptive immune responses - Protection of the therapeutic payload	[84–93]
	- Naturally high stability - Intracellular communication - Immunomodulation in a potential host - Assistance in the creation of bacterial biofilms - Reducing inflammation compared to commensal bacteria. - Presenting viral immunogenic antigens with innate adjuvant capabilities - High cancer cell affinity - Substantial antiproliferative effects - Robust protective immune response to the source infections - Triggering robust Th1 and Th17-biased cell responses against E. coli bacteria - Capture of cancer neoantigens - Protection of the encapsulated medications - Reduced cytotoxicity of drugs	
Dual membrane	- RBC and platelet membranes • Long circulation time in the bloodstream • Accumulated in micro thrombosis locations - Platelets and leukocytes • Avoidance of WBC contact • Targeting capacity to cancer cells - RBC membranes with B16-F10 melanoma cells • Long circulation time in the bloodstream • Melanoma-homogenous targeting	[94,96, 97]
Others	- Mosquito-medium-host-Aedes-albopictus shell • Absorbed ZIKV virus and suppressed ZIKV replication in ZIKV-susceptible cells • Reduced ZIKV-induced inflammatory and degenerative processes • Shuttling the ZIKV virus away from targeted cells • Anti-viral applications - Activated fibroblast cell membrane 1 Autologous targeting capability to cancer-associated fibroblasts	[15,21]

3.2. Erythrocytes, red blood cells (RBCs)

CMVs can evade early identification by the immune system and RES. Therefore, CMV-masking strategies allow nanocarriers to avoid immunological responses and increase the systematic circulation duration. In particular, RBCs are natural long-circulating units that circulate in the blood with long lifetimes by resisting cellular uptake [48] and transiting through vascular restrictions [49] because the natural erythrocyte membranes exhibited RBC membrane-associated proteins [50,51]. Furthermore, after RBC membranes use for the fabrication of CMVs, they retain CD47 antigens as a "don't-eat-me" signal and immunosuppressive proteins [50,51]. Because of the properties, compared to conventional nanomaterials, which were rapidly cleared upon the second injection [52], RBC membrane-coated nanoparticles showed prolonged circulation time in the bloodstream (72 h) by immune evasion after both the first and second doses of the particles [14]. The nanoparticles coated with CMVs from RBC showed considerably enhanced *in vivo* blood retention (9.7% ID/g) after 24 h, compared to PEG-coated counterparts (2% ID/g) [18]. Hence, coating nanoparticles with CMVs from RBCs would prolong stathe ability and longevity of the nanoparticles in the bloodstream.

3.3. Leukocytes, white blood cells (WBCs)

WBCs have an extended circulation time in the bloodstream via self-recognition receptors on their membranes, such as CD47-like RBCs. As a result, the nanoparticles coated with CMVs from WBCs offer various

promises in biomimetic camouflage tactics for avoiding opsonization and phagocytosis clearance [53]. For example, the liposomes coated with WBCs show the advantage of increasing the blood circulation time of the nanomaterials by evading the renal clearance mechanism [54]. WBC proteins can be used for detecting inflammation or diseased regions and for participation in biological activities [55]. Specifically, WBCs can bind to target cells via ligand-receptor-mediated recognition with numerous proteins on their membranes, such as lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (MAC-1) [55]. Furthermore, WBC membranes show the ability to migrate through tissues [56]. Thus, the coating approach with CMVs from WBCs demonstrates multiple advantageous properties, such as bypassing the vascular barrier, improving permeability across the endothelium, and effectively accumulating in the target region, including cancer cells [53,54,57]. For instance, leukocyte membrane-coated nanoparticles recognized and actively targeted HeLa cancer cells with a longer motion time and penetration capacity [58].

3.4. Platelets (PLTs)

PLTs are vital circulating sentinels in the bloodstream. In the realm of advanced biomaterials, the cloaking approach permits CMVs from PLTs to conceal various nanoparticles. The nanoparticles coated with PLT-derives CMVs exhibit Increased blood retention because of immune avoidance and phagocytosis evasion by the "self-recognized" proteins [59]. PLTs can respond to damaged vascular sites and invasive microbes by initiating repair processes. Meanwhile, due to its significant contribution to tumor metastasis via receptor-ligand interactions, such as P selectin-P selectin ligand, II6 3 integrin-fibrinogen, and integrins-collagen, the identification and interaction between platelets and cancer cells or circulating tumor cells (CTCs) in the bloodstream was recently revealed [59]. Thus, PLT-functionalized nanoparticles can be designed to target various cells, such as damaged vasculatures, tumor tissues, and CTCs [60,61]. The PLT-coated nanoparticles retain the surface proteins of the PLTs, which led them to target cancer cells and CTCs via P-Selectin and CD44-receptor-mediated receptor-mediated active targeting mechanisms. Thus, the encapsulated core agents were successful in delivering anticancer drugs [61]. Because CMVs from PLTs preserved their natural cancer cell-targeting capacity while reducing macrophage cell uptake [59,62], in comparison to naked nanoparticles, activated PLT-CMVs-coated nanoparticles targeted circulating tumor cells via receptor-ligand interactions. For example, Rao et al. demonstrated that PLT-CMVs coated nanocarriers effectively targeted squamous cell carcinoma while also lengthening blood circulation time [60].

