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Cells and cell derivatives as drug carriers for targeted delivery

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Abstract

For over a century, researchers have focused on how to optimize drug delivery. Systemic administration means that the drug becomes dilute and has the potential to diffuse to all tissues, which is only until the immune system steps in and rapidly clears it from blood circulation. Drug carriers are the solution for amplifying the intended effect and diminishing side effects. With drug carriers, tissue-specific drug delivery and controlled drug release is possible. Thus far, both synthetic and non-synthetic carriers exist. However, due to the numerous limitations of synthetic carriers, science has begun to concentrate on using live cells and cell-derivatives as drug carriers. The most problematic shortcomings of synthetic carriers are their limited biocompatibility and biodegradability. Most synthetic carriers are cytotoxic or induce immune responses. Moreover, synthetic carriers typically depend on passive diffusion and risk phagocytosis, further reducing their impact. On the other hand, live-cell carriers and their derivatives usually have a targeting mechanism and drug release is controlled, increasing the efficiency with which a drug accumulates and acts on a tissue. Still, both types of carriers face similar problems, including achieving high loading capacity, maintaining drug quality, efficiently accumulating in the target tissue, and minimizing side effects. This review aims to elucidate the advantages and disadvantages of each popular cell or cell-derived carrier and to spotlight novel solutions.

Keywords

Drug delivery; Immune cells; Red blood cells; Stem cells; Biomimetics; Exosomes

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Declaration of competing interest

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1. Introduction

As science and technology evolve, improving drug therapeutics, via the drug or the mechanism of delivery, has been a priority. Currently, existing drugs have the potential to effectively treat diseases but are unable to fulfill their function once they enter the patient. The drugs become degraded, cleared by the immune system, or are too dilute to be effective. Synthetic nanoparticles, such as micelles and liposomes, were the first type of effective drug carriers in which drug release could be controlled by the environment [1].

Micelles were–and despite their shortcomings, still are–attractive for hydrophobic drugs due to their ability to self-assemble in aqueous solutions into monolayer vesicles with hydrophobic cores. However, micelle formation requires a minimum concentration (critical micelle concentration; CMC) of amphiphilic polymers. When administered *in vivo*, the micelle concentration falls below the CMC and the micelles begin to disassemble, releasing their drug cargo. Therefore, researchers focused on using polymers that increase the stability of micelles–most of which are not biocompatible or biodegradable, negatively impacting healthy cells. This cytotoxic limitation [2–4], as well as potential immunological problems [2], can be overcome by using biocompatible and completely biodegradable materials [2,3,5,6]. Another shortcoming micelles have faced is their poor targeting ability [7] coupled with their tendency to be rapidly cleared from blood circulation via phagocytosis [8,9]. Their nanosize allows micelles to take advantage of the enhanced permeability and retention (EPR) effect to infiltrate and accumulate primarily in tumors, but this process is passive and micelles are still taken up by healthy cells. Different strategies have been applied to increase their targeting efficiency, such as relying on changing environments to activate micellar release of drugs [9] or adding specific cell-targeting ligands, namely mannose for cancer [8,10]. Even with the EPR effect and targeting ligands, clinical trials show nanoparticle accumulation in tumors is variable and, overall, disappointing [11,12].

On the other hand, liposomes are attractive for carrying hydrophilic drugs since they have bilayer membranes. Similar to micelles, liposomes face problems of cytotoxicity [4,13], inefficient delivery by the EPR effect [13,14], and rapid clearance by the immune system [5]. Unlike micelles, liposomes have *in vivo* stability, but liposome synthesis is typically expensive and complicated, and liposomes have poor storage stability [2,3]. Still, liposomes are widely used because their membranes can be modified with polymers, enzymes, and antibodies for targeting specificity, making them versatile structures [13,15–17]. They have been found to be effective in fighting general diseases through colonic delivery [16] and are used for cancers including breast [15] and colon [17] cancer. Polyethylene glycol (PEG) arose as a promising polymer capable of circumventing the immune system's mononuclear phagocyte system (MPS) and increasing the duration of blood circulation [13,17,18]. However, PEG's efficacy is limited since it is a foreign substance, resulting in the body eventually inducing an anti-PEG immune reaction after repeated dosing [8,13,18]. As a non-biodegradable polymer, PEG also poses a toxicity problem from potential tissue accumulation [8,13].

