Review Article

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Fabrication of Cell-Derived Biomimetic Drug Delivery System

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Abstract: Functional biomaterials that are capable of effectively carrying therapeutic agents and specifically delivering therapeutics to pathological sites have been widely investigated over decades. Recently, cellular carriers and cell derivative-based bio-hybrid delivery systems have drawn extensive attention as a promising branch of therapeutic delivery systems, owing to their low immunogenicity and intriguing biomimetic capabilities. Various approaches for the fabrication of these biomimetic carriers have been developed, and some products have already been commercialized as well. In this review, we summarized various processing methods for engineering cell-derived biomimetic drug delivery systems, and discussed their future outlooks.

Keywords: cellular carriers; biomimetic materials; drug delivery; nanomedicine; cell membrane-coated nanoparticles.

1 Introduction

Efficient delivery of active agents to pathological sites by carrier materials is of central importance for the improvement of therapeutic outcomes. Although many candidates of delivery carriers, including polymeric nanoparticles [1-4], inorganic nanoparticles [5-8], liposomes [9-11], stimuli-responsive delivery carriers [12-15], and other systems [16-18], have been developed in the past two decades and shown their great potentials to augment drug efficacy both *in vitro* and *in vivo*; however, several common issues, such as rapid clearance, poor serum stability, limited cellular uptake, and inefficient drug release, often hinder these drug delivery carriers from clinical translations [19]. To solve these issues, new strategies have been designed to improve the capabilities of an existing drug delivery carrier to overcome certain or multiple delivery barriers. For example, PEGylation of delivery carriers has been proven to prolong the blood circulation time and improve passive tumor-targeting capability *in vivo* through enhanced permeation and retention (EPR) effect, which in turn enhance the therapeutic efficacy of the delivered drug for cancer treatments [20]. In recent years, endogenous cells has drawn extensive attentions as a fascinating class of smart drug delivery carriers, largely owing to their inherent low immunogenicity, long circulation capability, inherent homing ability to some specific tissues or focus, high reactivity and sensitivity in response to specific cell microenvironment [44-54]. In general, these cellular carriers are living cells with ability to load, deliver, and release cargoes. Whereas they behave with normal cell functions with or without modifications, they are replicative and are able to serve as carriers to deliver drugs ranging from small molecules to biomacromolecules. One such typical representative is erythrocyte. As autologous cells, erythrocytes feature certain advantages as drug delivery carriers as appose to other widely used synthetic carriers, mainly due to unique membrane components. As a result, erythrocytes and their membranes hold great potentials for drug delivery and other biomedical applications. They can serve as circulating bioreactors for the degradation of toxic metabolites as well as the inactivation of xenobiotics, or as drug carriers to deliver antigens for vaccination purpose [21]. Similarly, other biomimetic carriers derived from leukocytes [47, 48], platelets [49, 50], stem cells [52, 56, 58], bacteria [62] have been recently proposed as cellular carrier systems towards various therapeutic applications, largely by taking advantage of their respective unique properties. Despite

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these excitements, using living cells as the drug delivery system suffers from a number of inherent limitations, such as sophisticated drug loading, difficult modification and handling, short *ex vivo* shelf-life as well as unknown fate *in vivo*.

Instead of using endogenous cells directly, cellular membranes, or cell-secreted vesicles like exosomes or outer membrane vesicles, have also been recently described as another biomimetic class of delivery carriers towards different biomedical applications [29, 33, 126]. Both mammalian cells or bacteria-derived vesicles and membrane cloaked particles, have been brought up recently to make the full use of natural properties of cell membrane and/or its components [95, 130, 153]. Though they are non-replicative, endogenous cell-derived drug carriers make full use of endogenous components, mostly membrane proteins, to evade immune clearance, or to achieve specific targeting. Thus, these cell-derived synthetic delivery carriers that are partially composed of non-living cellular components are able to mimic certain function of the native cells in the drug delivery process. These efforts bring new opportunities to improve the delivery efficiency for a wide range of therapeutics [22-34]. In this review, we mainly focus on the diverse fabrication approaches of biomimetic cellular carriers, and preparation of cell derivative-based bio-hybrid delivery systems.

2 Cellular Carriers

As the instinctive properties of certain cells, cell-based drug delivery systems have attracted wide attentions and are under rapid development in the past few decades. Cellular carriers can be considered as a Trojan horse, or so called as cellular hitchhiker to transport therapeutic agents to disease sites. Numerous reports have illustrated that drug delivery systems based on endogenous cells can prolong circulation time, diminish drug immunogenicity, lower cytotoxicity, extend drug release, and improve the targeting capability [43-54].

2.1 Cell types

Different types of cells, such as erythrocytes, leukocytes, platelets and stem cells, have been used to explore for the treatment of various diseases or disorders, including cancer [24, 35-37], chronic inflammatory diseases [38], ataxia telangiectasia [39], Gaucher disease [40], diabetes [41], autoimmune diseases [42], *etc*. (Table 1). Erythrocytes, also called carrier erythrocytes [25], have been developed as drug carriers since last century [43], owing to their biocompatibility, non-immunogenicity and easy-to-obtain sources [44]. As *in vivo* drug delivery carriers, the most striking feature of carrier erythrocytes is their relatively long life span in the blood circulation of human bodies [45]. By taking advantage of their native self-degradable fate by macrophages [45], erythrocytes primarily accumulate in the mononuclear phagocyte system (MPS) such as spleen, bone marrow and liver where they are metabolized. Another attractive feature of erythrocytes is their biconcave shape and absence of organelles, which makes them ideal carriers for loading diverse compounds both in the inner cavity and on the surface [46].

Leukocytes are another class of potential biomimetic delivery carriers due to the endothelium adhesive properties and the ability to interact with tumor cells both in vascular and in solid tumors. Their ability to phagocytose microorganisms and other particles facilitates themselves to encapsulate both small molecules and macromolecules. Moreover, monocytes can inherently migrate towards pathological sites, such as infections, inflammations and tumors. Leukocytes can even cross the blood brain barrier (BBB), and differentiate into macrophages after tissue infiltration [24, 47, 48].

