Review

Zhiwen Zhao, Dangge Wang* and Yaping Li*

Versatile biomimetic nanomedicine for treating cancer and inflammation disease

https://doi.org/10.1515/mr-2022-0046
Received December 21, 2022; accepted February 11, 2023;
published online April 7, 2023

Abstract: Nanosized drug delivery systems (NDDSs) have emerged as a powerful tool to optimize drug delivery in complex diseases, including cancer and inflammation. However, the therapeutic effect of NDDSs is still far from satisfactory due to their poor circulation time, low delivery efficiency, and innate toxicity. Fortunately, biomimetic approaches offer new opportunities to develop nanomedicine, which is derived from a variety of native biomolecules including cells, exosomes, bacteria, and so on. Since inheriting the superior biocompatibility and versatile functions of natural materials, biomimetic nanomedicine can mimic biological processes, prolong blood circulation, and lower immunogenicity, serving as a desired platform for precise drug delivery for treating cancer and inflammatory disease. In this review, we outline recent advances in biomimetic NDDSs, which consist of two concepts: biomimetic exterior camouflage and bioidentical molecule construction. We summarize engineering strategies that further functionalized current biomimetic NDDSs. A series of functional biomimetic NDDSs created by our group are introduced. We conclude with an outlook on remaining challenges and possible directions for biomimetic NDDSs. We hope that better technologies can be inspired and invented to advance drug delivery systems for cancer and inflammation therapy.

Keywords: biomimetic; cancer; immunotherapy; nanomedicine; nanoparticles.

***Corresponding authors: Dangge Wang**, State Key Laboratory of Drug Research & Center of Pharmaceutics, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, No. 555, Rd Zuchongzhi, Pudong District, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China; and Yantai Key Laboratory of Nanomedicine & Advanced Preparations, Yantai Institute of Materia Medica, Yantai 264000, Shandong Province, China, E-mail: dgwang@simm.ac.cn. https://orcid.org/0000-0003-3005-4272; and **Yaping Li**, State Key Laboratory of Drug Research & Center of Pharmaceutics, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, No. 555, Rd Zuchongzhi, Pudong District, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China; and Shandong Laboratory of Yantai Drug Discovery, Bohai Rim Advanced Research Institute for Drug Discovery, Yantai 264000, Shandong Province, China, E-mail: ypli@simm.ac.cn. https://orcid.org/0000-0002-0574-6966
Zhiwen Zhao, State Key Laboratory of Drug Research & Center of Pharmaceutics, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China; and University of Chinese Academy of Sciences, Beijing, China

Introduction

Cancer is one of the public health problems worldwide, leading to high mortality rates in humans [1]. The complexity, variety, and dynamic characteristics of cancer provide several difficulties for both research and therapy [2]. Conventional treatments such as surgical resection, chemotherapy, or radiotherapy might fail to achieve satisfactory efficacy due to tumor recurrence, drug resistance, and severe side effects [3]. Hence, researchers have utilized immunotherapy to elicit immune responses for cancer treatment, such as immune-checkpoint blockade (ICB) therapy [4]. However, some patients still have a low response rate to ICB therapy because of the multiple mechanisms to evade immune surveillance in the tumor microenvironment (TME) [5]. Additionally, inflammation is a protective response to injury or infection, which proved to be associated with many human diseases and even cancers [6, 7]. Inflammatory indicators, such as cell adhesion molecules, are typically involved with complex pathogenesis supporting the importance of inflammation to illness and have been investigated as diagnostic and therapeutic targets [8]. Since cancer and inflammatory diseases are difficult to treat by traditional methods, they need more effective treatment urgently.

Recent progress in materials science and nanotechnology have provided promising solutions to overcome the limitation of current therapeutics. A large variety of inorganic or organic materials with distinct properties such as shape, size, and surface charge, have been employed to construct nanosized drug delivery systems (NDDSs) [9]. Unfortunately, drug delivery through artificial NDDSs alone encounter unexpected challenges, limiting their clinical application. First, NDDSs based on inorganic carriers with cytotoxicity are hard to degrade and easy to bring

safety problems [10]. Moreover, many drugs delivered by liposomes are still found in the liver and other normal tissues due to low drug encapsulation and drug leakage, leading to a further improvement in the biodistribution characteristics of NDDSs [11]. In addition, before the synthetic nanoparticles (NPs) passively reach the target site through the permeability and retention (EPR) effect, they need to cross diverse biological barriers such as blood brain barriers, respiratory barriers, and gut mucus barriers, leading to low drug enrichment efficiency [12]. With the surface modification of polyethylene glycol (PEG), NDDSs intend to enhance their targeting abilities when navigating in the vascular, but may still rapidly bind blood proteins and are readily cleaved by immune cells due to the anti-PEG immunity [13]. Consequently, new adjustable active targeting methodologies and controlled cargo release strategies are necessary to improve the specific targeting and on-demand delivery abilities of NDDSs for treating cancer and inflammation [14, 15].