While synthetic vesicles were a good step towards developing effective drug delivery systems, their incompatibility produced as many problems as they solved. Therefore,

researchers are investigating cells and their derivatives, discovering that the human body already provides delivery pathways waiting to be used to fulfill their potential. In this review, we explore each type of cell and cell-derived drug carrier, its benefits and risks, and how to mitigate the risks (Fig. 1).

2. Immune cells as drug carriers

For using live cells as drug carriers, immune cells were quickly identified as promising delivery systems. In order to effectively protect against pathogens, immune cells rely on intercellular signaling and fast migration. In addition, because immune cells compose the immune system, they will not induce an adverse immune response. Due to their attributes–superior biocompatibility [2], minimal interactions with normal cells [2], and the ability to actively target specific cells and sites [19]–immune cells are strong candidates as carriers.

2.1. Macrophages

Macrophages are a type of phagocytic white blood cells, most recognized for their role in traveling to and clearing an injury site of foreign debris and cells as part of the innate immune system. Their unique properties, including their ability to cross the blood-brain barrier (BBB) [20,21] and natural homing abilities [19], make them particularly attractive for targeting and treating neurodegenerative disorders [20], inflammatory diseases [20], and cancers [7,19]. Although, as a result of their dual ability to be both pro- and anti-inflammatory, in regards to cancer, macrophages pose the risk of supporting tumor proliferation and migration instead of eliminating tumor cells [14,22]. Still, natural phagocytosis and active migration in response to cell signaling signifies that drug uptake and drug transport would be greatly improved, especially in comparison to the passive diffusion by which micelles and liposomes are restricted. Macrophage status as immune cells reduces interactions with normal cells, thereby increasing the volume of and the rate at which the drug arrives at the target site.

Still, macrophages have shortcomings as delivery systems. Because macrophages are live cells, high loads of drugs or drugs in nanoparticles can interfere with cell survival, migration, and function, limiting the drug load [19,20]. Another drawback is that because macrophages are phagocytic, they do more than just uptake. Macrophages release enzymes and acid to kill and digest pathogens. Therefore, after taking up drugs and drug carriers, macrophages will quickly digest most drug carriers [19] and degrade drugs, reducing drug release and efficacy [20]. To counteract these characteristics, Klyachko et al. [20] created “cellular backpacks” that encapsulate drugs that adhere to macrophages. Although the drugs were successfully transported, backpacking covers the plasma membrane and functions such as signaling, adhesion, and migration are restricted [19]. Furthermore, there is a risk of the macrophages internalizing the backpacks. Taking advantage of macrophage endocytosis, Zhang et al. [19] created drug-loaded capsules designed to withstand macrophage enzymatic and oxidative degradation. Moreover, slow drug release from the capsules minimized adverse effects on macrophages, which allowed time for migration and drug delivery to the site of injury [19].

2.2. T cells

Part of the adaptive immune system, T cells naturally produce receptors for a large variety of antigens [23,24], with each T cell only presenting receptors to one type of antigen. In other words, each T cell is extremely specific, making T cells excellent targeting cells. When a cytotoxic T cell encounters its respective antigen, the T cell receptor (TCR) causes the cell surface reduction potential to increase [25], signaling the cell to secrete proteins that induce the antigen-presenting cell (APC) to die [23]. These combined features–cell specificity and induced apoptosis–make T cells very attractive for carrying drugs to target and eliminate tumors. As an immune cell, T cells are capable of crossing the BBB [20,26], giving them unrestricted access to diseases throughout the body, including HIV [23] and cancers such as melanoma [25] and glioblastoma [25,26].

Furthering their use, T cells can be reprogrammed and repurposed in order to modify antigen receptors [23,24] and secretions [25,26]. Cytotoxic T cells have been modified to display chimeric antigen receptors (CARs) on their membranes, which takes advantage of the T cell targeting and elimination pathways, but changes their original target to, for example, cancer cells evading the immune system [23,25–27]. Tang et al. [25] have designed “backpacking” nanogels that carry proteins on the tumor-targeting T cell membranes and only release the proteins when the CAR-T cell binds to the cancer cell and initiates T cell surface redox activity. They found that the release of the IL-15Sa protein from the nanogels promoted T cell expansion, resulting in faster tumor inhibition and clearance [25]. Jones et al. [23] had a similar backpacking design, but depended on a different step of the cytotoxic T cell mechanism: only when T cells secreted lytic granules would the backpacks release their cargo. CAR-T cells are an efficient system, but they can be too efficient, resulting in cytokine release syndrome or B cell aplasia–neither of which yet have sustainable solutions [27].