Platelets are highly reactive and sensitive, and possess the natural targeting capability to migrate to the injury sites, or specific tissues such as tumors. Such unique properties of platelets are largely owing to the functional receptors on the platelet membrane [49, 50]. Earlier study showed that doxorubicin-loaded platelets can induce much higher cytotoxicity to tumor cells both *in vitro* and *in vivo*, as compared to the free drug [50].

Stem cells have gained much interest as well, due to their regenerative potential and the capacity of migrating towards pathological sites and malignant lesions [51, 52]. Apart from their intrinsic specific disease-tropic properties [53, 54], modified stem cells could also express or release various therapeutic agents, thereby greatly prolonging the short half-life of many chemotherapeutic agents [55, 56]. Our previous studies have also demonstrated that mesenchymal stem cells (MSCs) are potential efficient vehicles that are capable of targeting multiple sites to exert therapeutic benefits, which is exemplified for brain diseases [58] and cancer treatment [52, 56, 76, 88, 89] (**Figure 1**).

Live-attenuated bacteria can also be regarded as a subfield of cell carriers, which has been exploited as a potential vaccine vector for a number of infectious diseases and cancers [59-61]. Our previous studies

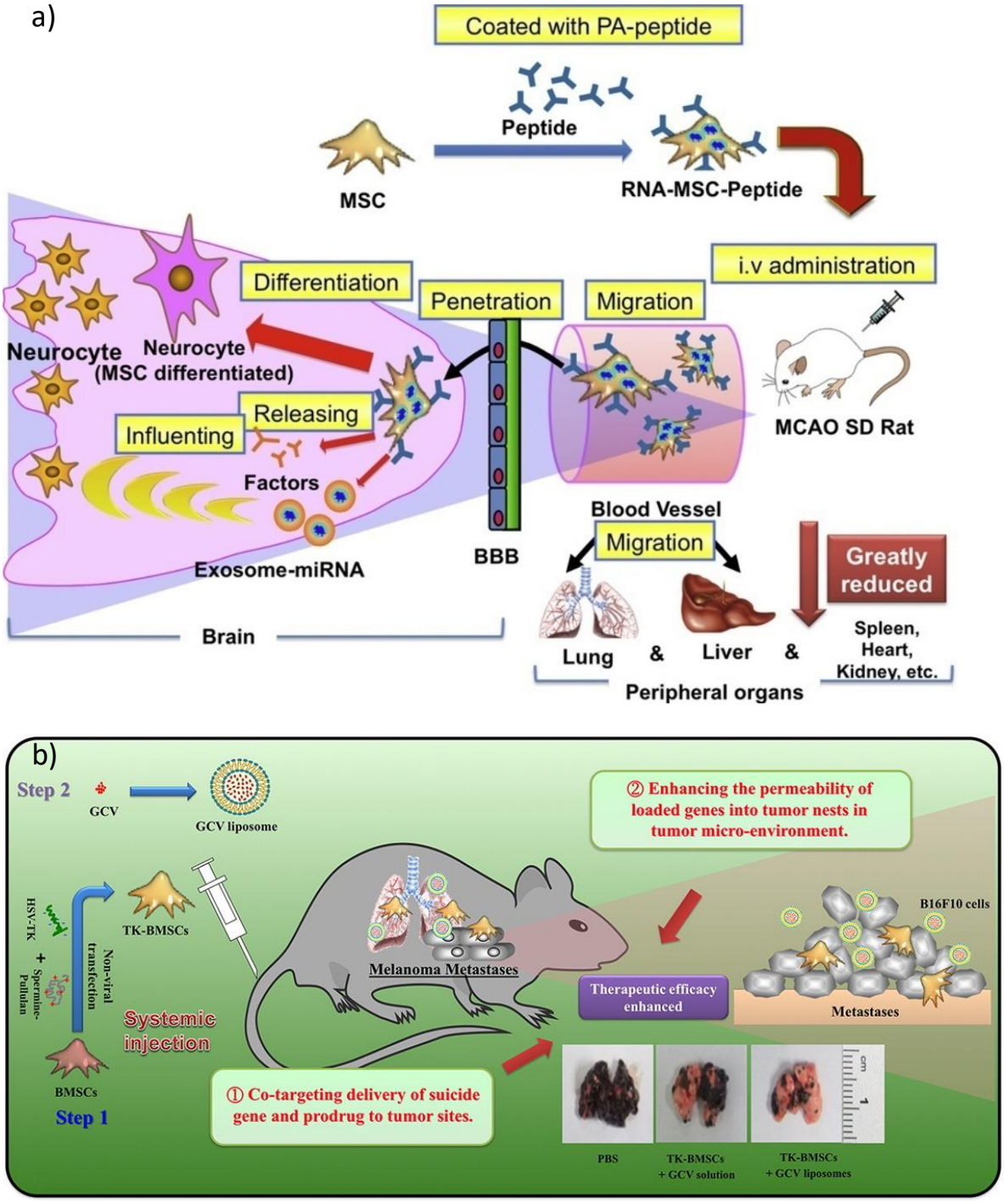

Figure 1: a) Peptide-modified mesenchymal stem cells (MSCs) transfected with miR-133b were exploited as the delivery system for the treatment of cerebral ischemia. With enhanced cell homing to ischemic tissues, MSCs modified with targeting peptide were able to penetrate through brain-blood barrier (BBB) to deliver therapeutic microRNA miR-133b, which greatly reduced off-target migration of MSCs to peripheral organs. Apart from releasing therapeutic agents, MSCs themselves would also act as the therapeutic agents by differentiating into neurocytes to improve recovery [58]. b) The co-targeting delivery system consisting of bone marrow-derived mesenchymal stem cells (BMSCs) and ganciclovir (GCV) liposomes enhances the efficacy of suicide gene therapy in aggressive lung melanoma metastases. Such a system could deliver the suicide gene simultaneously to the tumor tissue with improved permeability of BMSCs into tumor nests, and co-deliver the prodrug GCV via passive targeting of liposomes, which enhances the therapeutic efficacy [56]. (Copyright 2017, Elsevier. Copyright 2015, Elsevier.)

Table 1: Characteristics and limitations of different cells as drug carriers.