In light of this, by mimicking and replicating the processes in host biology, researchers are inspired by nature to propose novel solutions [16]. Through rational design, biomimetic approaches are currently developed to produce NDDSs which can recapitulate biological processes or inherent biological, chemical, and physical traits of living systems [17]. These strategies implement a variety of biomolecules, cells, cell-derived vesicles, bacteria and so on to realize development of NDDSs for the treatment of cancer and inflammation [18]. Taking advantages of synthetic nanomaterials and natural materials, biomimetic NDDSs offered an excellent platform for precise drug delivery and molecular imaging [19]. Biomimetic NDDSs prolong circulation and lower immunogenicity *in vivo* because of the protection of biological components, which exhibit favorable biocompatibility and reduce adverse effects [20]. With high efficacy and safety profiles, biomimetic NDDSs have the ability to broaden the therapeutic potential of payloads to a wider group of patients while minimizing immunotoxicity [21]. The extensive application of biomimetic NDDSs in complicated biological systems results in a growing demand for multifunctionality. Hence, features of biomimetic NDDSs can be further enhanced by introducing exogenous moieties beyond current natural properties. Researchers have developed strategies such as lipid insertion, membrane fusion, bioorgothonal chemistry, genetic engineering or multiple engineering to achieve efficient modification [22, 23]. Exploiting multiple functions through innovative engineering and novel targeting approaches enable biomimetic NDDSs to improve their performance and extend their utilization for cancer and inflammation therapy (Figure 1).

Herein, to clarify the significance of biomimetic nano drug delivery systems in the treatment of tumors and inflammation, we will first introduce recent advances in diverse biomimetic NDDSs with a focus on biomimetic exterior-camouflaged and bioidentical molecule-constructed delivery systems. Then we will discuss extra engineering strategies well suited for functionalizing biomimetic NDDSs. We will introduce a series of feature-packed biomimetic NDDSs for immunotherapy, which were developed by our group recently. Finally, we conclude the review with a discussion of the challenges and opportunities of biomimetic NDDSs, providing a thorough understanding of functionalizing biomimetic NDDSs for cancer and inflammation therapy.

Biomimetic NDDSs

There are two approaches to creating biomimetic NDDSs. First, biomimetic exterior-based NDDSs could utilize natural biomolecules to camouflage foreign nanoparticles in apparently native material. There are various feasible methods to put this into practice. One way is to directly modify synthetic nanoparticles with functional proteins, antibodies, or glycans by physical adsorption or chemical conjugation. Another facile method involves disguising a nanoparticle with a cell membrane coating to seem indistinguishable from the host's cells. Another strategy is hitchhiking nanoparticles with cells to hide them in the cells of interest.

For the second biomimetic approach, nanoparticles can be constructed exclusively by naturally-existing bioidentical components. This technique employs a variety of nanoscale biomaterials, including endogenous protein-like nanoparticles, lipoprotein-like nanoparticles, exosome-like nanovesicles, bacteria-like particles, and so on (Figure 2, Table 1).

Biomimetic exterior-camouflaged NDDSs

Biomolecule-coated NDDSs

Synthetic nanoparticles could be coated with biomolecules including proteins, polysaccharides and lipids for drug delivery, due to their excellent biocompatibility, biodegradability, and non-immunogenicity. One strategy to achieve such biomimetic nano delivery systems is through physical adsorption. For example, through interaction with host biology, nanoparticles can form a protein corona by adsorbing diverse plasma proteins during blood circulation [45]. Human serum albumin (HSA), as one of the most commonly discovered proteins in the protein corona, is more likely to accumulate in tumors since it can provide amino acids and energy