3.5. Macrophages

Macrophages exhibit a variety of phenotypes in response to various stimuli. They are categorized into two subsets known as M1 and M2 cells [63]. To eliminate infectious microbes and assist the Th1 immune response, activated macrophages (M1) generate proinflammatory cytokines. On the other hand, polarized M2 macrophages support Th2 immunity, suppress immune responses, and facilitate tissue remodeling and wound healing [63,64]. With the help of proteins on the cell membrane surface, macrophages enable to receptor-mediated actively target multiple cells and offer camouflage [65]. Macrophages are abundant in the tumor environment and are linked to tumor growth and metastasis [66], and actively adhere to metastatic cancer cells in lung metastases because macrophage integrins bind to vascular cell adhesion molecule-1 s (VCAM-1) expressed in cancer cells [67,68]. Thus, CMVs from M1 macrophages, which possess leukocyte-derived adhesion molecules such as LFA-1, enabled intravenously injected to target tumors [69]. Biological features of macrophages that were introduced to nanoparticles by macrophage cell-membrane coating include improved active-targeting efficacy by membrane proteins and extended blood circulation time for sustained systemic distribution for cancer therapy [70]. For instance, Doxorubicin-loaded nanoparticles coated with macrophage CMVs demonstrated tumor-tropic targeting, prolonged bloodstream circulation, and reduced RES organ accumulation in macrophages in the body [71]. Estansin-loaded liposome coated with CMVs from macrophages to enhance cellular uptake by metastatic 4T1 breast cancer cells. As a result, their capacity to target metastasis was improved, and lung metastasis was effectively mitigated [72]. Recently, gold nanorods coated M1 macrophage-derived CMVs maintain tumor homing effect from M1 macrophage-derived CMV [73]. M1 CMVs exhibited a targeting ability to lymph nodes, primarily taken up by dendritic cells and local macrophages, and they evoked the release of a Th1 cytokines pool [74]. Activated macrophages play a crucial role in innate immunity as well as the initiation of the adaptive immune response. As a result, CMVs from proinflammatory immune cells would be used to boost a vaccine's immune response [75,76]. CMVs from M1 macrophages repolarize protumor M2 macrophages to antitumor M1 macrophages, leading to a boost in the anticancer efficacy of immune checkpoint inhibitors like anti-PD-L1 in the tumor microenvironment via interactions between activated T cells and M1 macrophages [76]. For example, M1, but not M2, CMVs increased the efficacy of a lipid calcium phosphate (LCP) nanoparticle-encapsulated Trp2 vaccine and evoked a stronger antigen-specific cytotoxic response from T-cell. In melanoma growth inhibition research, M1 CMVs proved to be a more powerful immunopotentiator when combined with the LCP nanoparticle vaccine [74]. These results imply that CMVs from M1 can act as an endogenous immune regulator in cancer immunotherapy.

3.6. Cancer cells

Cancer cells carry abundant cell adhesion molecules on their membrane, exhibiting source cell-specific targeting capacity, reflecting the homotypic binding mechanism frequently observed in malignancies [77]. CMVs from cancer cells target recipient cells by particular receptor-mediated internalization since tumor cells have more overexpressed proteins on their surface than normal cells [78]. To employ cancer-homing capabilities, which originate from surface proteins behaving like tumor-specific antigens, R. Yang et al. developed an adjuvant called imiquimod-loaded nanoparticles coated with melanoma cancer cells [79]. Cancer nano-vaccines for cancer prevention and treatment successfully induced anticancer immune responses and improved tumor targeting with surface proteins acting as tumor-specific antigens [79]. Many researchers have created different cancer cell CMV-coated nanoparticles as DDSs for specific diseases because each type of cancer cell can target various tissues or cells. For example, Xiao, Long, et al. produced a nano-vaccine that has a tumor-tropic targeting ability by modifying biodegradable PLGA with cancer cell membranes [80]. The nanoparticles were composed of an antigenic outer shell that closely resembled the donor cancer cells. The nanoparticles coated with CMVs from cancer cells were used as a vaccination platform presenting tumor-associated antigens from the cancer cell membrane [80,81]. These nanoparticles were efficiently delivered to professional antigen-presenting cells and boosted anticancer immune responses while having the potential to target tumor cells. By virtue of the donor cell line, the nanoparticle, which was coated cancer cell membrane, escaped the immune system [82]. That is why tumors defend themselves from T cell attacks by employing immune checkpoints, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death ligand 1 (PD-L1), and programmed cell death protein-1 (PD-1) [83].

3.7. Bacterial cells

Bacterial membranes can allow nanocarriers to bind to and become internalized into mammalian cells. Furthermore, because of the robust protective immune response to the source infections, coating bacterial outer membranes onto synthetic nanoparticles could preserve the intricate biological properties of bacteria and bio-mimic the intrinsic

antigen presentation to the immune system. For example, Paukner et al. developed a Dox delivery system using bacterial CMVs produced from *Mannheimia haemolyticathe* [84]. These bacterial CMV-coated nanocarriers bound to human colon cancer cells with high mammalian cell affinity, resulting in substantial antiproliferative effects, compared to free DOX. Plus, these nanocarriers successfully reduced the severe toxic side effects of anticancer medicines due to the avoidance of immune response by bacterial CMVs [84]. Long-distance transport of proteins, toxins, antigens, virulence factors, microbicidal agents, and antibiotics is possible because the bacterial membrane can evade the host immune system, protect the therapeutic payload, and have naturally high stability due to a thicker peptidoglycan layer [85]. Gram-negative bacterial membrane-coated nanocarriers were stable liposome-like vehicles that can protect the encapsulated medications. Interestingly, these coated nanoparticles bound to and were ingested by most murine macrophages via interaction with proteins on mammalian cell surfaces, such as sugars of LPS-lectins, CD14 receptor, or Toll-like receptor TLR-4 [86–88]. Bacterial membranes have a vital function in bacterial infection in the human body, but they can also play a protective role in reducing inflammation caused by commensal bacteria in the gut [85,89]. Bacterial CMVs perform intracellular communication, including horizontal gene transfer between different bacterial species, immunomodulation in a potential host, assistance in the creation of bacterial biofilms, and many more. The *Escherichia coli* bacterial membrane comprises viral immunogenic antigens with innate adjuvant capabilities. Pathogen-associated molecular patterns (PAMPs) can play an important role in inducing both innate and adaptive immune responses [90,91]. For instance, outer-membrane vesicles from *Escherichia coli* were coated with nanoparticles to develop antibacterial vaccination [92]. These nanocarriers activated dendritic cells and induced their maturation. In the lymph nodes of vaccinated mice, the bacterial CMV-coated nanoparticles induced fast activation and maturation of dendritic cells. The bacterial CMV-coated nanoparticles also led to an increase in the production of interferon-gamma (IFN-γ) and interleukin-17 (IL-17), but not interleukin-4 (IL-4), showing that they can trigger robust Th1 and Th17-biased cell responses against E. coli bacteria [93]. Immune-activating nanoparticles coated with bacterial CMVs derived from *Mycobacterium smegmatis* achieved strong activation in the human immune system [92]. In addition, they successfully captured cancer neoantigens, resulting in a potent anticancer impact and antitumor immunological memory [92]. Therefore, bacterial membranes have emerged as a new material for DDSs or vaccines.