Cell type	Characteristics	limitations	References
Erythrocytes	Inherent long life-span in vivo, > 100 days High availability of preparation Natural MPS-targeting ability Good biocompatibility and non-immunogenicity Large volume and high surface-to-volume ratio with high drug loading potential Reversible deformation Well known catabolism in vivo Capability of loading diverse agents	Short ex vivo shelf-life Extra modifications for valid delivery to other targets apart from MPS Complicated ex vivo processing	25, 27, 38, 42-46, 72
Platelets	Relatively long life-span in circulation, typically 7-9 days High storage and trafficking capacity Inherent targeting to the injury sites or the sites with higher density of proliferating Good biocompatibility and non-immunogenicity High reactivity and sensitivity in response to cell micro-environment	Short ex vivo shelf-life Difficulty in genetic modification Difficulty in preparation Danger of thrombosis or bleeding upon undesirable activation	45, 49, 50
Leukocytes	Relatively long life-span in circulation, typically 7-14 days Adherence to endothelium; interaction with solid tumors and metastasis cancer cells Good biocompatibility and non-immunogenicity Simple encapsulation by phagocytosis Good capability of loading diverse agents Strong capability of crossing biological barriers, such as BBB	Difficulty in preparation and quality control (As the least component in blood, leukocytes have various sub-species with different morphologies) Risk of hampering host defense (over-loading the MPS and immune system) Risk of triggering or aggravating inflammation	24, 44, 47, 48
Stem cells	Strong capacity of migrating to pathological sites and malignant lesions Easy preparation and reproduction Natural anti-tumor properties Good biocompatibility and non-immunogenicity Strong capability of crossing biological barriers, such as BBB Good capability of loading diverse agents Ability to trans-differentiation and self-renew	Safety concern over long-term effects (risk of tumor progression and metastasis) Difficulty in preparation and quality control Expensive for individualized treatment	37, 51-56, 58, 76, 88, 89

indicated that live-attenuated *Salmonella* coated with synthetic nanoparticles could work as oral DNA vaccines for cancer immunotherapy [62]. As compared with bacterial formulation alone, such a living hybrid system offers several distinctive advantages including efficient phagosome escape, improved acid tolerance of bacteria in stomach and intestines, and enhanced antitumor immunity.

2.2 Modification methods for cellular carriers

2.2.1 Surface modification or attachment

Several approaches for the modification or attachment of certain bioactive moieties over the cell surfaces were developed in the past decades. These strategies can normally be divided into the following categories: i) ligand-receptor conjugation [26, 63, 64]; ii) biotin-streptavidin conjugation [65-67]; iii) covalent coupling [68]; vi) lipid fusion [57, 58]; v) adsorption, including hydrophobic binding [69, 70], electrostatic interaction [71], hydrogen-bonding, *etc*. (**Figure 2** and **Table 2**)

The former three approaches are dependent on the specific membrane proteins available on the cell surface. For instance, CD44 on leukocyte membrane interacts with hyaluronic acids [26, 63, 64], tumor-targeting streptavidin is readily conjugated on the biotinylated cell membrane [65, 66], and free thiols over T-cell membranes react with maleimide groups presented on the liposomes [67]. Lipid vesicles and lipid rafts, which are specialized membrane microdomains that usually contain functional receptors or

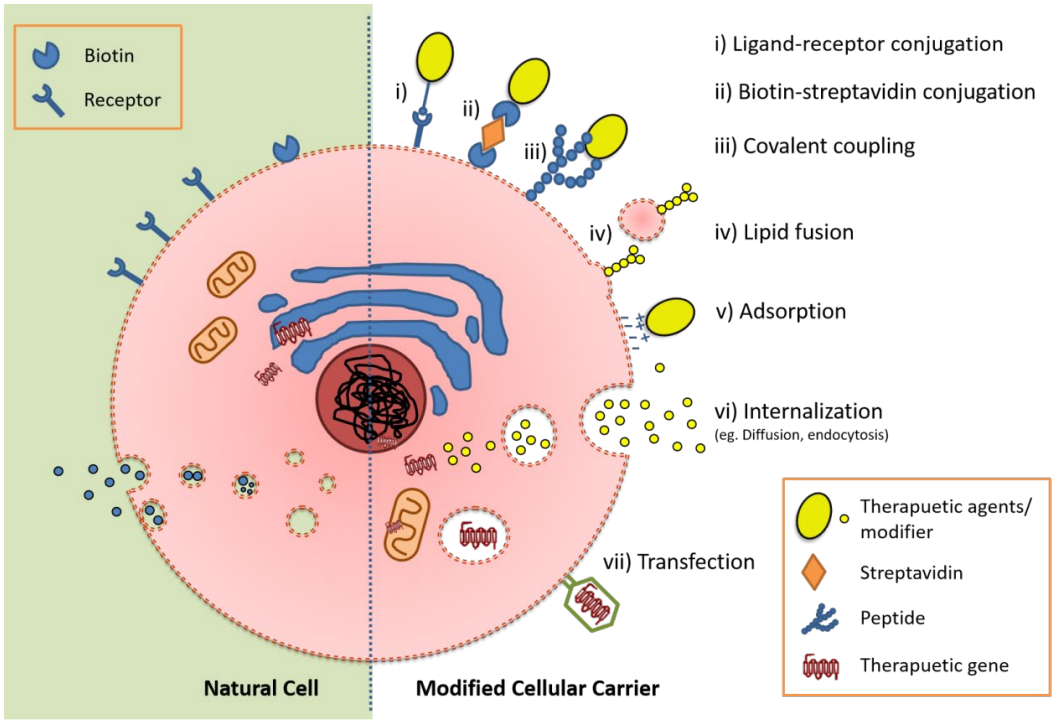

Figure 2: Modification methods of cellular carriers. The modification methods include ligand-receptor conjugation, biotin-streptavidin conjugation, covalent coupling, lipid fusion, adsorption, internalization, and transfection.

targeting ligands, are documented as effective tools for the modification of cell surface under the same mechanism of lipid fusion process, such as introduction of targeting peptide and biotin moieties onto the cell surface [57]. Our group has previously demonstrated that targeting peptide modified over the surface of MSCs would direct themselves to the specific tissues, such as ischemic lesion in the mouse model with middle cerebral artery occlusion (MCAO) (**Figure 3**) [58, 78].