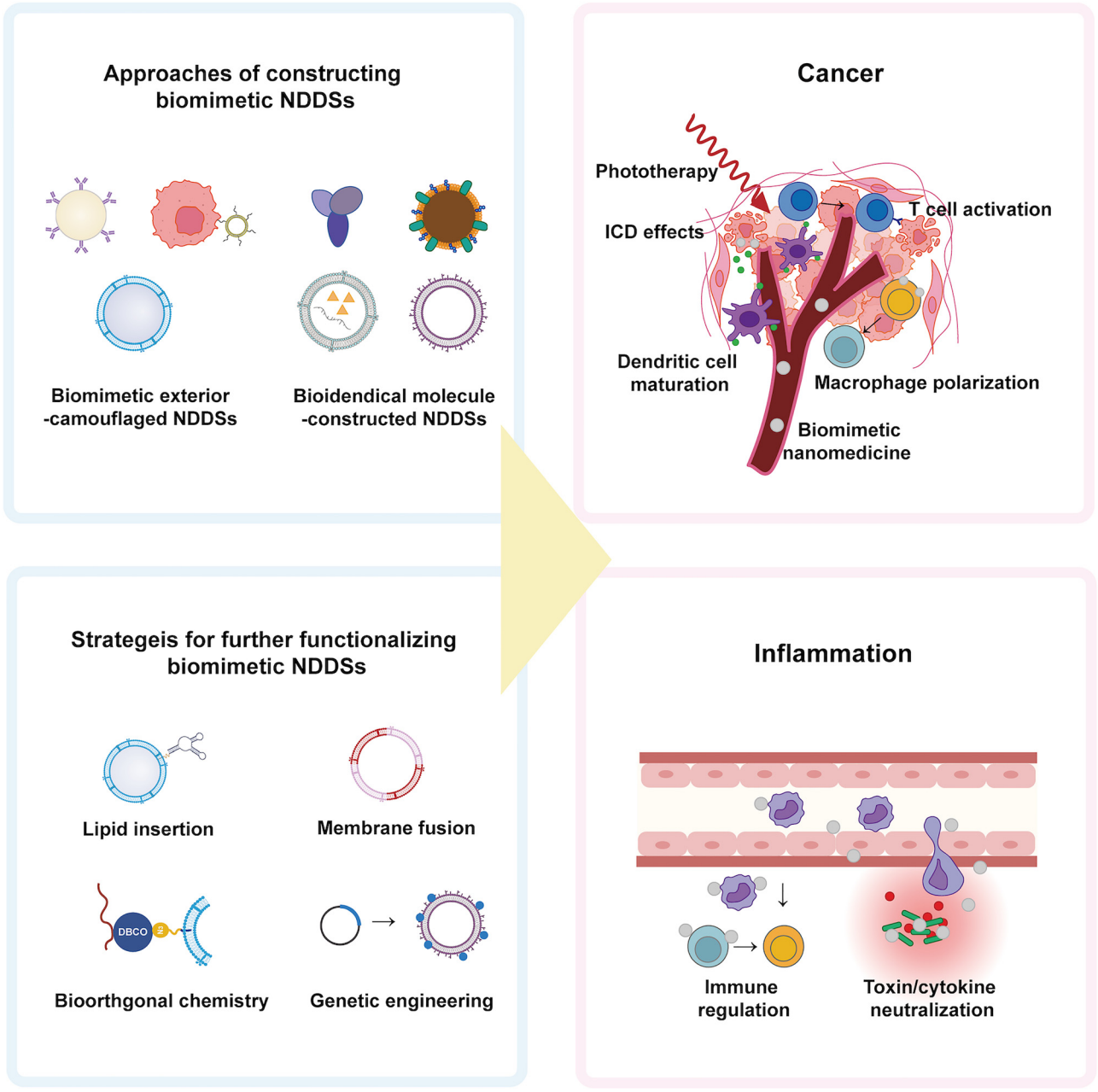

Figure 1: Treatment of cancer and inflammation by versatile biomimetic nanosized delivery systems (NDDSs). By taking advantage of the inherent properties of native biomolecules or cells, and functionalizing with novel strategies, biomimetic nanomedicine bestows a variety of functions in targeting, tracking and treating cancer and inflammation diseases. NDDSs, nanosized drug delivery systems; ICD, immunogenic cell death.