3. Blood cells as drug carriers

3.1. Platelets

Platelets are a type of red blood cell that prevents blood leakage from injured blood vessels by aggregating to form a clot. Therefore, platelets are able to precisely target specific sites and cells [2,3,28–30]. Coupled with their long lifespans, abundancy, high drug loading efficiencies, and immune system evasion, platelets are ideal drug carriers [2,3,5,31]. Moreover, a patient’s own platelets can be used for treatment [5]. Platelets have largely been used for wound healing [3,30,32], for hemostasis [2,3,33], to combat inflammation [2], and to treat vascular diseases such as lymphoma [2,3] and lung adenocarcinoma [5]. Xu et al. [2] demonstrated that platelets naturally release their cargo at faster rates in more acidic environments. Since cancerous tissues are more acidic than healthy tissues [9], drug release is controlled by the presence of tumor cells [6–8]. Metastatic cells naturally activate platelets such that platelets aggregate around tumor cells, helping them spread to new tissues through blood circulation [3,5,28]. Loading platelets with cancer therapeutics means that not only are tumors targeted, but also, tumors would not be able to metastasize. To further increase targeting efficiency, Xu et al. [3] conjugated platelets loaded with DOX to CD22 antibodies. CD22 is a marker for tumors, with the additional function of facilitating endocytosis [3]. In

other words, platelets not only release DOX near tumor cells, but rather, platelets release DOX inside tumor cells, increasing potency [3].

3.2. Red blood cells and red blood cell mimics

Though carrying oxygen throughout the body is the most common attribute of red blood cells (RBCs), they have emerged as superior drug carriers. Exhibiting many of the same characteristics as immune cells – biocompatibility [2,3,34–38], biodegradability [2,18,36], and targeting ability [2,21]–RBCs have the advantage of already being identified as clinically safe for transfusions [34]. Furthermore, RBCs express CD47 on their cell surface, signaling to the immune system to avoid RBC uptake [35]. For the purpose of drug delivery, CD47 is beneficial for prolonging the circulation and efficacy of RBC drug cargo, which can be loaded onto the surface or inside RBCs [18,21,35–39]. The effects of loading RBCs with drugs is currently a matter of contention, with some studies indicating that regardless of the loading method, drug loading will unfavorably affect RBC durability [37] and others showing no effects at or below a nanoparticle-to-RBC ratio of 200:1 [39]. Still, RBCs have been shown to be effective carriers for alleviating symptoms of inflammation [34,35] and pulmonary embolism [34]. Brenner et al. [34] determined that red blood cells could become organ-targeted drug carriers based on the injection site.

Maintaining the advantage of the RBC membrane and its proteins, RBC mimics differ from parent cells only in their core, which is composed of a drug-encapsulated nanoparticle. So far, platelet mimics have been used in cancer [28], acute liver failure [40], and myocardial infarction [29] models, but it has the potential to be applied to other vascular diseases as well [29]. Su et al. [41] even captured cardiac stem cell secretome inside a platelet mimic for regenerative purposes. Having a platelet membrane makes the mimic biocompatible and has the natural homing ability of platelets [29,37,42,43]. The platelet membrane also allows for the flexibility to travel through capillaries smaller than the mimic [44] and for antibody conjugation to redirect their natural targeting [45]. The immunogenicity of the nanoparticle held within is minimized, which prolongs the blood circulation of the nanoparticles [28,31,40,42,46,]. The production of platelet mimics is fast, straightforward, and safe [29], and mimics have better stability in storage [41]. For now, there is not an identified delivery advantage of using mimics instead of the whole cell. Although, it would be noteworthy if high drug loading would become possible in the mimics, or if doing so would produce an adverse effect on the RBCs membranes.

4. Stem cells as drug carriers

Stem cells are undifferentiated cells with the potential to give rise to different types of cells and received attention as carriers due to their ability to survive in cancerous tissues and tolerate chemotherapeutic drugs [47]. As live cells, they are biodegradable and biocompatible [2,49]. Stem cells also have regenerative, immunomodulatory [4,47,50] and anti-inflammatory [47,51,52] properties. Furthermore, stem cells are able to target specific cells [2,14,47] based on chemotactic signals [53] and infiltrate specific tumor types [14]. In addition to being effective carriers, stem cells themselves are effective therapeutics due to the trophic factors they secrete [47,50,54]. Therefore, stem cells have been mainly

used to regenerate disease-affected tissues and to combat cancer [47], including lung adenocarcinoma [14], glioblastoma [53], and leukemia [27].

