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Cell-Derived Nanocarriers for Monocyte-Mediated Therapeutic Delivery: Concept and Challenges

Seung Eun Yu[1*], Jueun Kim[1,2*], and Hak-Joon Sung[1,2]

[1]Department of Medical Engineering, Yonsei University College of Medicine, Seoul;
[2]Department of Medical Engineering, Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, Korea.

Nano-delivery has been largely focused on ligand-based navigational targeting, but several common limitations have been recognized. First, the same targeting ligand can be sporadically expressed by unintended cells and tissues across different temporal and spatial contexts. Second, clearance from blood circulation via the liver, kidney, lung, and spleen is largely uncontrollable, in addition to nonspecific uptake by immune cells during circulation or tissue accumulation. Accordingly, inherent characteristics of cells have recently been utilized as alternative strategic points for delivery. Cell-derived nanocarriers utilize plasma membranes as modulators of targeting and delivery mechanisms, including cell hitchhiking to alter carrier behavior, reprogram phenotypes, and enable drug hand-over. The membrane mediates contact with target cells in a manner analogous to cell-cell interactions, thereby enabling physical bridging between cells and natural homing to peer cells, in addition to user-specified molecular display through mother cell expression or chemical conjugation. Here, cell-derived nanocarriers for therapeutic delivery (CDNTD) are reviewed with emphasis on their mechanistic basis, distinctions from synthetic nanoparticles, and therapeutic potential. We recently introduced spleen-mediated delivery strategies that employ resident monocytes as second therapeutic carriers following uptake of primary nanocarriers. In this way, the natural targeting behavior of monocytes in response to inflammatory cues enhances payload delivery efficiency to ischemic sites. Future directions of CDNTD research are also discussed with respect to clinical translation.

Key Words: Nanomedicine, extracellular vesicle, exosome, therapeutic targeting, carrier change, clinical translation

OVERVIEW OF NANO-DELIVERY

The use of nanoparticles to deliver drugs enhances therapeutic efficacy and reduces systemic toxicity through selective targeting. Nanoparticles offer tunable surface properties and nanoscale dimensions, allowing improvement of drug solubility and stability during circulation and thereby prolonging the half-life of therapeutics. These features support progress toward clinical translation in areas such as cancer, immunotherapy, and antiviral treatment.[1,2]

Despite continuous progress, several limitations are realized. When nanoparticles are systemically administered, off-target clearance occurs through the liver, spleen, kidney, and lung via the reticuloendothelial system (RES), leading to a substantial level-down in therapeutic index.[3] During tumor progression, increased extracellular matrix density accompanied by elevated interstitial pressure limits deep tissue penetration.[4] In the bloodstream, protein corona formation promotes rapid immune clearance and can provoke undesired immunogenicity.[5] Furthermore, biological barriers such as the blood-brain barrier (BBB) and dense microvascular networks hinder effective access to target organs.[1,2]

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Corresponding author: Hak-Joon Sung, PhD, Department of Medical Engineering, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: hj72sung@yuhs.ac

*Seung Eun Yu and Jueun Kim contributed equally to this work.
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Cell-mediated delivery strategies have been developed to address these issues by leveraging the inherent structure and function of cells. First, cell-derived nanovesicles (CDNVs) are produced through self-assembly of plasma membranes via serial filtration of cells. Second, carrier change is achieved by using living cells as secondary drug carriers following in situ uptake of nanoparticles, serving as a means of cell hitchhiking or therapeutic hand-over. Collectively, cell-derived nanocarriers for therapeutic delivery (CDNTD) are defined by the ability of the cell membrane to enable prolonged circulation, immune evasion, and active homing to diseased tissues. The classification and mechanisms of action of CDNTD are compared with synthetic particles (Fig. 1).

CDNVs are typically produced with diameters of 100–200 nm through serial filter extrusion of cells as the source material of interest. Compared to extracellular vesicles (EVs),[1,3] mass production is easier and more scalable by controlling the incremental number of source cells, and preservation of protein and lipid profiles from the cell membrane enables natural homing to peer cells by adopting the mechanisms analogous to cell-cell interactions.

Immune cells (e.g., macrophages, T cells), stem cells, and red blood cells (RBCs) exhibit intrinsic migratory tendencies toward pathological sites. These cells can take up drugs through internalization or attachment on the membrane surface, enabling the drugs to be transported and released into the disease site.[6-9] The concept of live cell carriers renovates the conventional paradigm in nanocarrier targeting which considered accumulation of circulating therapeutics in clearance organs (e.g. liver, spleen, kidney, lung, etc.) and as a delivery failure. In particular, the RES (i.e., immune cell–macrophage network and spleen) limits targeted delivery due to nonspecific clearance of nanocarriers. From this perspective, the concept of handing off nanocarrier delivery to live cells renovates the conventional strategy as a therapeutic advantage rather than a drawback. As a major reservoir of abundant monocytes, spleen-mediated targeting is presented as a representative example in this review.

In our recent studies,[10,11] intravenous injection of nanoparticles results in accumulation in the spleen through the circulatory clearance process. Since abundant monocytes reside in the spleen, these monocytes take up the nanoparticles and function as secondary carriers of therapeutics, subsequently migrating to inflammatory sites without any control. In this way, targeting efficiency and therapeutic effectiveness are enhanced when payloads are released at the disease sites. As these studies represent different angles of CDNTD approaches, the fundamental principles, disease-specific applications, and current challenges of CDNTD warrant comprehensive review to suggest future directions of nano-delivery toward clinical translation.

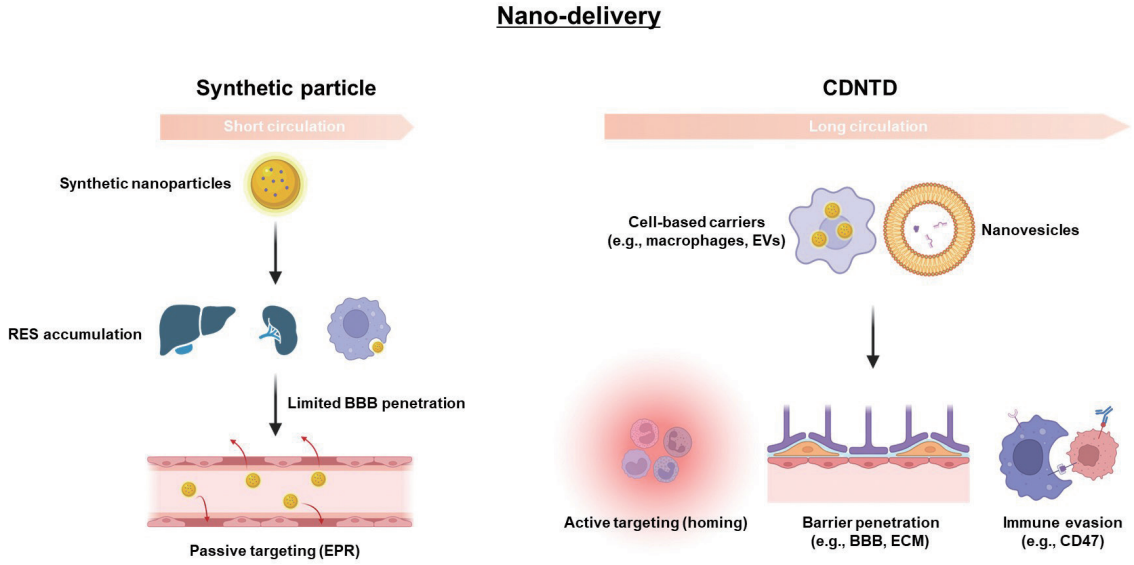

Fig. 1. Advantages of cell-mediated approaches in comparison with synthetic particles. When nanocarriers are absent in drug delivery, therapeutic efficacy is limited due to reliance on non-specific targeting and rapid clearance through the RES. Accordingly, synthetic particles have adopted ligand-based navigational targeting strategies. However, their clinical translation remains unclear because targeting ligands are sporadically displayed in unintended spaces and times, in addition to untargeted immune recognition during circulation and tissue deposition. In contrast, CDNTD utilizes the cell membrane to program intrinsic homing capacity with prolonged circulation by adopting the concept of cell-cell interactions, which enhances the effectiveness and efficacy of targeting and therapy. Nanoparticles can be conjugated onto the cell membrane by ligand—receptor interaction and biotin—streptavidin chemistry. As another means, β-cyclodextrin lipids can be inserted into RBC membranes, followed by attaching ferrocene-modified nanoparticles via host–guest interaction. Notably, RBC membrane–coated nanoparticles show over twofold longer circulation time compared to PEGylated counterparts, indicating a pharmacokinetic advantage of using cell membranes. The figure was created with BioRender.com. RES, reticuloendothelial system; CDNTD, cell-derived nanocarriers for therapeutic delivery; RBC, red blood cell; BBB, blood-brain barrier; EPR, enhanced permeability and retention; EVs, extracellular vesicles; ECM, extracellular matrix.