for tumor cells [46]. Accordingly, Cao et al. [24] designed biomimetic nanosystems masked with HSA in advance for synergistic therapy. They first linked Nine D-arginine (r9) peptide with dioleoyl-sn-glycerol-3-phosphoethanolamine (DOPE) to form r9-S-S-DOPE, and prepared self-assembly core (DRI) with DOPE, r9-S-S-DOPE, and the photothermal agent IR-780 iodide (IR-780). Then, they complexed Twist small interfering RNA (siRNA) with DRI, which was further camouflaged with free HSA (DRI-S@HSA) on the surface via electrostatic interactions. DRI-S@HSA can be massively internalized in metastatic 4T1 breast cancer cells and limit cell migration and proliferation when combined with laser irradiation. *In vivo* study indicated that DRI-S@HSA enhanced tumor accumulation by 2.5-fold in contrast with the undecorated group and facilitated the deep penetration in tumor mass. Additionally, DRI-S@HSA therapy combined with 808 nm laser irradiation inhibited tumor development by 83.6% and effectively prevented lung metastases. Zhao and her coworkers used a similar strategy to

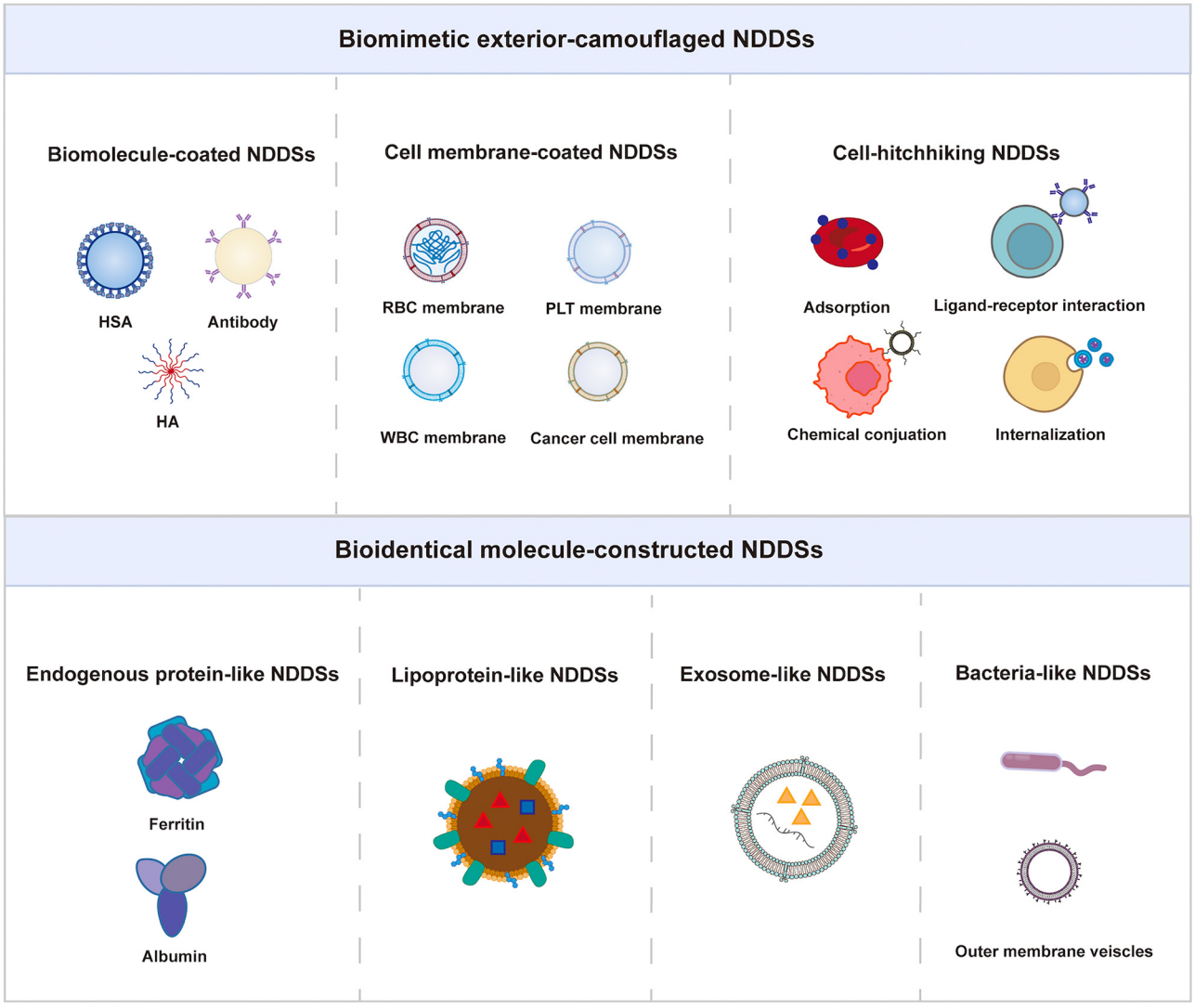

Figure 2: Schematic illustration of two categories of biomimetic nanosized drug delivery systems (NDDSs). Biomimetic exterior-camouflaged NDDSs: nanoparticles coated with HSA or other native biomolecules; cell membranes derived from the RBC, PLT, WBC and cancer cell are used to cloak nanoparticles; nanoparticles attached with the host cell surfaces by adsorption, ligand-receptor interaction or internalized by the host cell. Bioidentical molecule-based NDDSs: biomimetic NPs utilize endogenous protein, lipoprotein, exosomes, and bacteria for particle construction. NDDSs, nanosized drug delivery systems; HSA, human serum albumin; HA, hyaluronic acid; RBC: red blood cell; PLT, platelet; WBC, white blood cell.

construct bevacizumab-coated gefitinib-loaded nanoparticles for molecular targeted therapy against non-small cell lung cancer (NSCLC). Bevacizumab could readily be coated onto the surface of nanoparticles through electrostatic interactions by a corona pre-formation strategy. The biomimetic nanomedicine could be highly accumulated in tumor sites and released bevacizumab upon oxidation condition, whereas gefitinib was released at reduction circumstance of cytoplasm. In human NSCLC models, the controlled release of bevacizumab and gefitinib significantly suppressed tumor growth [25].