3.8. Multiple cell lines

After fusing multiple CMVs with some methods such as free-thawing, co-extrusion, and probe-sonication [94–97], the multiple CMVs cover nanoparticles to improve nanocarrier performance by combining the functionalities of different types of cell membranes. For example, fusing RBC and platelet membranes to produce hybrid vesicles is a great strategy as a DDSs because the hybrid vesicles exhibit increased circulation times and accumulated in micro thrombosis locations [95,97]. Therefore, the hybrid vesicles maintain both properties of RBC and platelet. Rao and colleagues hybridized two types of membranes for hybrid vesicles: platelet and leukocyte membranes [94]. The WBC membrane component of these hybrid vesicle-coated nanoparticles can avoid WBC contact. Because both WBC and platelet membrane enabled adhesion to cancer cells, these hybrid vesicle-coated nanoparticles sufficiently isolate circulating tumor cells with the magnetic property of nanoparticles [94]. Wang and colleagues combined RBC membranes with B16-F10 melanoma cells to achieve prolonged blood circulation times and melanoma-homogenous targeting [96]. After hybridization, they used these hybrid vesicles to coat the nanoparticle, and they successfully targeted melanoma cells as well as eradicated tumors via photothermal effects [96].

3.9. Others

The possibility of using other cell types for CMV sources offers great promise in the development of diverse drug delivery systems. For example, Anti-Zika virus (ZIKV) CMVs were made with camouflaged host cell membrane-derived vesicles from the mosquito-medium-host-Aedes-albopictus shell, which efficiently adsorbed ZIKV and suppressed ZIKV replication in ZIKV-susceptible cells. ZIKV virus can be captured by cell-membrane vesicles, reducing ZIKV-induced inflammatory and degenerative processes [15]. As a result, this approach can be used in anti-viral applications as the shell component can absorb viruses and shuttle them away from targeted cells. The activated fibroblast cell membrane-masked nanoparticles demonstrated homologous targeting ability to cancer-associated fibroblasts [21]. Therefore, opportunities lie in manufacturing customized nanocarriers by selecting appropriate nanoparticles and specific cell membranes.

4. Novel strategies by combining CMVs with nanomaterials for a DDS

Some technologies have been developed and employed to circumvent several issues of CMVs, such as a low yield in production and poor stability in a biological milieu. In this section, we introduce some strategies to overcome the CMVs' limitations of poor stability and low yield. One is the fabrication of hybrid vesicles composed of CMVs and synthetic liposomes (SLs) that have better stability due to cholesterol. Another is the core/shell nanostructure which is composed of the core part (nanoparticles) and the shell part (CMVs). The other is the CMVs-loaded hydrogel strategy. All strategies can successfully retain the unique properties of CMVs, and these nanoparticles exhibit better stability and higher yield (Fig. 3).

4.1. Membrane fusion with synthetic liposomes or amphiphilic polymers

One of the prominent techniques is membrane fusion with SLs composed of synthetic lipids and cholesterols or with synthetic amphiphilic polymers by several methods, including freeze-thaw, incubation-mediated, gently shaking, and extrusion-based membrane fusion processes [98–102] (Fig. 3). SLs also exhibit similar properties with cellular membranes, such as reduced toxicity, good biocompatibility, protected drug degradation, constant entrapment volume, excellent surface flexibility, ease of step-by-step functionalization, and improved site-specific targeting ability with specific ligands [103–106]. The size, surface charge, components, and other features of SLs can be finely tuned depending on their targeted applications [107]. However, SLs cannot effectively display the variety and complexity of natural features of the native cell membrane. Because SLs are artificially synthesized from artificial materials, they are generally considered not as safe as CMVs *in vivo*. Accordingly, hybrid vesicles produced by the fusion of CMVs, and SLs have recently been developed as an alternative to combining the beneficial properties of natural CMVs and artificial SLs. Especially, this approach is practical when producing functional nanovesicles with a small amount of CMVs which are hard to produce. As CMVs and SLs are structurally similar lipid bilayers in terms of size and components, a fusion of these two lipid-based nanomaterials is feasible and effective [26]. To validate the hybridization between the two types of cell membranes, researchers usually utilize förster or fluorescence resonance energy transfer (FRET) study and protein assays for surface proteins [95]. The hybrid vesicles can simultaneously exhibit the CMVs' endogenous nature (e.g., cell membrane proteins) and the liposomes' easy surface modification (e.g., size, surface charge, and protein conjugation). For example, hybrid vesicles, which are fused with activated natural killer (NK) cell membranes and doxorubicin (DOX)-loaded cationic liposomes, maintained biological properties of specific proteins (e.g., CD56, NKG-2D, NKp30) on the source cell membrane and successfully loaded the DOX. The hybrid vesicles can recognize and bind to