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CURRENT TRENDS IN NANOPARTICLE-BASED THERAPEUTIC DELIVERY

Concept of CDNTD

CDNTD utilizes living cells as active carriers for nanoparticle transport, and this strategy has been suggested as a promising solution to overcome the limitations of synthetic nano-delivery systems.[1,2] CDNTD takes advantage of inherent cellular traits, including spontaneous homing to inflamed tissues, prolonged circulation time, immune evasion, and enhanced penetration across biological barriers. Nanoparticles can be conjugated onto the cell membrane by ligand–receptor interaction and biotin–streptavidin chemistry. As another means, β-cyclodextrin lipids can be inserted into RBC membranes, followed by attaching ferrocene-modified nanoparticles via host–guest interaction.[6] Notably, RBC membrane–coated nanoparticles show over twofold longer circulation time compared to PEGylated counterparts, indicating a pharmacokinetic advantage of using cell membranes.[7] Consequently, the targeting specificity and delivery efficiency can be enhanced beyond the capabilities of synthetic platforms.[2,3]

In the early 2000s, initial efforts began to utilize immune cells as carriers of therapeutic payloads.[2] Since then, the field has expanded the range of carrier cell types to include RBCs, mesenchymal stem cells (MSCs), and platelets.[6,12] Recent studies have introduced EVs, exosome-mimetic nanovesicles, and hybrid membrane structures to replicate the functional and structural characteristics of source cells.[13-15] Accordingly, the field has shifted toward intrinsic programming of delivery vehicles by engineering molecular biomimetic architectures rather than simply employing cell carriers (Fig. 2).[15,16]

Synthetic nano-delivery systems rely on passive targeting through the enhanced permeability and retention (EPR) effect and/or active targeting via ligand–receptor interactions. These two strategies appear to be insufficient to improve targeting specificity because incremental formation of protein corona over time during blood circulation promotes uptake by immune cells and reduces the ability of nanocarriers to reach disease sites. Protein corona formation has been considered as a key effector of biodistribution, which is supported by alteration of organ distribution with reduction of RES capture when synthetic nanoparticles are coated with cell membranes.[17] On the other hand, incremental uptake by immune cells due to protein corona formation can provide a means of carrier change. Furthermore, protein corona formation enables the RES, such as the spleen, to capture nanoparticles, which also promotes uptake by splenic monocytes to deliver therapeutics to inflamed and ischemic sites, representing another strategy to apply protein corona formation beneficially. The targeting efficiency is also limited by nonspecific capturing of particles due to sporadic display of ligands in different spaces and times[18,19] in addition to protein corona formation. In comparison, CDNTD leverages the natural homing capacity of cells, and their nanoderivatives exhibit efficient targeting even without display of additional ligands. Hence, therapeutic accumulation increases at the site of disease.[1,20]

Current research aims to enhance the functions of cell- and EV-based systems by applying genetic engineering in addition to chemical modification and coating of the membrane surface. These approaches allow more precise control of the location and timing of drug release through programming of stimuli responsiveness,[1,21] thereby enabling payload release in response to photo, magnetic, inflammatory, pH, or oxidative stress triggers.[1,20] Cell-derived or membrane-coated nanoparticles are generally less immunogenic and can be naturally cleared or metabolized, minimizing toxicities during long-term circulation.[2,20] In this regard, CDNTD has emerged as an explorable platform for both preclinical and early-stage clinical studies.

Targeting principle and mechanism of CDNTD

Carrier changes to living cells renew CDNTD strategies and

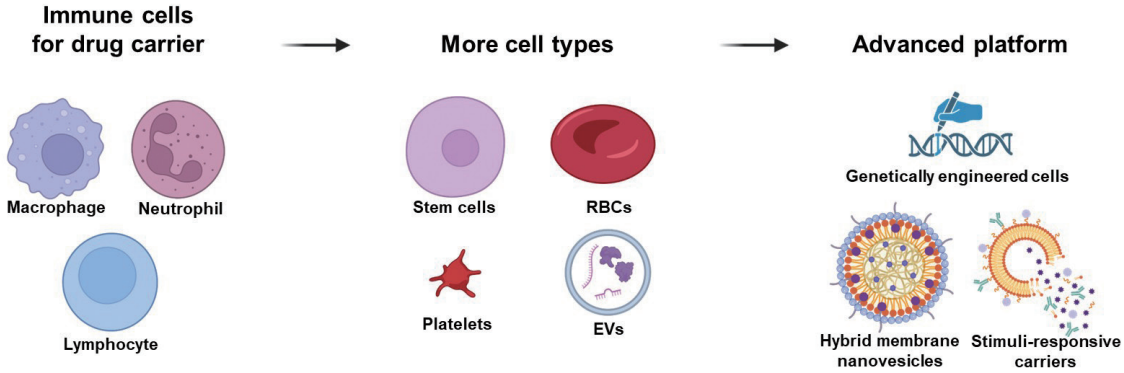

Fig. 2. Evolution of CDNTD. The initial generation of the CDNTD platform utilized immune cells as therapeutic carriers, which subsequently evolved to include stem cells, RBCs, and platelets, followed by the development of cell-derived nanovesicles. Compared to synthetic nano-delivery systems, this evolutionary progress enhances therapeutic effects through improved targeting specificity and better control of drug release by mimicking intercellular action and reaction. The figure was created with BioRender.com. CDNTD, cell-derived nanocarriers for therapeutic delivery; RBC, red blood cell; EVs, extracellular vesicles.

thus are classified as a different mechanism in comparison with direct delivery, which relies on inherent targeting of cell membranes such as CDNVs. These two mechanisms are discerned by the following aspects. 1) Carrier changes occur generally upon systemic circulation in contrast to local injections to elevate the chances of direct delivery. 2) Carrier changes utilize healthy living cells as the second carrier in contrast to targeting diseased cells by direct delivery. 3) Direct delivery ends at the spleen, where carrier changes start through uptake by splenic myeloid cells. 4) The display of navigational peptides should be preserved to operate direct delivery but becomes an option for carrier changes depending on the type of second carrier. 5) Direct delivery often ends up with a short circulation time due to protein aggregation in contrast to the relatively longer half-life of carrier changes. These differences are considered as pros and cons depending on the strategy of each CDNTD to approach a target disease together with the condition of delivery site.

CDNV

Due to self-assembly during serial filter extrusion, CDNVs retain the lipid bilayer structure and source cell-derived surface proteins.[14,22] As the production and release of EVs are intrinsically dependent on the physiological state, aging, and secretion activity of source cells, the membrane composition often exhibits batch-to-batch variations in addition to insufficient yields.[23] In comparison, CDNV production is relatively consistent to reach a sufficient amount as quantitatively validated.[24] For example, when nanovesicles are extruded using NK cells, the yield is about 402-fold compared to around 326-fold yield of EVs from the same number of NK cells.[25] This result is supported by over 100-fold increase in the production yield when a method of CDNV production is applied compared to a conventional means of exosome isolation.[24]

Moreover, although several cases of EV manufacturing are done at good manufacturing practice (GMP) levels, EV production is relatively more time-and-labor intensive as EV harvesting continues while handling mass cell culture by passaging for a long period of time (days). In contrast, CDNVs can be produced on-demand within a relatively short period of processing time (hours) in a manner proportional to the input number of source cells, indicating an advantage in the manufacturing aspect.[22,25] Lastly, CDNVs exhibit 79.1% homogeneity across biological replicates in proteomic profiles compared to 65.5% of EVs, indicating another advantage of CDNV production over EVs.[26] Nevertheless, CDNVs are formed by self-assembly through serial filtering of source cells to disrupt, indicating potential heterogeneities in the intra-vesicular composition.[23,26] Owing to their structural and functional similarities, exosomes serve as a conceptual model to describe the action mechanisms of CDNVs and EVs.[24,26] EVs and CDNVs are compared in Table 1.