Covalent conjugation has emerged as another common strategy for construction of biomolecule-functionalized NDDSs. Hyaluronic acid (HA) is a natural polysaccharide widely distributed in the extracellular matrix. Because of its immunomodulatory characteristics, HA could regulate macrophages, induce antimicrobial peptides and regulatory $CD4^+$ T cells. Consequently, Lee et al. [26] proposed a hyaluronic acid-bilirubin nanomedicine (HABN) system for targeted modulation of the microbiome and immune response in acute colitis. They linked hyaluronic acid (HA) with bilirubin (BR) based on a carbodiimide reaction. The amphiphilic conjugates HA-BR could self-assemble as a HABN system in the aqueous medium. After oral administration, hyaluronic acid-covered HABN can accumulate at the inflamed colonic epithelium of acute colitis mice. And the anti-oxidant property of bilirubin makes HABN

Table 1: Summary of representative work of biomimetic nanomedicine for cancer and inflammation therapy.

Type of biomimetic NDDSs	Natural materials	Payloads	Therapeutic effects	Refs.
Biomolecule-coated NDDSs	Human serum albumin	IR-780 and shRNA	Enhancing tumor accumulation and PTT	[24]
	Bevacizumab	Gefitinib	Enhancing tumor accumulation	[25]
	Hyaluronic acid	–	Enhancing inflammation accumulation and immune regulation	[26]
Cell membrane-coated NDDSs	RBC membrane	MB, Pt	Enhancing tumor accumulation	[27]
	Platelet membrane	FK506	Enhancing inflammation targeting and treatment of rheumatoid arthritis	[28]
	Macrophage membrane	–	Inhibiting bacterial dissemination against sepsis	[29]
	Neutrophil membrane	–	Eliminating cytokines and inhibiting synovial inflammation	[30]
	T cell membrane	Anticancer drug	Enhancing tumor targeting and immunotherapy	[31]
	Cancer cell membranes	neoantigen	Enhancing lymph nodes targeting and immunotherapy	[32]
Cell-hitchhiking NDDSs	Erythrocytes	Doxorubicin	Enhancing pulmonary accumulation and suppressing lung metastasis	[33]
	T cells	IL-2	Expanding T cells in tumors and allowing higher doses of cytokine	[34]
	TNBC cell corpses	Anti-PD-1, doxorubicin	Enhancing pulmonary accumulation and chemo-immunotherapy	[35]
	Monocytes	Docetaxel, NLG919 and HY19991	Enhancing tumor targeting and chemo-immunotherapy	[36]
Endogenous protein-like NDDSs	Bovine serum albumin	Zinc, sulfur	Enhancing effects of immunotherapy	[37]
	Ferritin	DiR, epirubicin	Enhancing tumor cells targeting and effects of PDT	[38]
Lipoprotein-like NDDSs	Lipoprotein	DiR, mertansine	Enhancing tumor cells targeting and PTT	[39]
	Synthetic high-density lipoproteins	DiR, immune primers	Enhancing the combinational effect of PTT and immunotherapy	[40]
Exosome-like NDDSs	Autologous exosomes	Gemcitabine	Enhancing tumor targeting ability and chemotherapy	[41]
	Mesenchymal cells-derived exosomes	siRNA or shRNA	Enhancing targeting ability and gene therapy effects	[42]
Bacteria-like NDDSs	Outer-membrane vesicles	Antibiotics	Improving delivery efficiency and bactericidal effects in the intestine	[43]
	Outer-membrane vesicles	Doxorubicin	Improving delivery efficiency and anti-tumor immunity	[44]