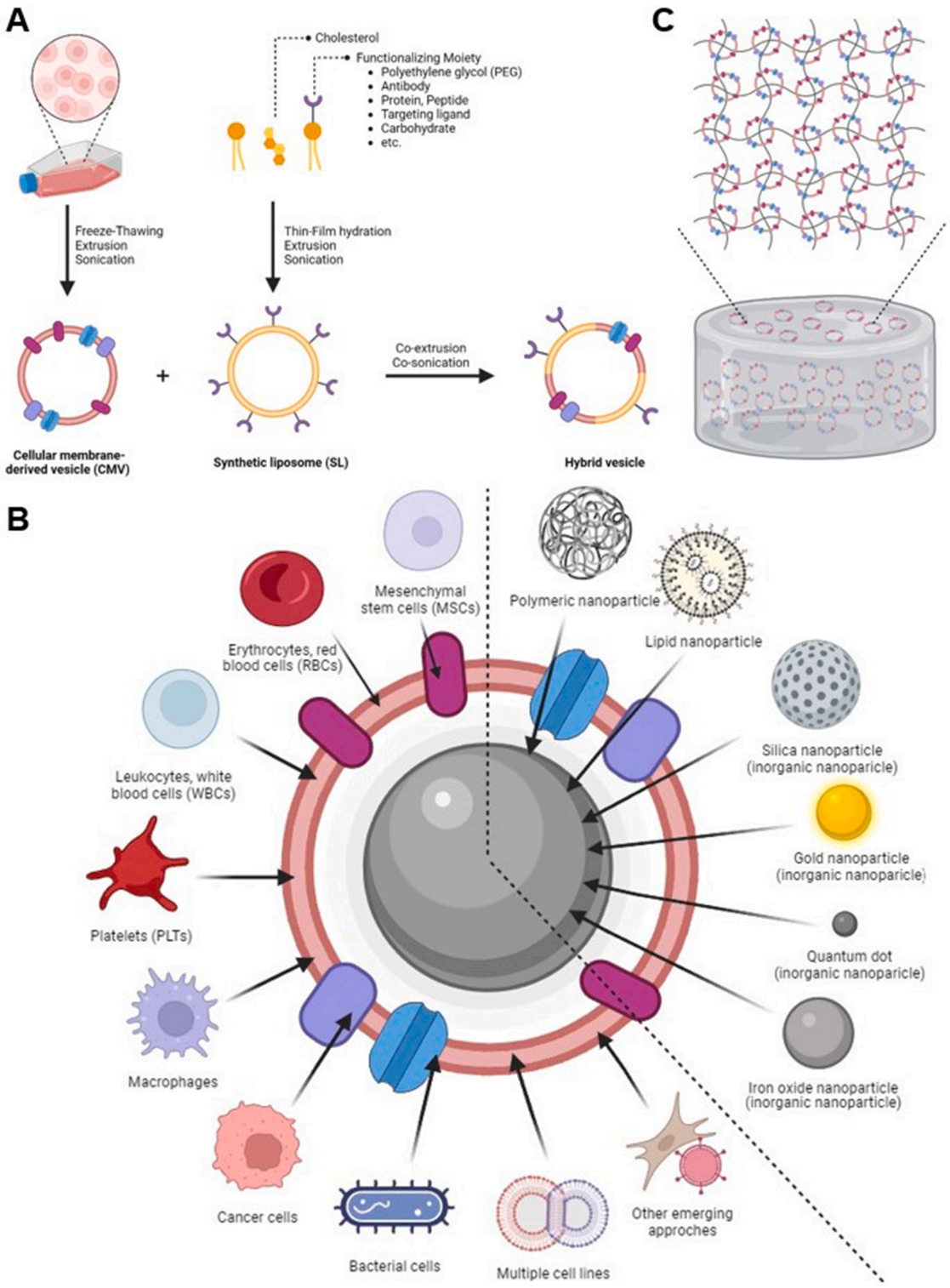

Fig. 3. Three strategies to overcome the limitation of cellular membrane-derived vesicles (CMVs) such as low yield and poor stability for applying CMVs as a drug delivery system (DDS). A: The hybrid vesicles composed of CMVs and synthetic liposomes (SLs) can maintain CMV's function such as active targeting ability and SL's functions with functionalizing moiety, including higher stability. Various methods, such as freeze-thawing, extrusion, sonication, and thin-film hydration, can be used for manufacturing CMVs or SLs, and the co-extrusion method is usually exploited for fabricating hybrid vesicles. Natural ligands from CMVs allow the hybrid vesicles to selectively target cells or tissues, while functionalized SLs improve the production yield and stability of CMVs. B: Various core/shell nanocarriers, composed of CMVs and nanoparticles, have been developed to increase low yield, and improve poor stability. The shell part (CMVs) gives the nanocarriers an active targeting mechanism and avoids immune response. CMVs, isolated from stem cells, red blood cells, white blood cells, platelets, macrophages, cancer cells, bacterial cells, multiple cell lines, and other cells, have the parent cell's properties such as targeting ability and presenting "do not eat me" antigens. Nanoparticles can be chosen based on bio-application proposals. C: Instead of modifying CMVs or adding nanoparticles, a hydrogel can be used for loading CMVs. Because hydrogel can protect CMVs, the structure exhibits excellent stability, resulting in sustained release of CMVs near the targeted sites. Created with BioRender.com.

the overexpressed surface-stress-markers on human breast cancer cells and enhance the tumor-homing ability due to the maintained CMV proteins [108]. A fusion of CMVs from macrophage-derived extracellular vesicles with SLs led to producing hybrid vesicles that retained the tumor-targeting capabilities of macrophages through the transmembrane proteins (CD9, CD63, and CD81), integrin alpha M proteins, and tumor susceptibility gene 101 proteins. Y.T. Sato et al. hybridized the HER3 receptor overexpressed CMVs from genetically engineered macrophage cells (RAW264.7) with SLs to generate hybrid vesicles presenting the HER3 receptors [99]. They further demonstrated that interactions between SLs and macrophages could be controlled by adjusting the composition of the synthetic lipids [99]. Hybrid vesicles can be further used to efficiently deliver genes to living cells. For example, Y. Lin et al. transfected mesenchymal stem cells with plasmids using hybrid vesicles prepared by hybridization of CMVs isolated from HEK293FT cells and lipofectamine 2000 [100]. The hybrid vesicles demonstrated enhanced encapsulation of large nucleic acids compared to CMVs, and showed characteristics of cargo release into mesenchymal stem cells, showing the strong potential of the hybrid vesicles as a DDS [100]. Hybridization tactics with SLs and CMVs have been shown to improve the weak stability of CMVs by borrowing the liposomes' improved **stability** upon freeze-drying, chitosan modification, surfactant addition, or incorporation of polymer gels [26,109]. The colloidal and lipid chemical stability of liposomes can be improved by surface modifications and functionalization [107]. For instance, the incorporation of polyethylene glycolylation (PEGylation)-lipid derivatives, such as PEG phospholipids, into the membrane of SLs can improve liposome stability by providing a sterically protective barrier against RES and plasma proteins and, thus, increasing blood circulation times [110–112]. There have been several attempts to improve the stability and yield of CMVs using various functional SLs. PEGylated liposomal doxorubicin (Doxil®, Caelyx®; Alza Pharmaceuticals, San Bruno, CA, USA) was shown to have a long-circulation time with a half-life of 55 h in humans [113]. Some researchers demonstrated that the hybridization of CMVs with PEGylated liposomes could improve the stability of CMVs. Sato et al. synthesized hybrid vesicles by fusing Raw264.7 cell-derived CMVs and PEG-modified liposomes [99]. The hybrid vesicles can extend the blood circulation time because of PEG structures [99]. Similarly, Piffoux et al. hybridized PEGylated liposomes with CMVs to produce hybrid vesicles with increased blood circulation time [98]. Song et al. examined the release performance of hybrid vesicles composed of platelet membrane and synthetic lipid, and platelet CMVs, resulting in a much slower release profile of hybrid vesicles than that from platelet CMVs [114]. The stability of CMVs was far less than hybrid vesicles. In contrast, compared with CMVs, hybrid vesicles composed of CD47-expressing tumor CMVs and cRGD-modified liposomes exhibited improved stability in the bloodstream because their particle size remained around 125 nm, and the PDI was less than 0.2 for 7 days [115]. Plus, when these hybrid vesicles were i.v. injected into tumor-bearing nude mice, a strong fluorescence signal in the tumor sites was observed after 4 h, which lasted for 48 h [115].