CDNVs preserve intracellular adhesion proteins such as CD9, CD63, and CD81 (tetraspanins) on the membrane surface, which serve as interactive mediators with target cells.[16,27] The display of CD47 enables recognition as a "self" to avoid clearance by the mononuclear phagocyte system, thereby enhancing circulation stability.[27,28] These membrane mimetics of CDNVs relative to their source cells lead to functional inheritance. For instance, CDNVs derived from macrophages exhibit spontaneous homing toward inflammatory lesions or pass across the BBB via surface proteins such as intercellular adhesion molecule 1 (ICAM-1).[16,29]

As an optional means of drug loading, donor cells can be treated with drugs in advance so that the payloads are encapsulated by CDNVs during the extrusion process. Alternatively, drugs can be directly loaded into vesicles after extrusion by temporarily increasing membrane permeability through osmotic shock, passive incubation, electroporation, sonication, freeze–thaw cycling, or saponin treatment.[16,22,27,28] Regardless of CDNV type, hydrophilic and hydrophobic drugs are encapsulated within the aqueous core and the lipid bilayer, respectively.[28,29] Vesicle integrity should be maintained during physical disruption of source cells to preserve the intact status of drug loading. Cryo-transmission electron microscope and nanoparticle tracking analysis have confirmed that CDNVs retain spherical morphologies with leakless features, and the size distribution indicates the lack of significant aggregation post-loading.[14] The drug loading capacity of CDNVs can be altered depending on the drug concentration to incubate with source cells during

Table 1. Comparisons between EV and CDNV

	EV	CDNV
Origin & biogenesis	Endosomal pathway (exosome) or plasma membrane budding (microvesicle)	Physical disruption of source cells by filtering to self-assemble plasma membrane with intracellular components
Production method	Secretion during cell culture for days to harvest via ultracentrifugation and filtration	Serial filter extrusion, sonication, microfluidics for hours
Yield	Lower than CDNV	Higher than EV
Scalability & GMP	Platform- and process-dependent Some cases reach GMP levels	On demand proportional to the number of input cells Most cases before GMP levels
Intra-vesicular compositional heterogeneity	Potential homogeneity: cargo sorting by regulating biogenesis pathways	Potential heterogeneity: insufficient control of self-assembly with plasma membrane and intracellular components

EV, extracellular vesicle; CDNV, cell-derived nanovesicles; GMP, good manufacturing practice.

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disruption. For example, incubation with 400 μg/mL of doxorubicin (DOX) results in loading 332.4 ng of drug per μg of vesicle protein.[30] Vigorous loading methods such as sonication and electroporation need to consider the trade-off between maximizing drug payload and minimizing membrane perturbation.[14]

CDNVs move into target cells primarily via receptor-mediated endocytosis. After binding to membrane receptors, CDNVs undergo endosomal internalization and subsequently release drugs into the cytosol.[16,31,32] When lysosomes are fused with endosomes upon internalization, CDNVs are degraded in endo-lysosomes, leading to exocytosis of degradation debris. Since this process hinders cytoplasmic drug release, several studies have suggested promoting endosomal escape by conjugating membrane fusion peptides to CDNVs.[32-34]

Despite continuous progress, clinical translation of exosomes remains limited because production efficiency of each batch is heavily dependent on long-term and consistent control of source cell culture to obtain sufficient quantities. In this regard, CDNVs offer advantages in production scalability and batch-to-batch quality consistency, as vesicles can be generated through snapshot extrusion of a defined number of cells. As a supportive strategy, microfluidics are used to extrude vesicles (~100 nm in diameter) consistently by controlling the quality and quantity of each batch while preserving membrane protein profiles.[22,23,35,36] In addition to ligand conjugation to target cells, the membrane can be hybridized with liposomes[37,38] to promote the functions of circulation, biological signaling, and drug loading, as demonstrated by improved delivery efficiency in tumor models.[38]

As a stimuli-responsive design, CDNVs can be tuned to release drugs locally in response to changes in pH by cleaving hydrolysable bonds such as benzoyl imine.[39] Instead of pH, light, reactive oxygen species (ROS), or temperature shifts can also be used as stimuli to program drug release at a specific target, time, and space.[40,41] In another approach, hydrogels can be designed to deposit CDNVs and to degrade crosslinking points in response to induction of matrix metalloproteinase (MMP), enabling CDNV release at inflammatory or tumor sites. A study reports that over 80% of vesicles are released within 20 days in response to MMP-2 induction, compared to less than 10% without this stimulus-responsiveness.[42,43] Together, CDNVs represent an advancement with superior targeting precision, biocompatibility, and controlled release compared to synthetic nanoparticles. They can prolong blood circulation time and promote user-specified targeting through stimuli-responsive release, thereby serving as a key modality of the CDNTD platform.[38,41]

Living cell carrier

Living cells can carry nanoparticles with drugs to reach targets actively due to their intrinsic functions to migrate into specific sites or to aggregate with peer cells in vivo. For example, owing to active responsiveness to chemokine signals, monocyte carriers can deliver therapeutics precisely and deeply into inflammatory lesions. In addition, delivery efficiency is enhanced when macrophage carriers infiltrate tumors under inflammatory conditions, and exosomes derived from activated macrophages can even pass across the BBB into the brain.[44,45]

In alignment with the general actions of T lymphocytes, cytotoxic T cells exhibit antigen-specific homing to tumors. Immune cells (e.g., CAR-T) can be attached to nanoparticles through conjugation to enable transport into tumors by taking advantage of antigen recognition, tissue penetration, and local release of therapeutic agents.[46,47] MSCs also naturally migrate to injury or tumor tissues via chemokine signaling such as SDF-1/CXCR4, allowing spontaneous delivery of therapeutics to promote anti-inflammatory and regenerative responses.[48] Along the same line, neutrophils rapidly target acute inflammatory lesions, and RBCs can serve as stealth carriers due to low immunogenicity and long circulation time.[6,49] Platelets adhere to the endothelium upon vascular injury or tumorigenesis and locally release therapeutic agents from α-granules.[50]

Living cells can carry nanoparticles through intracellular loading and surface conjugation. Accordingly, macrophages and monocytes can uptake nanoparticles via endocytosis or phagocytosis for intracellular loading,[51,52] whereas non-phagocytic cells (e.g., lymphocytes or stem cells) typically require surface conjugation facilitated by transient membrane permeabilization using electroporation or sonoporation.[53] Nanoparticles can be conjugated onto the cell membrane through ligand—receptor interactions or biotin—streptavidin chemistry. As an alternative strategy, β-cyclodextrin lipids can be inserted into RBC membranes, followed by attachment of ferrocene-modified nanoparticles via host–guest interaction. Surface antigens and antibodies can also be displayed to enable selective docking.[54,55]

As a trigger to stimulate drug release, local inflammation can be exploited to activate carrier cells. When PD-L1 nanoparticles are loaded into platelets, tumor vasculature can be targeted through thrombotic actions for immunotherapy by releasing them as microparticles.[20] In addition to magnetic fields and ultrasound, light can trigger site-specific release through photo-cleavable linkers in response to laser triggering.[56-58] Genetic engineering strategies can further augment carrier functions, enabling the expression of suicide genes or selective release of therapeutic exosomes in response to disease signals.[3]

As a synergistic therapy using living cell carriers, immune cells can boost systemic antitumor immunity in addition to releasing relevant therapeutics. Chemotherapeutic agents released by macrophages can induce immunogenic cell death, thereby generating a vaccination effect that activates T cells to suppress metastasis.[59] CAR-T cells can deliver nanoparticles with cytokines to sustain T cell activity during tumor engagement. As a stem cell-based therapy, MSCs can deliver anti-inflammatory genes to suppress local immune responses while promoting tissue regeneration.[3]

CDNTD provides advantages compared to synthetic nanoparticles as follows. First, circulation time can be prolonged by es-

caping phagocytosis using living cells such as RBCs or exosomes with the expression of CD47.[6,60] Second, CDNTD appear to be more biocompatible and less immunogenic.[3,6] Third, the BBB can be approached and crossed by using intrinsic cell functions.[61-63] Fourth, cells can penetrate deeply into pathological tissues, thereby reducing off-target effects.[1] Lastly, therapeutic effects can be multiplexed by combining immune activation, tissue regeneration, and anti-inflammatory actions within a single carrier platform.[3,64] Together, these benefits support CDNTD as a promising strategy for the next generation of medicine by bridging cell-based and nano-delivery therapies.

Applicable disease type

As reported, CDNTD has been applied to cancer, inflammatory, cardiovascular, and neurological diseases. This section elaborates on the relevant mechanisms, experimentation, and advantages in comparison with synthetic nano-delivery. As a newly introduced concept, the spleen can be used as a site of carrier change into resident monocytes, thereby enabling strategic control of delivery timing and targeting accuracy following immune responses to more efficiently handle inflammation and tissue regeneration.