Adsorption has also provided another solution for anchoring drugs to the cell surface. This approach largely relies on non-covalent binding between therapeutic agents or modifiers and cell membrane, and usually take place on the exterior surface of cell membrane. Motivated by the phenomenon of bacteria adhesion to erythrocyte, Mitragotri and co-workers demonstrated that coupling of nanoparticles (NPs) to the erythrocyte surface would effectively improve the delivery of NPs while avoiding MPS clearance [69, 70]. Compared with hydrophobic binding, electrostatic interaction would be a simpler option for positively charged therapeutic agents [71].

2.2.2 Therapeutic agent internalization

Encapsulation of therapeutic agents inside cellular carriers can avoid alteration of cell membrane and protect them from interacting with immune recognition residues as well as unexpected ligands *in vivo*.

Studies have already shown that a wide range of agents ranging from small molecular drugs to bio-macromolecular therapeutics can be encapsulated by erythrocytes owing to its simple constitutions [72]. To fabricate erythrocyte-based nanomedicine, various strategies, including electroporation [73], hypotonic treatment [46], co-incubation [27], have been developed for encapsulating therapeutic agents into erythrocytes. These approaches were mainly established for the transient improvement of membrane permeability. Apart from the passive diffusion, active endocytosis is also available for cells with phagocytosis capability to internalize drugs and/or drug-loaded NPs. The combination of nanoparticles and functional macrophagocytes/monocytes has been proven to be an efficient delivery system by numerous studies [74, 75]. For other cells without phagocytosis capability, peptide-mediated membrane permeation strategy has also been proposed [74]. This strategy mainly relies on the strong penetrating capability of low molecular weight protamine (LMWP) to mediate biomacromolecule delivery

Table 2: Modification methods, advantages and disadvantages of cellular carriers.

Modification method	Advantages	Disadvantages	References
Ligand-receptor conjugation	Reliable and reproducible Apart from ex vivo loading, this approach can also be applied to the decoration of targeting cells in vivo by directly injecting targeting agents	Possible influence of cell functions or phenotypes through specific signal pathway Binding constant is dependent on the ligand-receptor binding affinity May encounter unexpected competitive ligand exchange to decrease or lose the therapeutic response	26, 63, 64
Biotin-streptavidin conjugation	Wide range of therapeutic cargos Local and controlled release can be achieved via the alternative pathway of complement-induced lysis	Proper valence of avidin and the surface density of biotin on membrane are requested to avoid unexpected alternative complement pathway-mediated lysis of biotinylated cells	65, 66, 68
Covalent coupling	Stable conjugation, suitable for vehicles designed to the migration through endothelium	Chemical modifications of cell membrane are required Proper reactive groups are needed to be carefully selected according to the properties of both therapeutic agents and cell carriers	67
Lipid fusion	Relatively simple fabrication procedures	Directional control of the facet of fusing lipid rafts is difficult	57, 58
Adsorption	The simplest method with minimal limitation of therapeutic cargos	Particles may detach unpredictably in vivo due to the weak bonding Positively charged particles may cause damage to cell membranes	69-71
Internalization	Avoiding the alteration of cell membrane, and protecting therapeutics from unexpected interactions in vivo Diverse choices of therapeutic agents	Allogeneic therapeutics may affect original cell structure and functions Limited choices on cell types Drugs may be degraded within the cell before release Difficulties in controlling release of encapsulated drugs	27, 46, 73-75
Genetic modification	Suitable for any biologics with low immunogenicity Maintenance of the integrity of natural cells	Unknown influences on original cell functions or phenotypes Concerns on the intracellular stability and in vivo fate of genetic devices	76, 78-86, 88

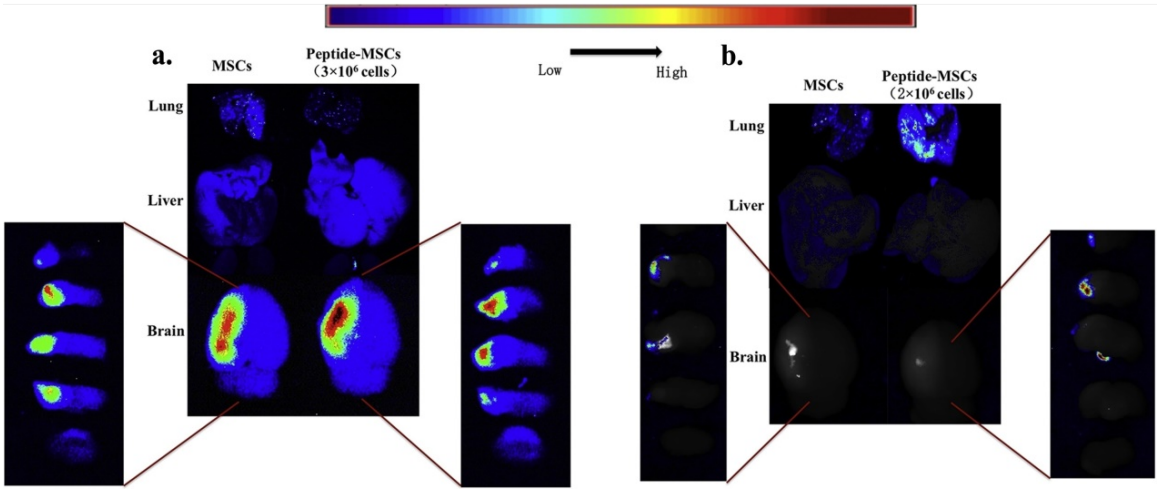

Figure 3: *In vivo* cell homing assessment. MSCs (stained with Dil) with or without PA–peptide coating were intravenously injected into rats at 3 d post-MCAO. Distribution of MSCs either (a) 3 × 10^6 cells or (b) 2 × 10^6 cells in the brain at 24 h after cell administration. Lung, liver and brain tissues and brain slices were analyzed using *in vivo* imaging systems. The fluorescence bar indicates the fluorescence intensity and is shown in different colors. [43] (Copyright 2018, Elsevier.)