NDDSs, nanosized drug delivery systems; shRNA, short hairpin RNA; PTT, photothermal therapy; RBC, red blood cell; MB, methylene blue; Pt, cisplatin; NK, natural killer; IL-2, interleukin-2; PD-1, programmed cell death protein 1; DiR, 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide; TNBC, triple-negative breast cancer; PDT, photodynamic therapy; siRNA, short interfering RNA.

protect colonic epithelial cells against apoptosis and promote epithelial barrier recovery. HABN can also regulate gut microbiota, improve the richness and diversity of flora, and increase the abundance of *Akkermansia muciniphila* and *Clostridium XIVa*, which are beneficial to intestinal homeostasis. HABN can combine with pro-inflammatory macrophages through HA-CD44 interaction, regulate innate immune response, reduce inflammatory cytokines, increase anti-inflammatory cytokines, and have a potent anti-colitis effect.

Cell membrane-coated NDDSs

Cell membrane-coated NDDSs have recently been investigated broadly for therapeutic and imaging applications. Such new drug nanocarriers were prepared by separating the bioactive cell membranes, combing cell membranes with nanoparticles through repeat extrusion, sonication, or electroporation [47, 48]. By utilizing membranes of red blood cells (RBC), platelets (PLT), white blood cells (WBC), and cancer cells, cell membrane-coated NDDSs inherent biocompatibility. Membranes from RBCs or PLTs could be eligible candidates for long circulation and immune evasion due to the "self-marker" CD47 on the surfaces [49, 50]. Additionally, specific adhesion and binding molecules on the surface of cell subsets help researchers design nanoplatforms that exhibit organotropism for targeted therapy [51, 52].

Recently, the use of red blood cell membranes as a biomimetic covering for nanodrugs has been carefully

exploited as a novel method to prolong nanodrug circulation *in vivo*, due to the presence of a "don't eat me" signal of CD47-signal regulatory protein alpha (SIRPα) [53]. In addition, it is relatively simpler to extract anuclear red blood cells than nucleated cells, and therefore RBC membranes are suitable for large-scale production at low-cost [19]. As a result, RBC membrane-coated NDDSs have been explored as innovative biomimetic carriers to enhance cancer therapy and detoxification treatment [54, 55]. Zhai et al. [27] utilized naturally derived gelatin and erythrocyte membranes to develop a nanoparticle (termed as MPV) containing water-soluble drugs methylene blue (MB) and cisplatin (Pt), which mimicked cytotoxic T cells to realize real-time monitoring, light-controlled stimulation, and cytoplasmic drug delivery. MPV exhibited prolonged circulation in the blood, and the photoacoustic characteristics of the high concentration methylene blue in MPV can be exploited to provide real-time tracking of drug accumulation in tumors. When highly accumulated in tumors, MPVs employed their photothermal/photodynamic properties upon infrared laser irradiation at the tumor site to improve the penetration of MPVs and enhance the delivery of MB and Pt to the tumor cell cytoplasm. Subsequently, combined photodynamic therapy with chemotherapy, apoptosis of tumor cells promoted, MPV regressed the triple-negative breast cancer (TNBC) *in situ* and inhibited the formation of lung metastases by 97%. This study created a new NDDS for visualizing real-time monitoring of drugs in tumors and provided a unique method for the optimal treatment of metastatic TNBC [27].