Cancer

When cancer cells are used as a cell source to produce CDNTD, the active homing nature of cancer cells to the tumor microenvironment is programmed in CDNVs, making the targeting mechanism independent of EPR effects. Macrophages and T cells have also been extensively explored for delivering nanoparticle payloads deep within tumor tissues, in addition to MSCs. When DOX is loaded into silica nano-capsules, macrophages uptake and deliver these capsules into glioblastoma lesions in mice by actively infiltrating the tumors and locally releasing DOX. This delivery results in the suppression of tumor progression under minimal systemic toxicity. As a platform for precise anti-cancer therapy, these capabilities position CDNTD as superior to synthetic nano-delivery systems with ligand-based navigational targeting and delivery.[1,65] Cancer is targeted by endowing CDNTDs with the ability of direct self-homing to tumor sites. Cancer cell membranes are isolated via mechanical disruption, which are then co-extruded with vesicles so that the membrane can be coated onto the vesicles.[66] Another approach is to apply the concept that immune cells (e.g., T cells, NK cells, macrophages) recognize and destroy cancer cells. Anticancer drugs are loaded into nanoparticles, which are phagocytosed by the immune cells through in vitro incubation to potentiate anti-cancer effects as carriers. These immune cells are injected for systemic circulation to target cancers naturally.[65]

Inflammatory disease

Chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) can be targeted using CDNTD with neutrophils or monocytes as carriers, which rapidly migrate to inflammatory lesions in response to chemokine gradients.[67,68] When anti-TNF-α siRNA is loaded into liposomes, neutrophils uptake and deliver these liposomes by homing to arthritic joints in a rheumatoid arthritis model. Upon arrival, the neutrophils release siRNA to suppress TNF-α overexpression, effectively controlling inflammation. Notably, apoptotic neutrophils can facilitate secondary delivery to macrophages by releasing cargo via NETosis. This strategy minimizes systemic immunosuppression by concentrating local drug effects, representing an efficient approach to augment the efficacy of anti-inflammatory therapies. Inflamed sites are targeted through capture of CDNTDs by immune cells (e.g., myeloid cells), which inherently recognize and move to the sites following chemotaxis. CDNTDs are prepared by thin-film hydration with drugs, followed by sonication to facilitate drug encapsulation into the CDNTDs. Then, the surface and physicochemical properties of CDNTDs are altered to promote phagocytosis by immune cells in vivo.

Cardiovascular disease

Ischemic diseases of the cardiovascular system (e.g., atherosclerosis) can be targeted using CDNTD with neutrophils and platelets as carriers, which naturally accumulate at lesions.[69] As an anti-inflammatory and antioxidative agent, glycyrrhetinic acid (GA) is loaded into nanoparticles, which are then coated with neutrophil membranes (i.e., neutrophil decoy, ND). In a myocardial ischemic model, the ND system releases GA in response to local ROS, significantly reducing infarct size and improving cardiac function. This approach enables simultaneous regulation of inflammation and oxidative stress without invasive procedures. The sites of cardiovascular disease are approached by relying on the targeting function of neutrophil membranes after their coating onto CDNTDs. Anti-inflammatory drugs are loaded into polymeric cores of CDNTDs, and neutrophils are activated by lipopolysaccharide treatment, after which they are subjected to membrane isolation via mechanical disruption, followed by co-extrusion with drug-loaded CDNTDs for surface coating.[70]

Neurological disorder

The BBB represents a critical challenge for treating neurological disorders. However, inflammation sets a niche condition of the BBB for CDNTD systems to pass through, as exemplified by receptor-mediated transcytosis of immune cell-derived CDNVs.[71] These CDNVs preserve the surface adhesion proteins (e.g., LFA-1, Mac-1) from the immune cells, which interact with ICAM-1 of brain endothelium upon inflammatory activation for extravasation. This type of interaction also facilitates active transport of CDNVs across other cases of endothelium.[30,63] Pro-inflammatory cytokines disrupt the tight junctions of the BBB, with incremental paracellular permeability,[63] thereby enabling nanocarriers to pass into the brain parenchyma.[61] Also, circulating immune cells, such as monocytes, macrophages,

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neutrophils, and neural stem cells can cross the BBB in response to inflammation,[5] which becomes a mechanism of cell-based migration (diapedesis) for use as carriers for CDNTD.[1,30]

Finally, living cell carriers leverage their intrinsic ability for cell-based migration (diapedesis). Circulating immune cells, such as monocytes, macrophages, neutrophils, and neural stem cells, can cross the BBB in response to inflammation,[5] and these cells have been explored as carriers for CDNTD.[1,30] When edaravone is loaded into RGD (Arg-Gly-Asp)-modified liposomes, neutrophils and monocytes uptake and deliver these liposomes into an ischemic stroke site by penetrating the BBB, thereby reducing infarct volume by 40%–50% and improving neurological function. Thus, BBB-impermeable agents can be delivered to central nervous system (CNS) lesions precisely while minimizing systemic side effects. The sites of neurological disorders are targeted through transmigration of monocytes or neutrophils across the BBB in response to inflammatory signals.[72] Lipids are functionalized with targeting peptides, which are then used to prepare CDNTDs by thin-film hydration with incorporation of a neuroprotective drug through solubilization. Upon systemic administration, these vesicles are selectively bound and endocytosed by monocytes or neutrophils, which pass across the BBB to release the drugs into the target sites.

Spleen-mediated delivery

Monocytes and macrophages reside predominantly in the spleen prior to circulation and can uptake nanoparticles that accumulate in the spleen following intravenous injection. Among the RES, the liver acts as a major clearance organ where sessile Kupffer cells reside without moving out, and the spleen functions as a dynamic reservoir of undifferentiated monocytes, which rapidly move out to inflamed sites.[73] While the liver clears a substantial fraction of CDNVs, uptake by splenic monocytes enables carrier changes of CDNVs as these monocytes reside abundantly in the spleen and move out to inflamed sites following signaling. In this way, therapeutic nanoparticles are transferred to resident splenic monocytes as secondary living carriers, in contrast to the sole option of particle clearance in other RES organs. This change mechanism represents an inherent drug delivery by splenic monocytes to inflamed sites such as ischemic or atherosclerotic lesions.[74] Since these immune cells naturally migrate to inflamed sites, the spleen can be considered as a site for converting the carrier of therapeutics from nanoparticles to immune cells.[10,11,68,75] A clear advantage of this mechanism is that this delivery action is activated when inflammatory events occur and is deactivated upon mitigation of the events. Furthermore, this delivery system does not require membrane display of navigational peptide ligands, which often target multiple or unintended sites, thereby improving targeting accuracy.

Glabridin is loaded into nanoparticles (NP_Gla-5k) and administered intravenously to target stroke sites. These particles accumulate in the spleen, where they are taken up by resident macrophages. Consequently, the macrophages are reprogrammed to an M2 phenotype, resulting in the exertion of protective and recovery functions against brain damage through spontaneous migration to the stroke site. In more advanced studies, we recently reported that splenic $CD11b^+$ monocytes uptake nanoparticles carrying hypoxia-inducible agents or aspirin in the spleen. The hypoxia-inducible agent triggers in situ reprogramming of monocytes toward a regenerative phenotype. As explored previously,[10,11] monocytes uptake liposomes with a hypoxic-mimetic agent ($CoCl_2$), resulting in phenotype switching to express regenerative and vasculogenic markers (CD34, Sca-1, VE-cadherin, and VEGFR) by reducing the expression of the inflammatory myeloid marker (CD11b). $CoCl_2$ induces intracellular hypoxia upon uptake by inhibiting the Fe^2-dependent activation of prolyl hydroxylases as a competitor, thereby stabilizing hypoxia-inducible factor-1α. In parallel, aspirin undergoes hand-over from the monocyte to target cells via caveolin-mediated endocytosis.[11] After uptake by splenic monocytes, drug-loaded liposomes are expected to undergo structural breakdown through endo-lysosomal processes. Notwithstanding, experimental evidence supports that the drugs are transferred to cellular vesicles by escaping lysosomal degradation.[11] Although the precise mechanisms should be elucidated further by high-resolution intracellular trafficking, substantial amounts of drug are detected in EVs from the monocytes, which initially uptake the drugs in liposomes. Then, neighboring monocytes uptake these drug-EVs and undergo phenotypic and functional alterations, which is defined as a "hand-over" action. Caveolin-mediated endocytosis facilitates this action to propagate the drug effects to neighbors through the release and uptake of EVs as dominant mediators of secondary drug delivery. These potent options enhance therapeutic effects in ischemic and atherosclerotic tissues.