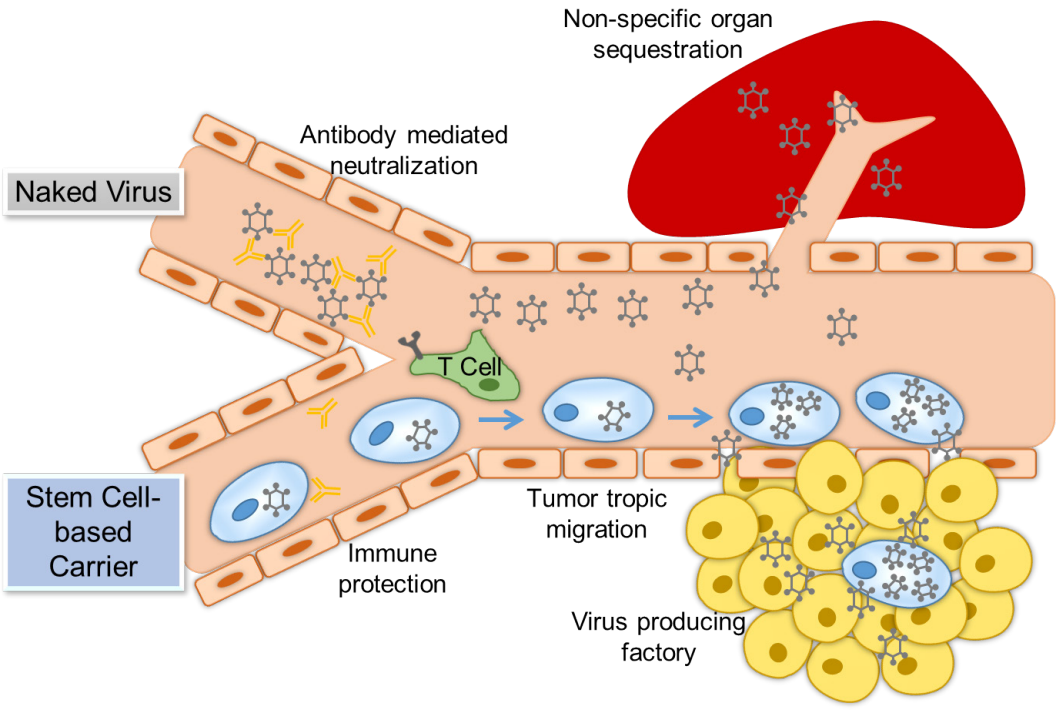

Figure 4: Illustration of cell carriers for targeted oncolytic virotherapy. Compared with naked virus, oncolytic viruses encapsulated by stem cells were able to evade immune clearance, achieve tumor tropic migration with less non-specific organ sequestration, and transfect tumor tissues.

by direct conjugation of peptides or proteins with LMWP [74]. It has also been widely applied to various other cargos, including plasmid DNAs, siRNAs, nanoparticles and liposomes [75].

2.2.3 Genetic modification

With the rapid development of cell therapy, genetically engineered cells present an autologous platform of therapeutic delivery.

The prerequisite of genetic modifications is the efficient gene transfection *in vitro*. Both viral, non-viral transfection and other transfection systems have been utilized on cellular carrier engineering previously, and different strategies for gene recombination of cells were reviewed elsewhere previously [52, 76, 77]. In general, retrovirus, lentivirus, adenovirus and adeno-associated virus have been widely used in gene transfection with high transfection efficiency. Example on oncolytic virus, which serves as gene vector as well as anti-tumor agent, has been showcased for anti-glioma and anti-pancreatic cancer therapy [78, 79]. Despite the initial success of oncolytic virus therapy with the ability to selectively target and lyse tumor cells in preclinical practices, the clinical success of oncolytic virus therapy has been significantly hampered due to the inability to target systematic metastasis and the virus-neutralizing mechanisms of the host immune system [80, 81]. To overcome this issue, alternative cellular carriers like mesenchymal stem cells have been explored for their immune suppression and tumor targeting characteristics (**Figure 4**). MSCs transduced with adenoviruses have been confirmed to be feasible for the treatment of glioma, breast cancer, ovarian cancer and liver cancer [82-86].

Though viral vectors could provide high transfection efficiency, some clinical trials using viral vectors have been interrupted due to the unexpected adverse effects such as immunogenicity and oncogenicity induced by viral vectors [87]. Therefore, an increasing number of non-viral vectors have been developed in recent years. Based on our previous researches, PEI600-Cyd [88] and spermine–pullulan [52, 89] are suggested as efficient gene vectors for cells which is hard for transfection, such as MSCs.

Utilizing different types of stem cells as gene delivery vehicles may lead to different outcomes. Whereas umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) suppress glioblastoma multiform proliferation, adipose tissue-derived mesenchymal

stem cells (AT-MSCs) support the proliferation, because the expression level of tumor necrosis factor-related apoptosis-inducing ligands by UCB-MSCs was higher than those by AT-MSCs [90].

The main concern of using genetic modified cells is the safety as well as their intracellular stability. Effective measures are needed to prevent genetic constructs from transferring to neighboring cells, altering their normal function, and inducing mutagenesis of oncogenesis [91-94]. Besides, the same infection approach applied on different cells may have different influences on cell properties, such as instinctive targeting ability [92-94].

3 Cell-derived hybrid delivery systems

Though cell therapy has been considered as a promising therapeutic option and has been approved for clinical application in some countries recently, it is undeniable that cell carriers are limited by many defects. For example, the difficulty in obtaining sufficient number of cells, the lack of ability to expand *in vitro*, its short *ex vivo* shelf-life and safety concern. Cell derivative-based bio-hybrid delivery systems could provide another delivery approach because they are easier to acquire, process and store.

3.1 Extracellular vesicles

The commonly studied categories of extracellular vesicles (EVs) are exosomes, microvesicles and apoptotic bodies. Exosomes originate from the exocytosis of endosomal multi-vesicular bodies (MVBs), 40-120 nm in size [95]. Microvesicles, also known as ectosomes, are approximately 50 nm to 1 μm in diameter. They are produced from the outward budding of the plasma membrane, while apoptotic bodies are generally bigger, ranging from 50 nm to 5 μm in size, produced by blebbing from cells undergoing apoptosis [96]. Exosomes were first harvested by Johnstone *et al.* from *in vitro* culture of sheep reticulocytes back to 1980s [97], and have gained increasing attention for their potential in pharmaceutical applications recently. We have previously summarized the characteristics of exosomes and discussed their potential to deliver drugs and genes [95]. Owing to their naturally cell-to-cell transporting ability and various contents from proteins, lipids to nucleic acids, exosomes released from specific cells can produce healing efficacy for relevant diseases [98-100]. Given the properties above, researchers have also developed exosomes as drug delivery vehicles to deliver therapeutic agents [33, 101, 102], some of which has reached clinical trial stage [103, 104]. For example, exosomes harvested from autologous dendritic cells are exploited to deliver tumor antigens in phase 1 study for patients with non-small cell lung cancer [105].