Taking the high expression of heparinase (Hpa) in tumor cells as a breakthrough, the biomimetic nano-delivery system sensitive to heparan enzyme was designed and constructed by integrating biomimetic nanotechnology and prodrug strategy. Firstly, heparan sulfate (HS) was chemically coupled to the chemotherapy drug docetaxel (DTX) to form an amphiphilic molecule HS-DTX, which can self-assemble to form micelles in the aqueous medium. Then wrapping the red blood cell membrane on the surface of the micelles to construct the bionic nano drug delivery system rHS-DTX. Studies showed that HS-DTX micelles in the rHS-DTX possess significant Hpa-sensitive properties. In MCF-7, a human breast cancer cell with high expression of Hpa, HS-DTX was hydrolyzed by Hpa to release DTX, thereby showing high cytotoxicity. In Hpa low-expression human breast epithelial cell MCF-10A, DTX was linked with HS, which in turn showed low toxicity. The red blood cell membrane shielded the negative charge of HS, ensuring that rHS-DTX would not be phagocytosed and cleared in the circulatory system, targeting drugs to the primary site of the tumor and metastases. In the nude mouse model of metastatic breast cancer, the rHS-DTX group showed a 6.35-fold amount of drugs in tumor than that of the free docetaxel group, with a tumor suppression rate of 98.2% and a lung metastasis inhibition rate of 99.6% [56].

In addition to RBC, platelets have been widely used for cell membrane coating. Platelets are small cellular fragments derived from the cytoplasm of mature megakaryocyte cells in bone marrow, with a lifespan of about 7–10 days [57]. PLTs are not only highly involved in hemostasis, but also play a significant role in the development of many diseases, such as cancer and inflammatory diseases [58]. Chen et al. synthesized Bi_2S_3-mesoporous silica nanorods (BMSNRs) cloaked by platelet membranes. By platelet membrane camouflage, BMSNR enhanced immune escape by reducing endocytosis in the mononuclear phagocyte system. Because phagocytosis was downregulated when SIRPα in the phagocytic cell was triggered by CD47 on PLTs. Besides, platelet membrane coating also changed the surface charge of BMSNR from positive to negative, which might reduce cellular uptake. In addition, platelet membrane coating enhanced the targeting of BMSNR to tumors compared with BMSNR alone, which can exert better radiotherapy effects. Studies showed that platelet membrane-coated BMSNR could effectively eradicate cancer cells in combination with photothermal therapy (PTT) and radiotherapy, significantly improving the survival rate of 4T1-bearing mice. The therapeutic effect of combination therapy is better than that of PTT alone and radiotherapy [59].

Inflamed synovial tissue cells such as macrophages, lymphocytes, and fibroblasts upregulate CD44 expression on their surface and can specifically bind with P-selectin overexpressed on activated platelets. Additionally, collagen IV abundantly exists in synovial tissues and can interact with glycoprotein VI (GPVI) expressed on the platelet membrane. In light of this, He et al. [28] constructed a platelet membrane-coated nanoparticle for rheumatoid arthritis (RA) therapy. Their studies indicated that platelet membrane-coated nanoparticles could specifically reach RA tissues through recognition mechanisms by P-selectin and GVPI, similar to natural platelets. Besides, platelet membrane-coated nanoparticles were used to treat RA by loading with FK506, a model drug. In the collagen-induced arthritis (CIA) mouse model, these nanoparticles showed significant anti-arthritic effects.

Besides, white blood cell membrane-coated nanoparticles play a critical role in immune modulation. White blood cells, including monocytes, macrophages, neutrophils, and lymphocytes, are highly involved in maintaining the balance of the body's immune system. They can recognize inflammation and accumulate in the lesion and have many specific immune recognition receptors on membranes [29].

WBC membrane-coated nanoparticles can act as decoys to attach and neutralize toxic molecules because they retain the antigenic exteriors of the parental cells, such as

macrophages and neutrophils. Thamphiwatana et al. reported the development of macrophage membrane-coated nanoparticles (MΦ-NPs) in the treatment of sepsis. MΦ-NPs maintained the same antigenic properties of source cells. In mouse *Escherichia coli* bacteremia models, the MΦ-NPs treated group showed strong therapeutic effects by neutralizing endotoxins, inhibiting the activation of inflammatory pathways, and reducing the release of pro-inflammatory cytokines [60]. Similarly, macrophage membrane-coated nanoparticles could be used to treat various inflammation diseases, such as SARS-CoV-2 infections, gram-negative infections, rheumatoid arthritis, and atherosclerosis [61–64]. Moreover, the neutrophil membrane was attached to the polymer core to prepare a neutrophil membrane-coated nanoparticle. Such a nanoparticle could neutralize proinflammatory factors such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), target deeply to the cartilage matrix, inhibit synovial inflammation, and have a strong chondroprotection on damaged joints. *In vivo* experiments showed that neutrophil membrane-coated nanoparticles could exert significant therapeutic effects through ameliorating joint damage and inhibiting arthritis [30].