Hence, these approaches serve as foundational strategies to overcome delivery barriers (e.g., the CNS) through immune modulation using nanotechnology, thereby advancing precision medicine toward clinical translation. As an example of spleen-mediated delivery, CDNTDs are prepared by injecting drugs into PEGylated lipid solution, followed by extrusion to form liposomes for intravenous administration. The uptake by splenic monocytes is facilitated more efficiently by controlling the molecular weight of surface polyethylene glycol to 5 kDa.[73] The representative examples of spleen-mediated carrier change are schematically illustrated in Fig. 3.

Experimental challenges and strategic solutions

Although CDNTD represents an emerging platform to advance nanomedicine by leveraging intrinsic cell functions, several technical barriers remain before clinical translation can be achieved. As each CDNTD strategy is currently approached with a different level of technical maturity, an engineering roadmap should be built up to critically analyze this maturity. When the status of clinical translation is considered as a key justifi-

cation of technological maturity, synthetic nanoparticles and EVs represent the most longstanding period of development and evaluation toward translation in comparison with other approaches in preclinical stages, as summarized in Table 2. Among synthetic nanoparticles, liposomes have been already used for global vaccine delivery for COVID-19 through mass engineering systems for production and analysis, thereby representing the most mature technology. On the other hand, CDNV and EV technologies remain at preclinical to early clinical stages and must overcome challenges related to mass manufacturing with quality control. The strategies for carrier changes to living cells are undergoing the earliest stage of development, and major engineering barriers include inter-body control of consistent carrier transition with immune interactions, in addition to regulatory complexity. Their technical maturity, engineering barrier, and strategic roadmap are discerned further in Table 2. In addition, living cell carriers, including immune, stem, and cancer cells, are compared among CDNTDs by distinguishing between strategies of ex vivo engineering and in situ switching to immune cells (Table 3).[76-80] These challenges encompass manufacturing standardization, large-scale production, cell maintenance for ligand display, immune compatibility, and control of drug release. The following section outlines key issues and potential solutions (Table 4).

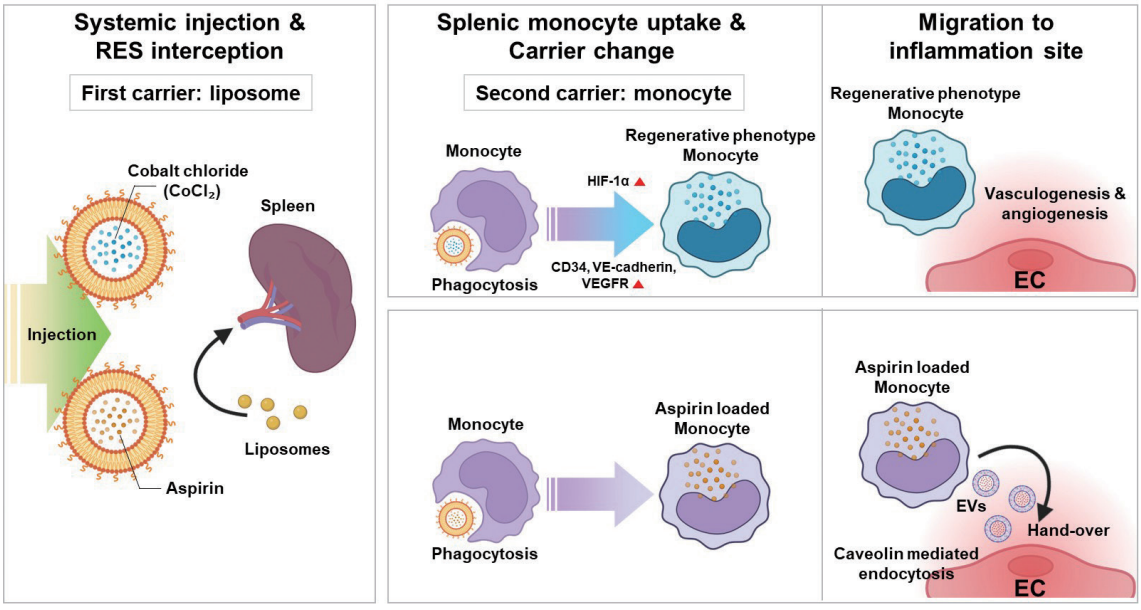

Fig. 3. Spleen-mediated carrier switching to immune cells for inherent targeting of drug delivery. When CDNTDs are intravenously administered, splenic monocytes uptake them as a means of carrier switching to enable drug delivery into inflamed or ischemic sites by the inherent migration of monocytes. Monocytes can be reprogrammed to improve the user-specified delivery of CDNTDs. The figure was created with BioRender.com. RES, reticuloendothelial system; CDNTD, cell-derived nanocarriers for therapeutic delivery; EVs, extracellular vesicles.

Table 2. Technological Maturity and Engineering Roadmap of Delivery Systems

Technology	Maturity	Major engineering barriers	Strategic roadmap	References
Synthetic NPs	High (clinically established, FDA approved)	Rapid clearance by the RES Non-specific targeting	Incremental ligand-based navigational targeting Tuning surface properties	[19,18]
Natural EVs	Medium (early clinical)	Low yield Batch-to-batch heterogeneity Purity & QC standardization	Genetic or biochemical engineering of source cells Surface chemical modification Purification standardization	[13, 35]
CDNVs	Preclinical (animal studies)	Batch-to-batch heterogeneity Purity & QC standardization Compositional control	Large-scale extrusion through serial filtering Microfluidic production systems Composition profiling	[23, 26]
Living cell carriers	Preclinical (animal studies)	Controlling "hand-over" efficiency Predicting off-target immune activation Tuning secondary uptake	Optimization of NP physicochemical properties (e.g., size, charge) to target uptake of secondary carriers Strategic use of organ-specific immune players (e.g., splenic myeloid cells)	[10, 11]

NP, nanoparticle; EVs, extracellular vesicles; CDNV, cell-derived nanovesicles; RES, reticuloendothelial system; QC, quality control.

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Manufacturing process with quality control

Batch-to-batch variation in CDNV production often arises from inconsistent donor cell conditions, culture, and extrusion processes. As a result, even though CDNVs are produced from the same cell source, the size, protein content, or membrane composition often vary. To address this, cell banking under GMP

Table 3. Comparisons of Representative Cell Sources among CDNTDs

Cell type	Source availability	Moving direction & targeting mechanism	Loading strategy & efficiency	In vivo half-life	Clinical stage & status	Key references
Ex vivo engineering						
RBCs	Rich Most abundant blood cells; easy to isolate from autologous or allogeneic sources	RES & vasculature Natural clearance by the RES (liver/spleen) Long circulation due to CD47 ("don't eat me" signal)	Encapsulation by hypotonic swelling Surface conjugation Large loading capacity due to organelle-free space	~120 days	Clinical	[7, 76]
Platelets	Rich Anucleate fragments; easy to isolate from blood	Injury, tumor & thrombosis Adhere to dysfunctional endothelium upon vessel damage (hemostasis) Recruited by tumor cells (P-selectin)	Internalization by endocytosis Surface conjugation Moderate to large loading capacity Cargo release upon activation	7–10 days	Early clinical	[50, 77]
Neutrophils	Rich Most abundant leukocyte (50%–70%), but short lifespan Ex vivo engineering only	Inflammation & infection Rapid chemotaxis upon inflammation Can pass through inflamed BBB and blood-tumor barriers	Particle uptake Hitchhiking Limited cytoplasmic volume but potent phagocytic ability	~19 hrs (circulation) Up to 5 days (tissue)	Preclinical	[78, 79]
Monocytes/ macrophages	Moderate 2%–8% of leukocytes can be differentiated from bone marrow or PBMCs	Tumor (hypoxia) & inflammation Chemotaxis to CCL2/CSF-1 Can pass through BBB Migration by pathogens	Phagocytosis (high) Surface conjugation Large internal loading capacity	Days to months (monocytes: 1–3 days/ tissue macrophages: months)	Early clinical (genetically engineered) Preclinical (NP carriers)	[80, 45]
T-cells	Moderate Requires isolation and ex vivo expansion (e.g., CAR-T protocols)	Tumor (antigen-specific) Active migration to antigen-expressing tissues Homing to lymph nodes	Surface conjugation Genetic engineering (CAR)	Variable (effector: days/ memory: years)	Clinically established (CAR-T) Early clinical for delivery applications	[46, 47]
Stem cells (MSCs)	Rare to moderate Requires culture expansion upon isolation from bone marrow, adipose tissue, and umbilical cord	Tumor & injury Homing to injured tissue and tumors via SDF-1/CXCR4 axis Lung clearance is a common issue	Internalization by endocytosis Surface coupling Moderate loading capacity Can be engineered to secrete drugs	Short retention (often cleared within days, but therapeutic effects persist)	Clinical	[12, 48]
In situ carrier switching to immune cells						
Monocytes/ macrophages	Rich Circulating or splenic reservoir cells Readily available without ex vivo manipulation	Inflammation & ischemia Spleen residence Rapid mobilization to inflamed or ischemic tissues	Phagocytosis by splenic myeloid cells after IV injection In situ hitchhiking by binding to surface ligands	1–7 days (circulation) >5 days (tissue)	Preclinical	[10, 11]

CDNTD, cell-derived nanocarriers for therapeutic delivery; RBC, red blood cell; MSCs, mesenchymal stem cells; PBMC, Peripheral Blood Mononuclear Cell; RES, reticuloendothelial system; BBB, blood-brain barrier.