3.1.1 Isolation of extracellular vesicles

Several methods have been developed for the isolation and collection of exosomes, including differential ultracentrifugation (UC), density gradient centrifugation, size exclusion chromatography (SEC), filtration, immuno-affinity isolation, *etc.* [106] The first protocol of exosomes isolation, which is commonly regarded as the 'gold standard', is based on differential ultracentrifugation approach [106]. Samples were pretreated by increasing speed centrifugation, usually 2,000-10,000 ×g, or other processes, such as filtration, to remove microvesicles and cell debris. Microvesicles can be then collected with centrifugation at 10,000-20,000 ×g. While apoptotic bodies request much lower centrifugation speed at about 2,000 ×g, the vesicles ranging from 40 to 120 nm can precipitate after ultracentrifugation above 100,000 ×g.

One of the drawbacks for UC approach is the incomplete separation of EVs from contaminants, like protein aggregates and lipoproteins. To further purify exosomes, sucrose density gradient centrifugation and size exclusion chromatography (SEC), which are based on density and size differences, have been applied. However, isolation through centrifugation may not be widely applied into clinical practice due to the time-consuming process, the possibility of aggregation and rupture of EVs due to high shear forces [107]. SEC is performed by neutral polymeric column which contains numerous pores to entrap macromolecules with different hydrodynamic diameters. These pores enable the separation of EVs and contaminants by differential exclusion or inclusion as they pass through the column [108]. SEC has been well used owing to its rapid isolation of relatively pure EVs. Ultrafiltration is another approach to avoid EVs from aggregation or loss of integrity [109]. Immuno-affinity isolation, based on selective capture of EVs that bear specific surface proteins, can be useful to isolate specific subtype of EVs [110]. Furthermore, antibody-coated magnetic beads [111] and microfluidic circuits [112] have been described as the adsorption platform. These methods are efficient for samples with small volume and well-defined EV markers. Based on the methods above, commercial products for exosome isolation have been

developed as well, such as OptiPrep™, ExoQuick™, Exospin™ and Izon qEV columns *etc*. [113]

3.1.2 Encapsulation of extracellular vesicles

Apart from endogenous proteins and nucleic acids from specific cells, EVs can also be fabricated to load therapeutic cargos, such as exogenous proteins, small interference RNA, therapeutic compounds, and protect therapeutic agents from phagocytosis and degradation. Loading approaches can be divided into two different ways. One is based on endogenous cell exocytosis pathway, the other is based on the direct loading into isolated EVs. The former approach is mainly applied for biological agents, where the transfection efficiency may be a vital issue to be concerned. Several studies have already shown that genetic fusion and cell transfection could provide feasible approaches to load small RNA and protein into EVs, or modify the surface of EVs [33, 100, 104, 115]. For phagocytic cells, such as murine macrophage RAW264.7 cells or human HEK293 cells, soluble proteins can be endocytosed through co-incubation with cells and released via EVs [116]. By using the similar approach, the encapsulation of chemotherapeutic drugs is successfully achieved as well. For example, paclitaxel (PTX) could be loaded into EVs by incubating mesenchymal stromal cells with a high dosage of PTX [117].

Post-loading of cargos into purified EVs can be achieved by directly mixing hydrophobic drugs and EVs, yielding the loading efficiency from 1 to 10% [118, 119]. Fusogenic liposomes and lipid rafts can serve as effective platforms for drug loading both before and after EVs isolation [120]. Whereas passive loading may be arduous for hydrophilic compounds and macromolecular proteins, various fabrication processes have been proved to improve loading capacity, such as sonication, freeze-thaw cycles, extrusion, detergent-mediated permeabilization (for example, saponin), *etc*. [121-123] Besides, electroporation is also effective and commonly used for the encapsulation of both hydrophilic drugs [102] and siRNA [33, 115]. However, this loading method has not been applied to the loading of miRNA and other functional RNA yet, probably due to the disruption of their functional structure during the electroporation process [124]. Above fabrication methods could induce unexpected damage to the integrity of exosome and cause exosome aggregation. Protective approaches using membrane stabilizers such as trehalose [125] have been investigated to avoid above-mentioned issues.

3.2 Outer-membrane vesicles

Other commonly used membrane vesicles in medical research are outer-membrane vesicles (OMVs) (20-300 nm in size), which carry proteins screened by a sorting mechanism similar to exosomes. OMVs are released from Gram-negative bacteria [126], and usually work as vaccines or vehicles engineered for the treatment of bacterial or viral diseases [34, 127-129]. They have also been explored as potential drug delivery vehicles for cancer therapy in recent years [126, 130].

OMVs can be naturally derived from the bacterial outer membrane or artificially produced with detergent extraction, sonication and/or vortexing. The contents, size and immunogenicity of artificially produced OMVs may be different [131]. Detergent (such as sodium dodecyl sulfate and non-ionic surfactants sodium deoxy cholate) extraction is a well-established approach to increase vesicle release and to remove lipopolysaccharide (LPS) so as to attenuate toxicity. For instance, Waterbeemd and co-workers have compared chelating agents EDTA and detergent-extracted OMVs with natural ones, and indicated that the fabrication of *N. meningitides* OMV vaccine in the presence of EDTA would improve efficacy and safety of the *N. meningitides* [132, 133]. To collect naturally produced OMVs, fabrication processes such as ultracentrifugation (at a speed of 50,000-200,000 × g) and filtration is usually used, which is similar to the procedures of exosome isolation [134-136]. The detailed purification procedure of OMVs was described previously [135]. Although the simplest way is to collect native OMVs from target pathogen, tailored OMVs obtained through bacterial engineering can provide a more sophisticated platform for vaccine preparation or delivery. Genetic means are widely used for detoxification [132], heterologous and/or recombinant formation of OMVs [137] as well as the modification of OMVs [134, 138]. Although OMVs usually act as antigen delivery vehicles, therapeutic agents like siRNA can be encapsulated through electroporation method as well [126]. (**Figure 5**)