Furthermore, synthetic amphiphilic polymers have been hybridized with CMVs. Natural CMVs and synthetic amphiphilic polymers were combined to synthesize cell-like hybrid nanocarriers for both artificial properties and cell-like advantages such as signaling and recognition [116]. For example, human membrane vesicles from HEK293 cells were hybridized with Janus dendrimer to produce self-assembled dendrimersomes [117]. Since the thickness between the Janus dendrimers and biological membranes was similar, they can be easily co-assembled to fabricate cell-like hybrid vesicles. The hybrid vesicles considerably enhanced their stability for at least a year [117]. Bacterial membrane vesicles from *Escherichia coli* cells were co-assembled with the same dendrimersomes. These hybrid vesicles contained YadA, a family of bacterial adhesion proteins on the outer membrane, allowing the identification of living cell membranes [117].

4.2. Core/Shell structure of CMV-coated nanoparticles

The other eminent technique is core/shell structure composing CMVs coated nanomaterials. These nanostructures are made up of two parts: an inner core (nanoparticles) and an outer shell (CMVs). Core/shell nanostructures provide unique advantages in DDSs, including improved stability, high loading efficiency, and sustained drug release profiles because of the nanoparticles' properties (Fig. 3). On top of that, we can utilize the unique features of various nanoparticles, such as silica nanoparticles [41,43,82], poly (lactic-co-glycolic acid) [50,79], magnetic particles (gadolinium, Fe_2O_3, Fe_3O_4) [14,59], gold nanoparticles [18,73,93], nanogel [61], synthetic liposome [72], and gelatin nanoparticles [15]. Coating nanoparticles within CMVs requires some techniques, such as reverse-phase evaporation [118–120], sonication [121, 122], extrusion [123–125], freeze-thawing [120,126], ethanol interdigitation [127,128], and double emulsification technique [129]. Additionally, when nanoparticles and vesicles have opposite charges, they can assemble due to electrostatic attraction [130,131]. Core/shell nanocarriers have much-improved stability, allowing nanoparticles to be maintained in biological solutions (e.g., buffers or aqueous phases) during extended periods [132]. The core/shell nanocarriers can overcome the difficulties of duplicating specific components and functions of cells since the shell can carry natural elements. In other words, cloaking nanoparticles with outer surface composing CMVs is a bioinspired approach that gives bio-mimics to the core and exhibits the functions of the cell membrane.

With the adaptability and intricacy of cellular membranes, directly coating nanoparticles with CMVs endows nanoparticles with various biological benefits, such as participating in cellular signaling pathways, and active targeting [133]. CMV-coated nanoparticles can display the original CMV characteristics, including immune evasion and targeting ability. Like CMVs, CMV-coated nanoparticles can bind to specified tissues or cells in an active and non-destructive manner [16]. Furthermore, cell-specific functionalities would be exploitable as functional coating components [134,135]. Not only may cell membrane-coated nanoparticles utilize complicated biological contents and functions that are otherwise difficult to produce, but they can also keep the highly controllable physicochemical properties of synthetic nanoparticles, such as particle size and shape [136].

Based on CMV-coating platforms, various nanoparticles have been examined to replicate natural cellular functions from stem cells, erythrocytes, leukocytes, platelets, macrophages, bacteria, cancer cells, and dendritic cells [69,137]. Masking nanoparticles with CMVs from various cell types has allowed the incorporation of the unique biological characteristics of source cells for diversiform applications in biomedical engineering. In particular, CMVs from autologous cells improve the immune tolerance of the encapsulated agents. Different types of cell membranes can be hybridized with various nanoparticles for specific aims via a membrane fusion mechanism [82]. Plus, the original functionalities of nanoparticles can be maintained for DDSs after CMV coating. When nanoparticles and CMVs are together, the nanostructure can process both benefits from the nanoparticles and CMVs. For example, silica-based nanoparticles, such as porous silica nanoparticles (SiO_2NPs) and mesoporous silica up-conversion nanoparticles (UCNPs@SiO2), can be successfully coated with CMVs from MSC [41, 43]. These nanoparticle types exhibit high loading efficacy of multiple cargoes because of the porous structure, and directly home to tumors with extended blood circulation compared to naked nanoparticles due to the properties of MSCs after intravenous injection, resulting in effectively delivering photosensitizers to the target cells [41,43]. RBC CMVs coated gold nanoparticles maintained the adjustable near-infrared (NIR) absorbance and photothermal conversion efficiency from gold nanoparticles even after RBC-membrane coating and also exhibit long circulation time in the bloodstream by RBC CMVs [18]. Engineering the core and shell nanostructures of leukocyte membrane-coated gallium nano-swimmers (LMGNSs) successfully provided multifunctionality for