Table 4. Key Challenges and R&D Directions of CDNTD

Category	Key challenges	R&D points
Manufacturing process with quality control	Batch-to-batch variation	Cell banking, GMP compliance, CQCP setup, and quality control with standardization
Large-scale production	Low yield and limited scalability	Cell vesicle extrusion, microfluidic systems, and production variable control
Cell maintenance for ligand display	Cell health during expression in large-scale culture	Low-stress loading techniques (e.g., thiol–maleimide or click chemistry) with optimized surface conjugation
Immunogenicity and toxicity handling	Immune and complement reactions upon repeated administration	GLP-based toxicity testing, cytokine/immune cell profiling, and cargo-specific safety assessments
Drug release control	Targeting accuracy with low systemic effects	Stimuli-responsive release (pH, light, temperature, magnetic field, and ultrasound) and drug activation programming

CDNTD, cell-derived nanocarriers for therapeutic delivery; GMP, good manufacturing practice; CQCP, critical quality control points; GLP, good laboratory practice.

compliance is recommended for the entire production pipeline, from cell expansion to vesicle purification. In a study on the production of CDNVs from MSCs, critical quality control points were defined to include sterility testing, viral screening, and CD9/63/81 profiling. Consequently, five independent production batches maintained particle size reproducibility within the range of 100–150 nm and a relative standard deviation below 30% for surface marker expression. Reproducibility of drug loading efficiency should be controlled across production batches for clinical translation. GMP-compliant protocols for mass production are required to manage reproducibility, and production should be monitored through quality control measures to ensure batch-to-batch consistency.[14,81]

Large-scale production

EV production relies on secretion from cultured cells, which often results in low yields and limits scalability. In comparison, filter extrusion enables high-throughput production of exosome mimetics as shown by high yield production of CDNVs through mechanical extrusion of neutrophils using microfilters. Several patents describe reliable protocols to control particle size and ensure uniform output, with validation of structural and biological equivalence to EVs.[82]

Cell maintenance for ligand display

When drugs are loaded directly into cells without nanoparticle protection, they may be degraded by cytoplasmic enzymes or induce cytotoxicity. Therefore, nanoparticles can be attached to the plasma membrane instead of cellular uptake, as demonstrated by functionalizing nanoparticles with maleimide to bind with thiol groups on the membrane surfaces of T cells. In this way, a single T cell carries approximately 150 nanoparticles while preserving cell function and more than 97% of the membrane area. Other methods for surface attachment include electroporation, click chemistry, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)-N-hydroxysuccinimide (NHS) coupling.[3,83]

Immunogenicity and toxicity handling

Despite the autologous or biocompatible nature of CDNVs, repeated administration can trigger immune responses due to allogeneic or xenogeneic activation of the complement cascade and cytokine storming. Therefore, immunotoxicity testing under good laboratory practice compliance is required through cytokine profiling, immune cell phenotyping, and histopathology. For example, repeated administration of EVs from HEK293T cells does not induce significant toxicity or inflammatory cytokine release. Additionally, compositional assessment of surface and drug cargo is required to address potential immunogenicity.[3]

Drug release control

Precise spatiotemporal control of drug release is critical to minimize systemic effects. To address this, several stimuli-responsive strategies have been explored:[3,84,85]

pH-responsive: tumor progression and inflammation create acidic microenvironments. Drugs are released upon cleavage of linkers in nanocarriers in response to decreased pH, concentrating therapeutic effects locally.

Light-triggered: user-specified timing of light exposure cleaves linkers between the drug and the nanocarrier, enabling precise spatial and temporal control of release.

Thermal-triggered: incremental temperature changes from room to body temperature induce a solution-to-gel transition in nanocarriers, allowing drugs to be encapsulated in the gel and delivered to the target point.

Magnetic/Ultrasound-responsive: magnetic fields and ultrasound locally increase temperature or membrane permeability of nanocarriers, enabling controlled drug release through these triggers.

Enzyme-responsive: drugs are released from nanocarriers through linker cleavage upon activation of local enzymes, such as MMPs during cancer progression.

CONCLUSION

Barrier blocking, non-specific tissue accumulation, and rapid systemic clearance are considered to limit the successful ap-

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plication of synthetic nano-delivery. CDNTD is suggested by programming the inherent characteristics of living cells into nanocarriers, as exemplified by the plasma membrane to enable active targeting, prolonged circulation, and immune evasion. CDNV is a major type, including exosomes, microvesicles, and exosome-mimetic nanovesicles, with excellent biocompatibility and BBB penetration ability. Advances in large-scale production and stimuli-responsive drug release accelerate translation to the clinic.

Protein corona formation occurs in not only synthetic nanoparticles but also CDNVs upon protein adsorption from body fluids. In the case of synthetic nanoparticles, the protein composition of the corona usually includes albumin, complement proteins, and immunoglobulins. On the other hand, nanoparticles with cell membrane coating preserve adhesion molecules and CD family proteins, in which the CD47 signal ("don't eat me") reduces opsonization.[71,86] These differences provide strategical options to handle targeting and delivery rather than representing a superiority of one to the other. The spleen-mediated delivery converts the conceptual disadvantage of natural clearance into an advantage in carrier switching to targets by monocytes. In this regard, promotion of monocyte uptake by protein corona formation appears to be beneficial due to the inherent homing to target ischemic and inflamed sites.

As a second carrier of drug-nanoparticles, living cells can uptake these particles, including immune cells, stem cells, and RBCs. These cells exhibit spontaneous homing to target sites, efficient tissue penetration, and phenotypic changes to synergize therapeutic effects with drugs in the nanoparticles. Our recent studies suggest the spleen as a site for carrier change from nanoparticles to monocytes, allowing these monocytes to deliver therapeutics by homing to inflamed sites, in addition to enabling a reprogramming strategy to induce a regenerative phenotype in the monocytes.

Despite continuous progress, further efforts are required to standardize manufacturing processes and ensure batch-to-batch consistency. Drug loading and release should be further optimized to support therapeutic action with minimal immunogenicity and systemic toxicity. GMP-manufacturing and immuno-evasiveness are also important areas for further development. Interdisciplinary collaboration is required to improve scalable production with robust quality control under rigorous regulatory evaluation.

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AUTHOR CONTRIBUTIONS

Conceptualization: Seung Eun Yu and Hak-Joon Sung. Funding acquisition: Hak-Joon Sung. Supervision: Hak-Joon Sung. Visualization: all authors. Writing—original draft: Seung Eun Yu and Jueun Kim. Writing—review & editing: Hak-Joon Sung. Approval of final manuscript: all authors.

ORCID iDs

Seung Eun Yu https://orcid.org/0000-0002-9690-8739
Jueun Kim https://orcid.org/0009-0009-1263-1321
Hak-Joon Sung https://orcid.org/0000-0003-2312-2484