However, using stem cells as therapeutic carriers introduces many problems from isolation to administration [40,50,51,55,56]. To prevent immunogenicity, autologous stem cells must be used [47,51,53]. The cells must be grown, stored, and survive transportation [40,50,56,57]. Administering stem cells by transplantation results in poor retention [29,41,45,52,58,59], and the transplantation process can cause infections [27]. Injecting stem cells intravenously means filtration by the lungs, reducing the amount that can travel to the target organ [40]. A risk posed by stem cells is tumorigenicity because they are actively proliferating cells [51,56,58].

Similar in concept to platelet mimics, biomimetic stem cells have nanoparticle cores covered by stem cell membranes and reflect the ability to evade the immune system [50,56] and the regenerative functions of stem cells [56]. Biomimetic stem cells are superior to stem cells in that they are more stable *in vivo* and in storage [56]. In addition, biomimetic stem cells are more standardized and do not pose the risk of tumorigenicity [50]. Tang et al. [56] tested the application of biomimetic stem cells in a myocardial infarction model.

5. Exosomes as drug carriers

Exosomes are extracellular vesicles, formed and released by cells, and were originally believed to merely be a cell's waste disposal system. After the discovery that exosomes carry DNA, RNA, and proteins between cells, their role as intercellular messengers earned them the nickname of "natural nanoparticles" [4,57,59–63]. Created from a cell's own membrane, exosomal membranes also contain the cell's membrane proteins, along with some of the cell-specific functions [57,61,64]. As with cells, the exosomal membrane proteins can even be engineered to, for instance, display PD-1 receptors to interfere with cancer cell upregulation of PD-L1 and enable T cell infiltration into tumors [65]. The properties that bring attention to exosomes include their high availability [60], biocompatibility [4,60,63,66], cargo-protective membranes [50], and the ability to cross the BBB [60]. Exosomes overcome two major stem cell complications, tumorigenicity and graft-*versus*-host disease [4], while retaining all targeting and parent cell type advantages [61,67]. The variety and accessibility of exosomes allows for practically unlimited disease applications from cancer [4] to arthritis [55] to neurodegenerative disorders [60].

Additionally, even if allogenic, exosomes do not cause an adverse immune response [4,46,63,66], because exosomes are too small for the mononuclear phagocyte system (MPS) to remove [67]. This enables exosomes to act as a "cloaking" device for drugs [4]. One notable benefit of exosomes is that, compared to other drug carriers, exosomes have a relatively high loading capacity [4]. Also, Kim et al. [4] demonstrated that when paclitaxel-loaded exosomes were used to inhibit MDR tumors, the exosomes amplified the drug's potency. Therefore, combining the high drug loading capacity with increased drug potency, exosomes are effective beyond simply just being drug carriers.

6. Adipocytes as drug carriers

Primarily known as fat cells, adipocytes store energy and secrete factors (adipokines) that regulate metabolic homeostasis [68,69]. Due to lipolysis and secretion of pro-inflammatory cytokines, adipocytes provide cancer cells leverage for developing into tumors and metastasizing [69,70]. Their abundance, biocompatibility, and close interactions with cancer cells makes adipocytes ideal for targeting cancers [69,70]. As adipocytes typically uptake lipids, drug-loading is largely limited to nonpolar drugs [69]. However, investigation into adipocytes for drug-loading and delivery is relatively new, with most research involving adipose tissue focused on targeting it, rather than using it to target. Wenet al. [70] have spearheaded the studies into using adipocytes as drug carriers, exploiting cancer cell-induced lipolysis for accelerated release chemotherapeutics rumenic acid (RA) and DOX prodrug [69]. Wenet al. [70] demonstrated that loading RA and DOX prodrug into adipocytes both increase the survival of B16F10 melanoma mice and reduce tumor recurrence in a tumor-resection model. Considering the prevalence of adipose tissue in the body and the far-reaching effects of adipocyte secretions, it would be worthwhile investigating the viability of adipocyte-mediated drug delivery as a treatment for other diseases.