a targeted medication delivery method [58]. The asymmetric needle-like core of the nanoparticles allowed controlled guidance by an acoustic field, and the leukocyte membrane recognizes and actively targets HeLa cancer cells with extended motion time and effective penetration due to the leukocyte membrane [58]. PLT membrane-coated gold nanorods (AuNRs) showed potential as a DDS for photothermal therapy owing to the core's photothermal capabilities and natural cancer-targeting capacity while also lengthening blood circulation time because of PLT membrane [60], resulting in the encapsulated core agents were successful in delivering anticancer drugs [61]. Fe_3O_4 nanoparticles coated with PLT-derived vesicles can be utilized for photothermal therapy and tumor magnetic resonance imaging based on the unique optical and magnetic properties of Fe_3O_4 nanoparticles and preferential adherence to tumor tissues from PLT membrane [59]. The shell and core of activated fibroblast cell membrane-masked semiconducting polymer nanoparticles demonstrated homologous targeting ability to cancer-associated fibroblasts and efficiently produced photodynamic and photothermal characteristics [21]. Furthermore, the unique properties of various nanoparticles are retained after coating with hybrid vesicles from different two types of cell lines. For example, Rao and colleagues developed hybrid vesicle (platelet and leukocyte membrane) coated Fe_3O_4 magnetic beads, which can WBC membrane component of these hybrid vesicle-coated nanoparticles can avoid WBC contact [94]. Both components from WBC and platelet membrane enabled adhesion to cancer cells. These coated nanoparticles sufficiently isolated circulating tumor cells with the preserved magnetic property of Fe_3O_4 [94]. In another study, hybrid vesicles produced by co-extrusion of RBC and platelet membranes exhibited increased circulation times and accumulated in micro thrombosis locations. The dual membranes were subsequently coated onto polypyrrole nanoparticles and subsequently utilized for photothermal anti-tumor therapy [97]. Wang and colleagues combined RBC membranes with B16-F10 melanoma cells to achieve prolonged blood circulation times and melanoma-homogenous targeting. After hybridization, they used these hybrid vesicles to coat hollow copper sulfide nanoparticles and successfully targeted melanoma cells as well as eradicated tumors via photothermal effects [96]. In Table 2, We describe various studies of core/shell nanostructures composed of CMV-coated nanoparticles for DDS applications. The core/shell strategies improve the stability of CMVs, and the shell part (CMVs) can be surface modified. For instance, natural RBC membranes can spontaneously possess active-targeting capabilities by translating targeting ligands to RBC membrane-coated nanoparticles for cancer therapy by adding lipid-tethered targeting ligands due to the improved stability of RBC membrane with nanoparticles [138]. Because E-selectin (ES) and tumor-specific apoptosis-inducing ligand (TRAIL) bioconjugated liposome coated with WBC, adhesion receptors to lymphatic tissues and tumor necrosis factor, respectively, they can bind to cancer cells via ligand-receptor-mediated recognition and induce apoptosis because of the liposome and increasing blood circulation time of liposome by evading renal clearance mechanisms [54]. Apoptosis mediated by the TRAIL-death receptor can selectively kill cancer cells by the cytotoxic activity of NK cells [54].

4.3. Combination with scaffold materials and CMVs

CMVs greatly limit the therapeutic function because of the rapid degradation from circulation and short half-life in less than 24 h post-injection [139,140]. Rapid clearance from the target site may reduce the efficacy of systemically administered CMVs. Above two methods, we focused on improving CMVs' stability by hybridizing with SLs or coating with nanoparticles. But in this section, we introduce the potential in sustained release of therapeutic agents from CMVs by using a scaffold structure. The CMV/scaffold complexes can be applied directly to disease sites, acting as sustained-release DDSs by extending the CMVs' retention time, preventing enzymatic digestion or mass diffusion away from the area. This strategy is preferable to CMVs or drug intravenous injection, which may result in off-target CMV accumulation. Recent *in vivo* studies have shown that CMV/scaffold complexes are superior to EV bolus injection in terms of EV retention rates [141–143]. Interestingly, the sustained release of CMVs loaded therapeutic drugs exhibit a more prominent therapeutic effect rather than the conventional bolus injection [144]. Hydrogel can preserve CMVs, resulting in improved stability of components in CMVs by the adjustable mechanical and physical properties of hydrogels, which exhibit high elasticity and capability to retain the shape [145]. Because of the gradual degradation of hydrogel, loaded agents in CMVs are sustainably released over the long term, minimizing the drawback caused by the rapid clearance of CMVs [146, 147]. When applied to injury sites, CMVs on the scaffold would be protected and released from the scaffold in a sustained manner, and allowing them to communicate with endogenous cells and CMVs' components for the remodeling process [141]. For example, MSC-derived CMVs in chitosan hydrogel can induce the prolonged release of CMVs, and dramatically increase the retention of CMVs *in vivo* due to the chitosan hydrogel [148]. Moreover, MSC-derived CMVs successfully retain the potential of CMVs for skin aging treatment. MSC-derived CMVs can significantly enhance the biological functions of senescent fibroblasts, resulting in boosting the synthesis of extracellular matrix proteins, and preventing the overexpression of matrix metalloproteinases [148]. Tang Q et al. combined thermosensitive chitosan-based hydrogels (CHI hydrogel) and CMVs isolated from induced pluripotent stem cell-derived MSCs (iPSC-MSCs) [149]. The CHI hydrogel sustained released iPSC-MSC CMVs that contained miR-432–5p, resulting in effectively enhancing stroma and corneal epithelium regeneration, downregulating coding of mRNA expression for the three richer collagens (collagen type I alpha 1, collagen type V alpha 1 and collagen type V alpha 2) in the corneal stroma and lowing scar formation *in vivo* [149]. Therefore, the iPSC-MSC-induced CMV thermosensitive hydrogel system has the potential for reducing the injury of the corneal epithelium, lowing scar formation, and accelerating their healing. Mardpour Soura, et al. developed biodegradable hydrogel for encapsulation and sustained release of liver-targeting embryonic stem cell-derived MSC-CMVs [144]. Gradual swelling of the CMV-laden tetra-PEG hydrogel during biodegradation resulted in sustained CMV release *in vitro* and *in vivo* over 4 weeks [144]. Furthermore, the sustained systemic release (Gel-CMVs) exhibits superior anti-inflammation, anti-apoptosis, anti-fibrosis, and regenerative effects of the CMVs to nearly 50, 40, 40, and 50% respectively, when compared to the conventional bolus injection [144]. Therefore, prolonging the bioavailability of MSC-CMVs through sustained systemic delivery may enable them to exert therapeutic effects. According to these studies, the strategy of sustained systemic release can be considered a novel paradigm for DDSs with CMVs loaded with therapeutic agents, which offers long-lasting effects, particularly for chronic diseases. CMV/scaffold complexes can be developed via various biomaterials like hydrogel and optimized for tissue-specific or disease-specific applications.

5. Conclusion

CMVs have sparked great interest in DDSs because CMVs can exhibit the biological characteristics of source cells, such as high biocompatibility, targeting ability, cell communication, and signaling with specific cells. However, several limitations need to be overcome for their use in clinical settings, such as low yield and poor stability. Three novel solutions have been recognized as promising methods to address such issues. First, cell-like hybrid vesicles prepared from natural CMVs, and SLs display respective beneficial properties. Furthermore, bioengineered SLs can be easily incorporated into native CMVs, promoting the product yield and stability of the vesicles. The second approach is to coat nanoparticles with CMVs to disguise the nanoparticles and create a core/shell nanocarrier. The advantages of the synthetic nanoparticles and the biological features of source cells (i.e., intrinsic cellular processes) are preserved. These core/shell nanocarriers have the potential

Table 2
Core/Shell nanocarrier consisting of CMVs and nanoparticles for various applications.