REFERENCES

1. Cheng R, Wang S. Cell-mediated nanoparticle delivery systems: towards precision nanomedicine. Drug Deliv Transl Res 2024;14:3032-54.
2. Batrakova EV, Gendelman HE, Kabanov AV. Cell-mediated drug delivery. Expert Opin Drug Deliv 2011;8:415-33.
3. Choi A, Javius-Jones K, Hong S, Park H. Cell-based drug delivery systems with innate homing capability as a novel nanocarrier platform. Int J Nanomedicine 2023;18:509-25.
4. Duan X, Li Y. Physicochemical characteristics of nanoparticles affect circulation, biodistribution, cellular internalization, and trafficking. Small 2013;9:1521-32.
5. Anselmo AC, Mitragotri S. Cell-mediated delivery of nanoparticles: taking advantage of circulatory cells to target nanoparticles. J Control Release 2014;190:531-41.
6. Liu W, Cheng G, Cui H, Tian Z, Li B, Han Y, et al. Theoretical basis, state and challenges of living cell-based drug delivery systems. Theranostics 2024;14:5152-83.
7. Villa CH, Anselmo AC, Mitragotri S, Muzykantov V. Red blood cells: supercarriers for drugs, biologicals, and nanoparticles and inspiration for advanced delivery systems. Adv Drug Deliv Rev 2016;106(Pt A):88-103.
8. Zhang SS, Li RQ, Chen Z, Wang XY, Dumont AS, Fan X. Immune cells: potential carriers or agents for drug delivery to the central nervous system. Mil Med Res 2024;11:19.
9. Jindal AB. Nanocarriers for spleen targeting: anatomo-physiological considerations, formulation strategies and therapeutic potential. Drug Deliv Transl Res 2016;6:473-85.
10. Chung S, Kim SY, Lee K, Baek S, Ha HS, Kim DH, et al. In situ reprogrammings of splenic CD11b+ cells by nano-hypoxia to promote inflamed damage site-specific angiogenesis. Adv Funct Mater 2023;33:2302817.
11. Yu SE, Kim J, Kim DH, Baek S, Park S, Chung S, et al. Time-controlled dual targeting to program systemic and intercellular transfer of therapeutic effects. Adv Funct Mater 2025;35:2418560.
12. Labusca L, Herea DD, Mashayekhi K. Stem cells as delivery vehicles for regenerative medicine-challenges and perspectives. World J Stem Cells 2018;10:43-56.
13. Herrmann IK, Wood MJA, Fuhrmann G. Extracellular vesicles as a next-generation drug delivery platform. Nat Nanotechnol 2021;16:748-59.
14. Jang SC, Kim OY, Yoon CM, Choi DS, Roh TY, Park J, et al. Bioinspired exosome-mimetic nanovesicles for targeted delivery of che-

motherapeutics to malignant tumors. ACS Nano 2013;7:7698-710.
15. Jiang Y, Yu M, Song ZF, Wei ZY, Huang J, Qian HY. Targeted delivery of mesenchymal stem cell-derived bioinspired exosome-mimetic nanovesicles with platelet membrane fusion for atherosclerotic treatment. Int J Nanomedicine 2024;19:2553-71.
16. Kim HI, Park J, Zhu Y, Wang X, Han Y, Zhang D. Recent advances in extracellular vesicles for therapeutic cargo delivery. Exp Mol Med 2024;56:836-49.
17. Prasad R, Mendes BB, Gorain M, Chandra Kundu G, Gupta N, Peng B, et al. Bioinspired and biomimetic cancer-cell-derived membrane nanovesicles for preclinical tumor-targeted nanotheranostics. Cell Rep Phys Sci 2023;4:101648.
18. Nakamura Y, Mochida A, Choyke PL, Kobayashi H. Nanodrug delivery: is the enhanced permeability and retention effect sufficient for curing cancer? Bioconjug Chem 2016;27:2225-38.
19. Alshawwa SZ, Kassem AA, Farid RM, Mostafa SK, Labib GS. Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. Pharmaceutics 2022;14:883.
20. Yu H, Yang Z, Li F, Xu L, Sun Y. Cell-mediated targeting drugs delivery systems. Drug Deliv 2020;27:1425-37.
21. Jena GK, Patra CN, Jammula S, Rana R, Chand S. Artificial intelligence and machine learning implemented drug delivery systems: a paradigm shift in the pharmaceutical industry. J Bio-X Res 2024;7:0016.
22. Goh WJ, Zou S, Ong WY, Torta F, Alexandra AF, Schiffelers RM, et al. Bioinspired cell-derived nanovesicles versus exosomes as drug delivery systems: a cost-effective alternative. Sci Rep 2017;7:14322.
23. Lou S, Hu W, Wei P, He D, Fu P, Ding K, et al. Artificial nanovesicles derived from cells: a promising alternative to extracellular vesicles. ACS Appl Mater Interfaces 2025;17:22-41.
24. Jo W, Kim J, Yoon J, Jeong D, Cho S, Jeong H, et al. Large-scale generation of cell-derived nanovesicles. Nanoscale 2014;6:12056-64.
25. Zhang J, Guan W, Guo T, Zhang Y, Gong C, Ye R, et al. Comparison of the cytotoxicity, internalization and anti-cancer drug delivery efficacy of nature killer cell derived nanovesicles and extracellular vesicles. Int J Nanomedicine 2025;20:10683-700.
26. Wen Y, Fu Q, Soliwoda A, Zhang S, Zheng M, Mao W, et al. Cell-derived nanovesicles prepared by membrane extrusion are good substitutes for natural extracellular vesicles. Extracell Vesicle 2022;1:100004.
27. Antimisiaris SG, Mourtas S, Marazioti A. Exosomes and exosome-inspired vesicles for targeted drug delivery. Pharmaceutics 2018;10:218.
28. Ingato D, Edson JA, Zakharian M, Kwon YJ. Cancer cell-derived, drug-loaded nanovesicles induced by sulfhydryl-blocking for effective and safe cancer therapy. ACS Nano 2018;12:9568-77.
29. Saari H, Lázaro-Ibáñez E, Viitala T, Vuorimaa-Laukkanen E, Siljander P, Yliperttula M. Microvesicle- and exosome-mediated drug delivery enhances the cytotoxicity of Paclitaxel in autologous prostate cancer cells. J Control Release 2015;220(Pt B):727-37.
30. Liang Y, Iqbal Z, Lu J, Wang J, Zhang H, Chen X, et al. Cell-derived nanovesicle-mediated drug delivery to the brain: principles and strategies for vesicle engineering. Mol Ther 2023;31:1207-24.
31. Rajput A, Varshney A, Bajaj R, Pokharkar V. Exosomes as new generation vehicles for drug delivery: biomedical applications and future perspectives. Molecules 2022;27:7289.
32. Hagedorn L, Jürgens DC, Merkel OM, Winkeljann B. Endosomal escape mechanisms of extracellular vesicle-based drug carriers: lessons for lipid nanoparticle design. Extracell Vesicles Circ Nucl Acids 2024;5:344-57.
33. Giudice J, Brauer DD, Zoltek M, Vázquez Maldonado AL, Kelly M, Schepartz A. Requirements for efficient endosomal escape by designed mini-proteins. bioRxiv [Preprint]. 2024 [accessed on 2025 July 16]. Available at: https://doi.org/10.1101/2024.04.05.588336.
34. Chatterjee S, Kon E, Sharma P, Peer D. Endosomal escape: a bottleneck for LNP-mediated therapeutics. Proc Natl Acad Sci U S A 2024;121:e2307800120.
35. Ou YH, Zou S, Goh WJ, Wang JW, Wacker M, Czarny B, et al. Cell-derived nanovesicles as exosome-mimetics for drug delivery purposes: uses and recommendations. Methods Mol Biol 2021;2211:147-70.
36. Gangadaran P, Hong CM, Oh JM, Rajendran RL, Kalimuthu S, Son SH, et al. In vivo non-invasive imaging of radio-labeled exosome-mimetics derived from red blood cells in mice. Front Pharmacol 2018;9:817.
37. Liu H, Su YY, Jiang XC, Gao JQ. Cell membrane-coated nanoparticles: a novel multifunctional biomimetic drug delivery system. Drug Deliv Transl Res 2023;13:716-37.
38. Kroll AV, Fang RH, Zhang L. Biointerfacing and applications of cell membrane-coated nanoparticles. Bioconjug Chem 2017;28:23-32.
39. Tang L, Yang Z, Zhou Z, Ma Y, Kiesewetter DO, Wang Z, et al. A logic-gated modular nanovesicle enables programmable drug release for on-demand chemotherapy. Theranostics 2019;9:1358-68.
40. Yang W, Zhang F, Deng H, Lin L, Wang S, Kang F, et al. Smart nanovesicle-mediated immunogenic cell death through tumor microenvironment modulation for effective photodynamic immunotherapy. ACS Nano 2020;14:620-31.
41. Sun L, Liu H, Ye Y, Lei Y, Islam R, Tan S, et al. Smart nanoparticles for cancer therapy. Signal Transduct Target Ther 2023;8:418.
42. Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential. Theranostics 2016;6:1306-23.
43. Liu A, Yang G, Liu Y, Liu T. Research progress in membrane fusion-based hybrid exosomes for drug delivery systems. Front Bioeng Biotechnol 2022;10:939441.
44. Liang T, Zhang R, Liu X, Ding Q, Wu S, Li C, et al. Recent advances in macrophage-mediated drug delivery systems. Int J Nanomedicine 2021;16:2703-14.
45. Visser JG, Van Staden ADP, Smith C. Harnessing macrophages for controlled-release drug delivery: lessons from microbes. Front Pharmacol 2019;10:22.
46. Schmid D, Park CG, Hartl CA, Subedi N, Cartwright AN, Puerto RB, et al. T cell-targeting nanoparticles focus delivery of immunotherapy to improve antitumor immunity. Nat Commun 2017;8:1747.
47. Radhakrishnan H, Newmyer SL, Javitz HS, Bhatnagar P. Engineered CD4 T cells for in vivo delivery of therapeutic proteins. Proc Natl Acad Sci U S A 2024;121:e2318687121.
48. Joshi S, Allabun S, Ojo S, Alqahtani MS, Shukla PK, Abbas M, et al. Enhanced drug delivery system using mesenchymal stem cells and membrane-coated nanoparticles. Molecules 2023;28:2130.
49. Usman WM, Pham TC, Kwok YY, Vu LT, Ma V, Peng B, et al. Efficient RNA drug delivery using red blood cell extracellular vesicles. Nat Commun 2018;9:2359.
50. Li QR, Xu HZ, Xiao RC, Liu Y, Tang JM, Li J, et al. Platelets are highly efficient and efficacious carriers for tumor-targeted nanodrug delivery. Drug Deliv 2022;29:937-49.
51. Donahue ND, Acar H, Wilhelm S. Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine. Adv Drug Deliv Rev 2019;143:68-96.
52. Aldarondo DA, Huynh C, Dickey L, Bilynsky C, Lee Y, Wayne EC. Nanoparticle endocytosis is driven by monocyte phenotype rather than nanoparticle size under high shear flow conditions. bioRxiv [Preprint]. 2023 [accessed on 2025 July 16]. Available at: https://doi.org/10.1101/2023.06.29.547038.
53. Kang G, Carlson DW, Kang TH, Lee S, Haward SJ, Choi I, et al. Intracellular nanomaterial delivery via spiral hydroporation. ACS