7. Conclusion

Since the advent of therapeutic drugs, efficient carrier mechanisms have been examined to both improve drug delivery and reduce unwanted side effects. Each discovery and advance has far-reaching clinical impacts: although cancer and cardiovascular diseases are the most pertinent applications, drug delivery mechanisms to treat these diseases can be applied to a variety of diseases (Table 1). Already, exosomes have been shown effective as drug carriers for cancer [4], arthritis [55], and neurodegenerative diseases [60]. Live cells and cell derivatives have demonstrated superiority over synthetic nanocarriers [71,72]. They are naturally capable of unrestricted, actively targeted drug delivery with controlled drug release. Solely in terms of delivery, RBCs and immune cells hold the most promise as cell carriers, since they do not induce cytotoxicity or unfavorable immune system activity. The regenerative abilities of stem cells, though, cannot be ignored despite the risk of tumorigenicity. Exosomes and biomimetics have gained traction as optimized delivery systems, encapsulating the benefits of their parent cells without any of the associated hazards.

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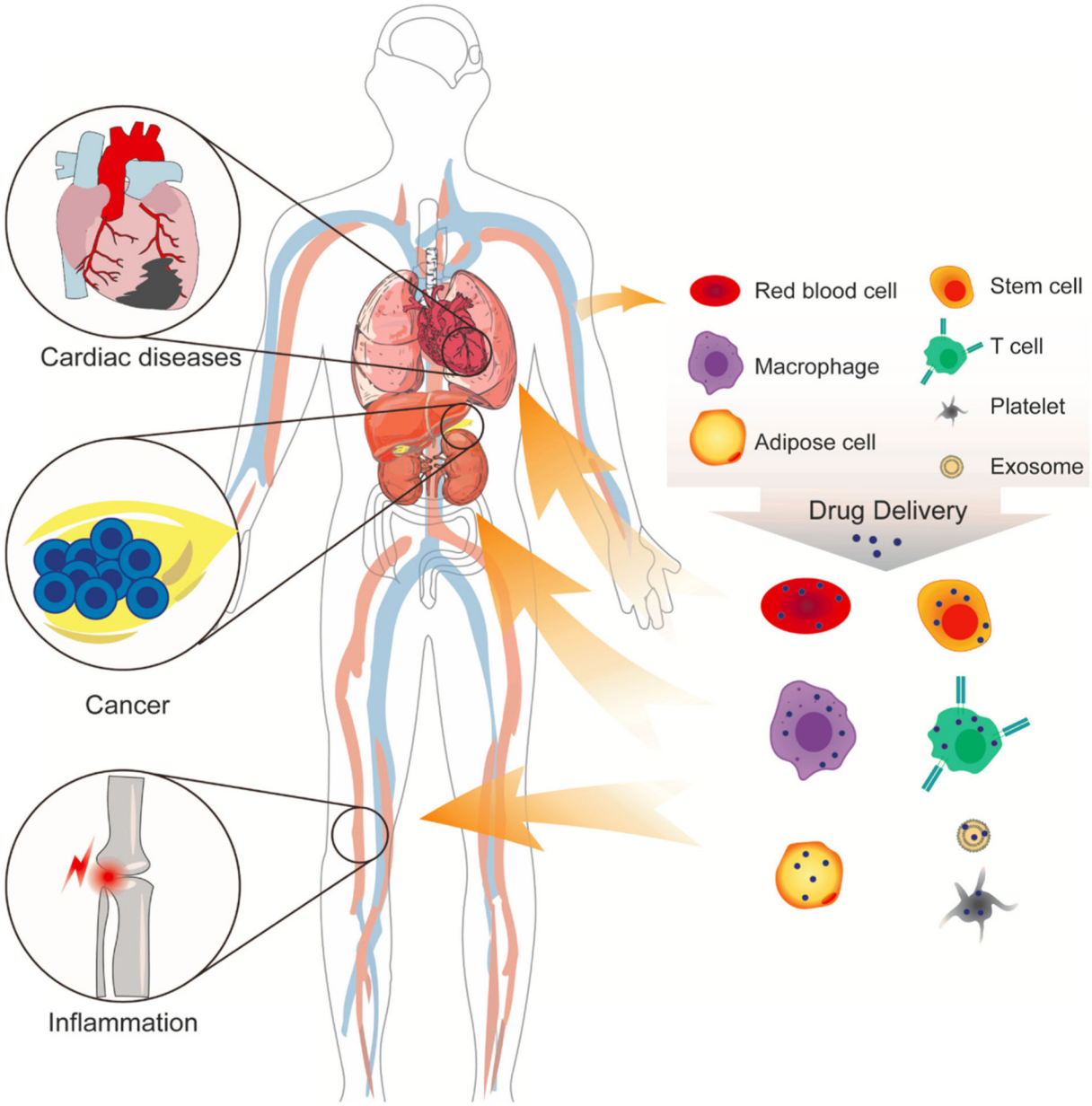