3.3 Nanoghosts --- artificial membrane vesicles

Despite the low immunogenicity, natural targeting capacity and versatility of EVs, the low yield from various fabrication approaches still represents the major hurdle in both scientific research and clinical translation. Artificial membrane vesicles such as nanoerythrosome, seem to be an attractive alternative [139-141]. To stimulate

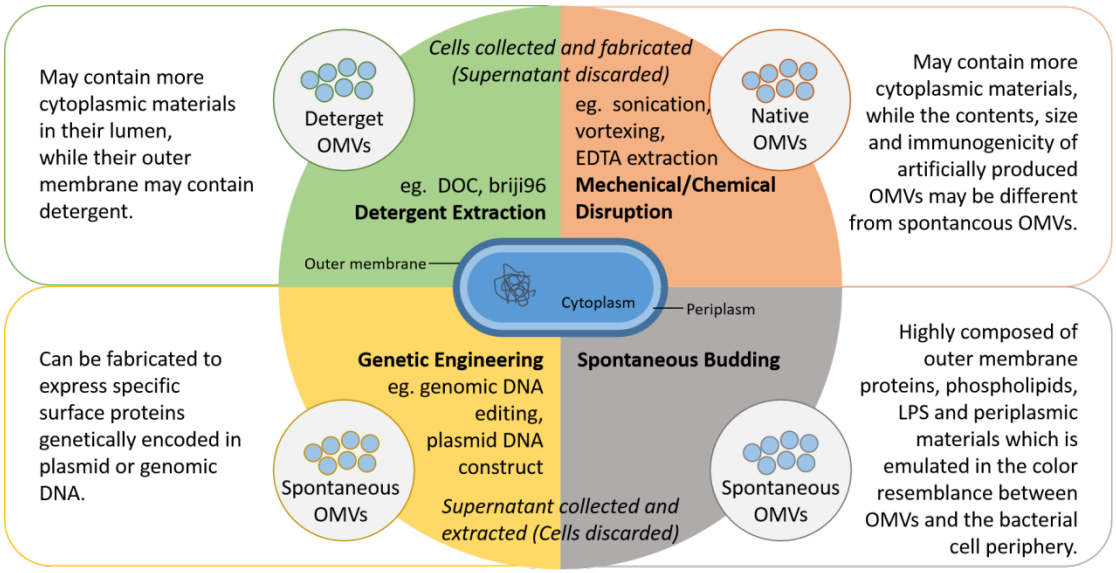

Figure 5: Characteristics and Fabrication Methods of Outer-membrane Vesicles.

the formation of EVs, eukaryotes were irradiated with ultraviolet light to induce apoptosis [32]. Other approaches for producing nanoghosts were also investigated. For example, hypotonic lysis and resealing following the restoration of isotonicity were also carried out to prepare erythrocyte ghosts back to 1970s [139].

Encapsulation of drugs by passive diffusion can be sorted by the properties of agents used. Diverse approaches have been explored for diffusible drug loading to enhance the permeability of cell membrane, such as hemolysis and resealing method, antibiotics-inducing approach using amphotericin B [142], *etc*. Dilutional hemolysis with hypotonic solution (0.4% NaOH) at 0 °C and resealing at 37 °C could obtain membrane ghosts that loaded low molecular weight drugs directly such as β-glucosidase and β-galactosidase, though with relatively lower encapsulation efficiency (1-8%) [143]. In order to improve the loading efficiency, preswell dilutional hemolysis has been developed. Initial swelling of erythrocytes with slightly hypotonic solution, followed by low speed centrifugation ahead was investigated to increase the loading efficiency up to 72% on thyroxin, ibuprofen, *etc*. [144]. Likewise, methods of the loading of cell-derived vehicles introduced in the former section can be applied to the entrapment of non-diffusible drugs and/or surface modification. The nanoerythrosomes (NEs) were obtained by consecutive extrusions of the erythrocyte ghosts through 400-1000 nm filter in a thermostatically controlled extrusion device at 37 °C [140]. Apart from the well-developed technique of extrusion [141], sonication [145] and electrical breakdown method [146] are also reliable approaches to prepare NEs. In addition, nanoghosts derived from other cells, for example, monocytes [147], mesenchymal stem cells [148, 149], and even non-tumorigenic epithelial cells (MCF-10A cell line) [150], were utilized as deliver vehicles as well to target multiple cancers, and showed impressive therapeutic effects against tumor growth.

3.4 Membrane-cloaked nanoparticles

To take advantages of both synthetic nanoparticles and biogenic platforms, scientists have come up with a biomimetic strategy by which nanoparticles are camouflaged with endogenic membranes. This new membrane-cloaked platform can be built as a dual drug release system, where the rapid release of one drug could be realized from the surface membrane layer, and sustained release of the other drug could be achieved from the nanoparticle core. Nanoparticles coated with different membranes exhibit different characteristics. For example, hemolytic membrane coating usually prolongs the circulation time of NPs [151, 152], platelet membrane-coating promotes the adhesion of NPs to damaged vasculatures as well as platelet-adhering pathogens [29], and cancer cell membrane-coating enhances tumor-specific immune response [153].

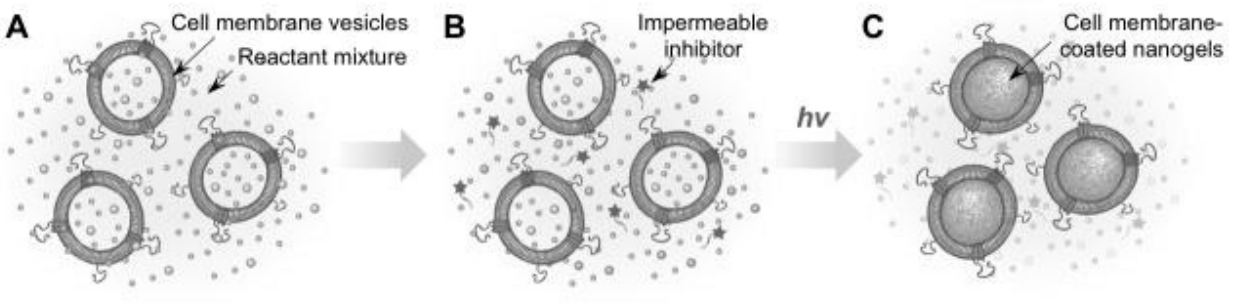

Figure 6: Schematic illustration of the fabrication procedure of cell membrane-coated nanogels [159]. (A) Cell membrane-derived vesicles are formed from cell membrane ghosts together with desirable monomers, crosslinkers, and photo initiators via an extrusion method. (B) The mixture is added with a membrane-impermeable macromolecular inhibitor. (C) The hydrogelation process is then initiated and allowed to proceed under UV light at room temperature. (Copyright 2015, John Wiley and Sons)