Shell	Core	Agent	Shell function	Core advantage	Core disadvantage	Platform function	Refs.
Stem-cell CMV	Porous hollow silica nanoparticle (SiO_2NP)	Hydrophobic photosensitizer drug (purpurin-18 (Pp-18))	- Cancer-targeting	- High loading capability - Uniform cylindrical pores - Easy to fabricate - Tunable properties - High bioavailability - High chemical and thermal stability	- Low tumor affinity - Systemic toxicity - Poor biodegradability - Scattered size distribution - Formation of stable-colloidal suspension	- Antitumor efficacy - Photodynamic therapy (PDT) system	[41, 150]
	Poly (lactic-co-glycolic acid) (PLGA)	Vascular endothelial growth factor (VEGF)	- High penetration - Decreased uptake by macrophages - Bioconjugation with CXCR4-receptors	- High loading capability - Biocompatible - High stability -Tunable properties - Sustained release	- Harsh fabrication processes enzymes and proteins - High aggregation - Difficulty in handling	-Targeted delivery to ischemic hindlimbs	[45, 151]
	Mesoporous-silica-coated upconversion nanoparticles (UCNPs@mSiO2)	Multiphotosensitizers (ZnPC and MC540)	- Long blood circulation - Tumor-targeting - Overcoming vascular barriers	- Nano-transducer - Remarkable anti-Stokes shift capability - Deep penetration into tissue - Uniform cylindrical pores - High chemical and thermal stability	- Poor dispersion in tumors - Limited immune escaping ability - Low tumor affinity - Unfit for i.v. injection	- Antitumor efficacy - Tumor-targeted PDT system	[43]
Red blood cell (RBC) CMV	Fe_3O_4	–	- Long blood circulation - Little change between the first and second doses - No accelerated blood clearance (ABC)	- Magnetic properties	- Poor active targeting ability - Systemic toxicity - Poor biodegradability	- Efficient drug delivery system - Molecular imaging system	[14, 152]
	Poly (lactic-co-glycolic acid) (PLGA)	Fluorophore	- Long blood circulation - Equivalent serum stability	- High loading capability - Biocompatible - High stability -Tunable properties - Sustained release	- Harsh fabrication processes enzymes and proteins - High aggregation - Difficulty in handling	- Long-circulating cargo delivery platform	[50, 151]
	Poly(vinylpyrrolidone) gold nanocage (PVP-AuNC)	–	- Long blood circulation - Conjugation with lipid-tethered targeting ligands - Good colloidal stability	-Tunable near-infrared (NIR) absorption - High photothermal conversion efficiency - Porous and hollow structure - Biocompatible	- Short blood circulation lifetime - Limited tumor uptake - Possible toxicity issues from chemical contaminants during synthesis - Less direct anti-cancer effect	- Photothermal therapy (PTT) system - Anticancer efficiency	[18]
Leukocytes, white blood cells (WBC) CMV	Nanoporous Silicon particle (NPS)	Doxorubicin	-Long blood circulation -Binding inflamed endothelium - Facilitating transport across the endothelial layer	- Loading various cargoes - Protection of the cargoes	- Short blood circulation lifetime due to opsonization and non-specific clearance	-Tumor endothelium targeting platform	[57]
	Needle-shaped gallium core	Doxorubicin	- Anti-biofouling - Prolonged motion in biological medium - Cancer-targeting	- Ultrasound-propelled motion - Tunable velocity and direction by alternating frequency and voltage in ultrasound field	- Poor anti-biofouling - Poor active targeting ability	- Anticancer efficiency	[58]
Platelet (PLT) CMV	Fe_3O_4 magnetic nanoparticle (MN)	–	- Long blood circulation - Tumor-targeting - Selective adhesion to damaged vasculatures - Lack particle-	- Magnetic properties - Broad optical absorption properties in the near infrared range	- Poor active targeting ability - Systemic toxicity - Poor biodegradability	- Personalized cancer theragnostic - Tumor magnetic resonance imaging (MRI)	[59, 152]

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Table 2 (*continued*)

Shell	Core	Agent	Shell function	Core advantage	Core disadvantage	Platform function	Refs.
			induced complement activation			system	
	Gold nanorod (AuNR)	–	- Long blood circulation - Cancer-targeting - Accumulation in injured tissues	- Photothermal property - Good colloidal stability - High NIR penetration - No change in morphology	- Poor active targeting ability - Short blood circulation lifetime - Poor bio-distribution	- PTT system - Targeted platform - PTT system - Antitumor efficacy	[60, 153]
	Nanogel	Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), doxorubicin (Dox)	- Minimized immunogenicity - Long blood circulation - Tumor-targeting - Vascular injury site-targeting	- Loading capability of hydrophilic and hydrophobic agents - Various administration route - Controlled release	- Interaction between agents and polymer, resulting in reduced hydrophilicity, wrecked structure, and irreversible entrapping of agents - Presence of surface-active agents or monomers - Restrained drug loading capability	- Sequential and site-specific delivery platform - Anticancer efficacy	[61, 154]
	Monodisperse silica (Si) particle	Tumor-specific apoptosis-inducing ligand cytokine, TRAIL	- Long blood circulation - Tumor-targeting	- Improved stability of the ligand - High bioavailability - Easy to fabricate	- Systemic toxicity - Poor biodegradability - Scattered size distribution - Formation of stable-colloidal suspension	- Neutralizing CTCs to attenuate metastasis	[62, 150]
Macrophage CMV	Mesoporous silica nanoparticles (MSNs)	Hydrochloride doxorubicin (DOX)	- Arrested immune system - Long blood circulation - Camouflage function - Tumor targeting ability	- High loading capability - Uniform cylindrical pores - Easy to fabricate - Tunable properties - High bioavailability - High chemical and thermal stability	- Low tumor affinity - Systemic toxicity - Poor biodegradability - Scattered size distribution - Formation of stable-colloidal suspension	- Biomimetic drug-delivery platform - Antitumor efficacy - Targeted delivery system	[65, 150]
	Silica-Coated Gold nanoshells (AuNS)	–	-Tumor endothelium targeting ability - Long blood circulation	- Photothermal property - Good colloidal stability - Effective optical adsorption	- Poor active targeting ability - Short blood circulation lifetime - Less direct anti-cancer effect -Altered sensitivity dependent on tissues to heat exposure	-PTT system -Antitumor efficacy	[70, 153]
	Drug-carrying liposome	Emtansine	- Metastatic cells-targeting ability	- Loading capability of hydrophilic and hydrophobic drug - Biocompatible - Flexibility of membrane components - Capability of surface modification - Modifiable pharmacokinetic behavior	- Physical instability in liquid state - Lysolipid formation by chemical degradation - Drug leakage - Disruption in the stomach - Low permeability of intact liposome in the GI tract	- Targeted delivery system - Anticancer efficacy	[72, 155]
	Gold nanorods	Gemcitabine, CpG ODN, PD-L1	-Tumor-specific targeting ability - Long blood circulation - immune-reprogramming - Regulating the tumor immune microenvironment	- Photothermal property - Good colloidal stability - High NIR penetration - No change in morphology	- Poor active targeting ability - Short blood circulation lifetime - Poor bio-distribution	- Cancer immunotherapy - Photoacoustic imaging system - Photo-controlled cargo delivery system - PTT system	[73, 153]
Cancer cell CMV	Poly (lactic-co-glycolic acid) (PLGA)	Toll-like receptor 7 agonist, imiquimod (R837)	- Tumor-specific targeting ability - Enhanced bone-marrow-derived	- High loading capability of adjuvant - Biocompatible - High stability	- Harsh fabrication processes enzymes and proteins - High aggregation	- Cancer immunotherapy - Cancer vaccine - Long-term tumor-specific	[80, 151]