Fig. 1.

Currently, drug delivery focuses primarily on transporting cancer therapeutics. But each delivery mechanism is applicable to a variety of diseases, such as cardiovascular and inflammatory diseases.

Table 1

Publications using cells and cell derivatives as drug carriers.

Reference	Cell carrier	Disease	Animal model
Brenner et al. 2018 [34]	Red blood cells	ARDS Pulmonary embolism	C57BL/6 mouse; LPS i.t. C57BL/6 mouse; Plasma microemboli of fibrin clots i.v.
Wan et al. 2018 [35]	Red blood cells	Inflammatory diseases	C57BL/6 mouse
Klyachko et al. 2017 [20]	Macrophages	Encephalitis	C57/BL mouse; LPS intracranial
Zhang et al. 2018 [19]	Macrophages	Cancer (driven by inflammation)	U87MG tumor-bearing nude mouse
Xie et al. 2017 [7]	Macrophages	Melanoma	1205Lu cell and WM35 cell
Xu et al. 2017 [2]	Platelets	B Cell lymphoma	Tumor-bearing BALB/c nude mouse
Xu et al. 2017 [3]	Platelets	B Cell lymphoma	Tumor-bearing BALB/c nude mouse
Sarkar et al. 2013 [5]	Platelets	Human lung adenocarcinoma	Swiss albino mouse; Ehrlich ascites carcinoma cells i.p.
Layek et al. 2018 [14]	Stem cells	Lung carcinoma	SCID beige mouse; A549 cell i.v.; C57BL/6 mouse; Lewis Lung Carcinoma cell i.v.
Bagó et al. 2017 [53]	Stem cells	Glioblastoma	Mouse; U87, GBM4, or GBM8 cells stereotactically implanted
Hu et al. 2018 [27]	Stem cells	Acute myeloid leukemia	C57BL/6 J mouse; C1498 or WEHI-3 cell i.v.
Kim et al. 2016 [4]	Exosomes	Lung carcinoma	C57BL/6 mouse; Lewis lung carcinoma cell i.v.
Wang et al. 2017 [32]	Exosomes	Osteoarthritis	C57BL/6 J mouse; Destabilization of medial meniscus surgery
Kojima et al. 2018 [60]	Exosomes	Parkinson's	C57BL/6 J mouse; 6-OHDA solution intracerebral injection
Tang et al. 2018 [56]	T Cells	Solid cancers (melanoma and glioblastoma)	C57BL/6 mouse; B16F10 cell s.c.
Jones et al. 2017 [23]	T Cells	HIV	NSG mouse; CXCR4-tropic HIV molecular clone LAI i.p.
Pohl-Guimarães et al. 2019 [26]	T Cells	Brain tumors	C57BL/6 mouse; B16F10 OVA cell implant
Tang et al. 2017 [57]	Synthetic stem cells	Myocardial Infarction	SCID beige mouse; LAD artery ligation
Luo et al. 2017 [50]	Synthetic stem cells	Acute myocardial infarction	SCID beige mouse; LAD artery ligation
Hu et al. 2015 [28]	RBC mimics/nanovesicles	Cancer (general)	Nude mouse; MDA-MB-231 cell s.c.
Tang et al. 2018 [52]	RBC mimics/nanovesicles	Myocardial infarction	WKY rat; LAD artery ligation, followed by reperfusion; adult farm pig; LAD coronary balloon occlusion
Liang et al. 2018 [40]	RBC mimics/nanovesicles	Acute liver failure	C57BL/6 mouse; Carbon tetrachloride i.p.

i.p., intraperitoneal; *i.t.*, intratracheal; *i.v.*, intravenous; *s.c.*, subcutaneous; *LAD*, left anterior descending.