Nano 2020;14:3048-58.
54. Di Marco M, Shamsuddin S, Razak KA, Aziz AA, Devaux C, Borghi E, et al. Overview of the main methods used to combine proteins with nanosystems: absorption, bioconjugation, and encapsulation. Int J Nanomedicine 2010;5:37-49.
55. Udofa E, Zhao Z. In situ cellular hitchhiking of nanoparticles for drug delivery. Adv Drug Deliv Rev 2024;204:115143.
56. Ding C, Tong L, Feng J, Fu J. Recent advances in stimuli-responsive release function drug delivery systems for tumor treatment. Molecules 2016;21:1715.
57. Raza A, Rasheed T, Nabeel F, Hayat U, Bilal M, Iqbal HMN. Endogenous and exogenous stimuli-responsive drug delivery systems for programmed site-specific release. Molecules 2019;24:1117.
58. Liu JF, Jang B, Issadore D, Tsourkas A. Use of magnetic fields and nanoparticles to trigger drug release and improve tumor targeting. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2019;11:e1571.
59. Zhao B, Li X, Kong Y, Wang W, Wen T, Zhang Y, et al. Recent advances in nano-drug delivery systems for synergistic antitumor immunotherapy. Front Bioeng Biotechnol 2022;10:1010724.
60. Shimizu A, Sawada K, Kobayashi M, Yamamoto M, Yagi T, Kinose Y, et al. Exosomal CD47 plays an essential role in immune evasion in ovarian cancer. Mol Cancer Res 2021;19:1583-95.
61. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. Signal Transduct Target Ther 2023;8:217.
62. Li YJ, Wu JY, Liu J, Qiu X, Xu W, Tang T, et al. From blood to brain: blood cell-based biomimetic drug delivery systems. Drug Deliv 2021;28:1214-25.
63. Banks WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whiteside TL. Transport of extracellular vesicles across the blood-brain barrier: brain pharmacokinetics and effects of inflammation. Int J Mol Sci 2020;21:4407.
64. Heo JS, Kim S. Human adipose mesenchymal stem cells modulate inflammation and angiogenesis through exosomes. Sci Rep 2022;12:2776.
65. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, et al. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Front Mol Biosci 2020;7:193.
66. Fang RH, Hu CM, Luk BT, Gao W, Copp JA, Tai Y, et al. Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery. Nano Lett 2014;14:2181-8.
67. Wang S, Lei B, Zhang E, Gong P, Gu J, He L, et al. Targeted therapy for inflammatory diseases with mesenchymal stem cells and their derived exosomes: from basic to clinics. Int J Nanomedicine 2022;17:1757-81.
68. Oh C, Lee W, Park J, Choi J, Lee S, Li S, et al. Development of spleen targeting H2S donor loaded liposome for the effective systemic immunomodulation and treatment of inflammatory bowel disease. ACS Nano 2023;17:4327-45.
69. Yang F, Xue J, Wang G, Diao Q. Nanoparticle-based drug delivery systems for the treatment of cardiovascular diseases. Front Pharmacol 2022;13:999404.
70. Han D, Wang F, Jiang Q, Qiao Z, Zhuang Y, An Q, et al. Enhancing cardioprotection through neutrophil-mediated delivery of 18 β -glycyrrhetinic acid in myocardial ischemia/reperfusion injury. Adv Sci (Weinh) 2024;11:e2406124.
71. Gupta D, Wiklander OPB, Wood MJA, El-Andaloussi S. Biodistribution of therapeutic extracellular vesicles. Extracell Vesicles Circ Nucl Acids 2023;4:170-90.
72. Hou J, Yang X, Li S, Cheng Z, Wang Y, Zhao J, et al. Accessing neuroinflammation sites: monocyte/neutrophil-mediated drug delivery for cerebral ischemia. Sci Adv 2019;5:eaau8301.
73. Li S, Wang Y, Wu M, Younis MH, Olson AP, Barnhart TE, et al. Spleen-targeted glabridin-loaded nanoparticles regulate polarization of monocyte/macrophage (Mo/M φ) for the treatment of cerebral ischemia-reperfusion injury. Adv Mater 2022;34:e2204976.
74. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, et al. Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science 2009;325:612-6.
75. Huang Z, Sun K, Luo Z, Zhang J, Zhou H, Yin H, et al. Spleen-targeted delivery systems and strategies for spleen-related diseases. J Control Release 2024;370:773-97.
76. Rossi L, Serafini S, Cenerini L, Picardi F, Bigi L, Panzani I, et al. Erythrocyte-mediated delivery of dexamethasone in patients with chronic obstructive pulmonary disease. Biotechnol Appl Biochem 2001;33:85-9.
77. Anselmo AC, Modery-Pawlowski CL, Menegatti S, Kumar S, Vogus DR, Tian LL, et al. Platelet-like nanoparticles: mimicking shape, flexibility, and surface biology of platelets to target vascular injuries. ACS Nano 2014;8:11243-53.
78. Xue J, Zhao Z, Zhang L, Xue L, Shen S, Wen Y, et al. Neutrophil-mediated anticancer drug delivery for suppression of postoperative malignant glioma recurrence. Nat Nanotechnol 2017;12:692-700.
79. Wang S, Pang M, Huang J, Zhao X, Zhang Y, Guo X, et al. Transporting via neutrophil as a key mechanism for nanoparticle redistribution to tumor and spleen. ACS Nano 2025;19:42402-18.
80. Brynskikh AM, Zhao Y, Mosley RL, Li S, Boska MD, Klyachko NL, et al. Macrophage delivery of therapeutic nanozymes in a murine model of Parkinson's disease. Nanomedicine (Lond) 2010;5:379-96.
81. Xu G, Jin J, Fu Z, Wang G, Lei X, Xu J, et al. Extracellular vesicle-based drug overview: research landscape, quality control and non-clinical evaluation strategies. Signal Transduct Target Ther 2025;10:255.
82. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol 2009;27:26-34.
83. Regmi S, Raut PK, Pathak S, Shrestha P, Park PH, Jeong JH. Enhanced viability and function of mesenchymal stromal cell spheroids is mediated via autophagy induction. Autophagy 2021;17:2991-3010.
84. Wei W, Zhang Y, Lin Z, Wu X, Fan W, Chen J. Advances, challenge and prospects in cell-mediated nanodrug delivery for cancer therapy: a review. J Drug Target 2023;31:1-13.
85. Rodzinski A, Guduru R, Liang P, Hadjikhani A, Stewart T, Stimphil E, et al. Targeted and controlled anticancer drug delivery and release with magnetoelectric nanoparticles. Sci Rep 2016;6:20867.
86. Miao Y, Li L, Wang Y, Wang J, Zhou Y, Guo L, et al. Regulating protein corona on nanovesicles by glycosylated polyhydroxy polymer modification for efficient drug delivery. Nat Commun 2024;15:1159.