(*continued on next page*)

Table 2 (*continued*)

Shell	Core	Agent	Shell function	Core advantage	Core disadvantage	Platform function	Refs.
			dendritic cell uptake and maturation	- Tunable properties - Sustained release	- Difficulty in handling	immunity system - Immune memory establishment - Anti-tumor efficacy	
	Poly (lactic-co-glycolic acid) (PLGA)	Toll-like receptor 7 agonist, imiquimod (R837)	- Modified with mannose -Tumor-specific targeting ability - Enhanced dendritic cell uptake and maturation	- High loading capability of adjuvant - Biocompatible - High stability - Tunable properties - Sustained release	- Harsh fabrication processes enzymes and proteins - High aggregation - Difficulty in handling	- Cancer immunotherapy - Personalized tumor-specific vaccines - Combination with checkpoint-blockade therapy	[79, 151]
	Lipid-bilayer-coated a mesoporous silica nanoparticle MSN (LM)	Doxorubicin (DOX), Mefupari Hydrochloride (MPH), Poly (ADP-ribose) polymerase (PARP) inhibitor	- Immune escape - Homologous tumor-specific targeting effect - Directly internalized by membrane fusion	- Moderated rigidity - Robust intracellular trafficking - Excellent perinuclear aggregation - Tumor penetration via transforming into an ellipsoidal shape	- Low tumor affinity - Systemic toxicity - Rapid clearance	- Antitumor efficacy - Cancer chemotherapy system	[82]
Bacterial CMV	Gold nanoparticles (AuNPs)	–	- Rapid maturation and activation of dendritic cells - Potent protective immune responses - Stimulating innate/adaptive immune responses	- Enhanced stability - Highly tunable physicochemical properties - Tailored to favor immunization applications	- Poor active targeting ability - Short blood circulation lifetime	- Antibacterial vaccine system	[93]
	pH-responsive polymer PC7A (endosome disruption) and anionic CpG (TLR9 agonist) (PC7A/CpG polyplex core)	–	- Strong immunogenicity - Modified with maleimide groups to capture cancer neoantigens - Facilitating dendritic cell uptake - Good stability	- Boosting innate immunity - Activation of dendritic cells - High bioavailability	- Hydrophobic properties	- Antitumor effect - Antitumor immune memory - Antitumor immune response - Radiation therapy	[92]
Multiple CMV	Magnetic beads (MBs): Fe_3O_4 core	–	- PLT CMV: Enhanced cancer cell-binding ability - WBC CMV: Reducing homologous WBC interaction - Modify with CTC-targeting antibodies	- Magnetic properties	- Poor active targeting ability - Systemic toxicity - Poor biodegradability	- Circulating tumor cells (CTCs) isolation system	[94, 152]
	Polypyrrole nanoparticles (PPy NPs)	–	- RBC CMV: Long circulation times - PLT CMV: Self-targeting properties and recruiting to the microthrombosis sites	- Photothermal Properties - High photostability - Excellent photothermal conversion efficiency - Biocompatable	- Rapid cleared by RES	- Antitumor efficacy - PTT system	[97]
	Hollow copper sulfide nanoparticles	Doxorubicin (DOX)	- RBC CMV: Prolonged circulation lifetime - Melanoma cancer cell CMV: Melanoma homogeneous targeting abilities	- Photothermal conversion property - High loading efficacy - Biodegradable - Biocompatible	- Poor tumor targeting ability - Rapidly clearance by RES	- Antitumor efficacy - PTT and chemotherapy system	[96, 156]
Mosquito medium host *Aedes albopictus* CMV	Gelatin nanoparticles (GNPs)	–	-Trapping and diverting ZIKV away from its targets	- High stability - Easy to bridge - Controlled release by crosslinking density - Biodegradable - Biocompatible	- Low mechanical strength - Rapid degradation rate	- Antivirus efficacy	[15, 157]

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Table 2 (*continued*)

Shell	Core	Agent	Shell function	Core advantage	Core disadvantage	Platform function	Refs.
Activated fibroblasts (AF) CMV	Semiconducting polymer nanoparticle (SPN): Poly (cyclopentadithiophene-alt-benzothiadiazole) (PCPDTBT)	–	- Cancer-associated fibroblasts-targeting ability	- Strong NIR fluorescence - Strong photoacoustic signals - Photodynamic property - Photothermal properties	- Fast clearance by the RES - Low accumulation at the tumor site	- Tumor imaging - Anticancer efficacy - Combinational PTT and PDT system	[21]

to treat a wide range of diseases upon the proper selection of the source cells and nanoparticles, while also possessing enhanced product yield and stability. The last strategy is combining scaffold with CMVs for sustained release profile. Because the scaffold prevents CMVs in circulation and tissue area, the bioavailability of CMVs and therapeutic agent can reach to target site. Altogether, lipid-based nanocarrier platforms for drug delivery systems can be exquisitely designed, built, and modified as needed. With the various benefits from the organic and inorganic components of these novel hybrid vesicle-coated nanocarrier systems or hybrid vesicle/scaffold complexes and the extensive work being done for further development, these systems demonstrate high potential to be applied in the future as DDSs in the clinical setting.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

No data was used for the research described in the article.

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