3.5 Fabrication method of membrane cloaking

Zhang and co-workers demonstrated that membrane cloaking can be easily accomplished by dispersing and fusing purified cell membrane vesicles with negatively charged particles via sonication at a frequency of 42 kHz and a power of 100 W for 2 min [29], or by co-extrusion through porous polycarbonate membrane with specific pore diameter (usually 100-200 nm) [153]. It has been verified that particles were fully coated and retained membrane functions owing to the asymmetric charge of the cell membranes [154, 155]. Cell membrane purification technique is based on the isolation approaches as mentioned above, including ultracentrifugation, sonication, freeze-thaw cycles, filtration, extrusion, and hypotonic treatment *etc*. Besides PLGA, many other types of materials [31, 156], such as gold and silica NPs, can also be used as the inner templates for the membrane coating [157, 158]. In contrast to the pre-formed nanoparticle-templated membrane coating strategy, the other feasible approach is to grow cell membrane-derived vesicles over the nanoparticle cores *in situ*. To fabricate cell membrane-coated hydrogel nanoparticles (nanogels), the cell membrane-derived vesicle serves as a nano-reactor to encapsulate the precursors of the nanogel, including monomers, crosslinkers, and initiators. In order to prevent possible macrogelation outside the vesicles while keeping the inner reaction active, membrane-impermeable macromolecular inhibitor is synthesized by conjugating (2, 2, 6, 6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to polyethylene glycol (PEG) [159]. The process is summarized in **Figure 6**.

4 Cell-mimicking particles

Cell-mimicking particles belongs to a brand new category, bottom-up synthesis delivery system. As this type of mimic delivery carriers mainly depends on the particle morphology, erythrocyte and platelet are therefore commonly chosen as the paradigms due to their unique shapes. For example, RBC-like flexible particles were fabricated via electrospraying methods based on electrospinning and were demonstrated to have a dual-modality for MRI and fluorescence imaging [160]. Platelet mimetic nanoparticles can be fabricated through lithographic techniques and film stretching method [161, 162]. Mitragotri and co-workers also fabricated erythrocyte-mimicking nanoparticles through hollow polymer spheres based on layer-by-layer assembly of cationic and anionic polymers [163]. These biomimetic nanoparticles, which integrate the biophysical properties of endogenous cells and the versatility of synthetic particles, may become an alternative class of drug delivery systems for a wide range of biomedical applications.

5 Future Outlook

Cellular carriers and their derived bio-hybrid delivery systems have gone through a rapid development in the past decades, and a variety of fabrication methods have been developed and applied for different biomedical applications. Thanks to their inherent characteristics (including low immunogenicity, long circulation capability, inherent homing ability to some specific tissues or focus, high reactivity and sensitivity in response to specific cell microenvironment), cell-derived biomimetic drug delivery systems have been widely explored into

the treatment of various diseases or disorders in order to achieve enhanced therapeutic results. Diverse approaches for the fabrication of these biomimetic carriers have been developed and improved continuously. Furthermore, a number of strategies of integrating synthetic materials with cellular derivatives have been put forward in recent years.

Given numerous advantages of the biogenic nanomaterials, hybrid biomimetic carriers are expected to endow additional capabilities of the existing carriers, such as intelligent site-specific delivery and long circulation capabilities. Considering the complexity of cellular structure and function, many uncovered issues still need to be carefully figured out in the future. For example, microstructure deformation during the integration of synthetic materials with cellular carriers needs to be considered to make sure such integration does not affect the intended function of the cellular carriers. Moreover, safety and functional evaluation on engineered cellular carriers in more dimensions, clear molecular mechanism of homing or targeting ability of carriers should be studied. In addition, the mechanism of actions and the fate of the synthetic biomimetic delivery systems *in vivo* must be carefully studied before further clinical studies. In terms of fabrication techniques, several issues such as low yield and unstable production still limit the larger-scale production of these biomimetic carriers, which may also be the reason why most engineered biogenic carriers were only tested on small animals. At this stage, it is unclear whether these delivery systems are effective in larger animal models. Excitingly, some ongoing clinical trials and many positive results on cell transplantation, as well as a few of new starting attempts on extracellular vesicles in the clinical study clearly indicate that the field of cell-derived biomimetic carriers is worthy of further exploration.

In the past few years, significant progresses have been made in the field of polymeric artificial cells through bottom-up synthesis. With the advances in synthetic biology and material science, bottom-up engineering approaches are becoming a promising approach to construct a minimal cell from natural molecular components [164]. Giant unilamellar vesicles, which are synthetic models of biological membranes mimicking the size and curvature of the plasma membrane, have been fabricated through multiple methods [165, 166]. In addition, the rapidly developed microfluidic technology presented a useful platform for fabricating micrometer-sized vesicles with precise control over size and composition [167, 168], which offers a potential solution to above-mentioned issues, such as low and unstable production of existing hybrid biomimetic carriers in fabrication process. Microencapsulated therapeutic agents or even functional allogeneic cells were already applied as detoxification components for the treatment of acute poisoning [169, 170], in cell transplantation [171, 172] as well as in gene therapy [173]. Furthermore, high-throughput experimentation and machine learning accelerate the integration of biological parts and modules based on comprehensive analysis of biological functions and biological reaction networks [174, 175]. Thanks to the above engineering technologies, giant unilamellar vesicles with functional constituents closely mimic the characteristics of native cells, and even possess the functions of those natural cells [176, 177]. Whereas the capabilities of biological cells are currently far more advanced than synthetic cells [178], it is predictable that synthetic cells with particular functions would be a promising and controllable drug delivery system in the near future.

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