Dendritic cells (DCs) are essential for triggering T cell immune responses against infections and cancer [65]. Chen et al. [66] reported a cascade coating strategy for the preparation of biomimetic nano-DCs vaccines (BNs). They first encapsulated polymer nanoparticles with cancer cell membranes and further matured DCs through incubation. Lastly, they extracted DC cell membranes to coat the surface of polymer nanoparticles. Presenting all antigen epitopes on cancer cell membrane surfaces and retaining intact DC cell membrane components, BNs inherited and enhanced the cross-presentation ability of DCs. Thereby antigen-specific T-cell immune responses were significantly enhanced. Notably, BNs can be used as personalized anti-tumor vaccines. Compared with traditional DC vaccines, this biomimetic nanovaccine has the good lymphatic homing ability and would not be disturbed by biosystem while avoiding the harsh storage and transportation conditions required for DCs vaccines. Researchers demonstrated that BNs could elicit a robust antigen-specific anti-tumor immune response in various mouse models such as melanoma, hepatocellular carcinoma, and cervical cancer. When combined with the programmed death protein 1 (PD-1) immune checkpoint inhibitor, BNs obtained significant effects of further enhancing tumor regression and prolonging the survival of mice [66].

Lymphocytes such as T cell and NK cells have also been investigated for their specific function in immune modulation. Kang et al. [31] developed T-cell-membrane-coated nanoparticles (TCMNPs), which showed better antitumor effects than programmed death ligand 1 (PD-L1) antibodies in mouse melanoma models, due to the tumor-targeting capabilities and the multiple therapeutic mechanisms. Similar to cytotoxic T cells, TCMNPs can target tumors through T cell membrane-derived proteins, which in turn kill cancer cells by releasing anti-tumor molecules and inducing Fas ligand (FasL)-mediated apoptosis. But unlike cytotoxic T cells, TCMNPs are resistant to immunosuppressive molecules such as transforming growth factor-β1 (TGF-β1) and PD-L1 by the exhibited membrane molecules. Furthermore, TCMNPs could also enhance therapeutic effects through synergistic application of chemotherapeutic drugs or a cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) blockade. Additionally, NK cell membrane coated biomimetic vectors can target tumor cells through cell membrane surface proteins. Deng et al. [67] developed a cell membrane immunotherapy strategy capable of disguising nanoparticles through NK cell membranes (NK-NPs) to eliminate primary tumors and inhibit distant tumor growth. By analyzing the protein composition and function of NK cell membranes by proteomic methods, the researchers found that the presence of NK cell membranes enabled NK-NPs to target the tumor and induced macrophages to polarize to M1 type to generate anti-tumor immunity. At the same time, the photosensitizer in NK-NPs can elicit immune-induced death of tumor cells through photodynamic therapy to produce damage-related molecules, thereby enhancing the efficiency of tumor immunotherapy.

Cancer cells can also be used as membrane sources for biomimetic nanodrug delivery systems. Since cancer cells possess unlimited proliferative capacity, they can be efficiently cultured and produced by *in vitro* methods. Cancer cell membranes have many unique properties, including immune escape and extended circulation time. At the same time, cancer cell membranes also inherit the functions of homologous targeting and an array of tumor antigens of source cells, which have been employed in the field of tumor targeted therapy and immunotherapy [68].

Cancer vaccines have been made using autologous tumors, especially personalized cancer vaccines [69]. Xiao et al. [32] proposed a novel approach to combine neoantigen-loaded nanovaccines with adoptive DC transfer for realizing personalized immunization. Neoantigen-loaded nanoparticles were coated with the cancer cell membrane to construct nanovaccines, while autologous tumor lysate-loaded DC vaccines (DCVs) were formed *in vitro* (Figure 3A). After the hybrid administration of vaccines, the study indicated that nanovaccines could deliver neoantigens to resident antigen-presenting cells (APCs) in lymph nodes (LNs) selectively and facilitate the delivery of DCVs to LNs by improving the secretion of chemokine C–C motif ligand 2 (CCL2), CCL3, and C–X–C motif ligand 10 (CXCL10) from macrophages (Figure 3B and C). This synergic strategy initiated the T cell immune response

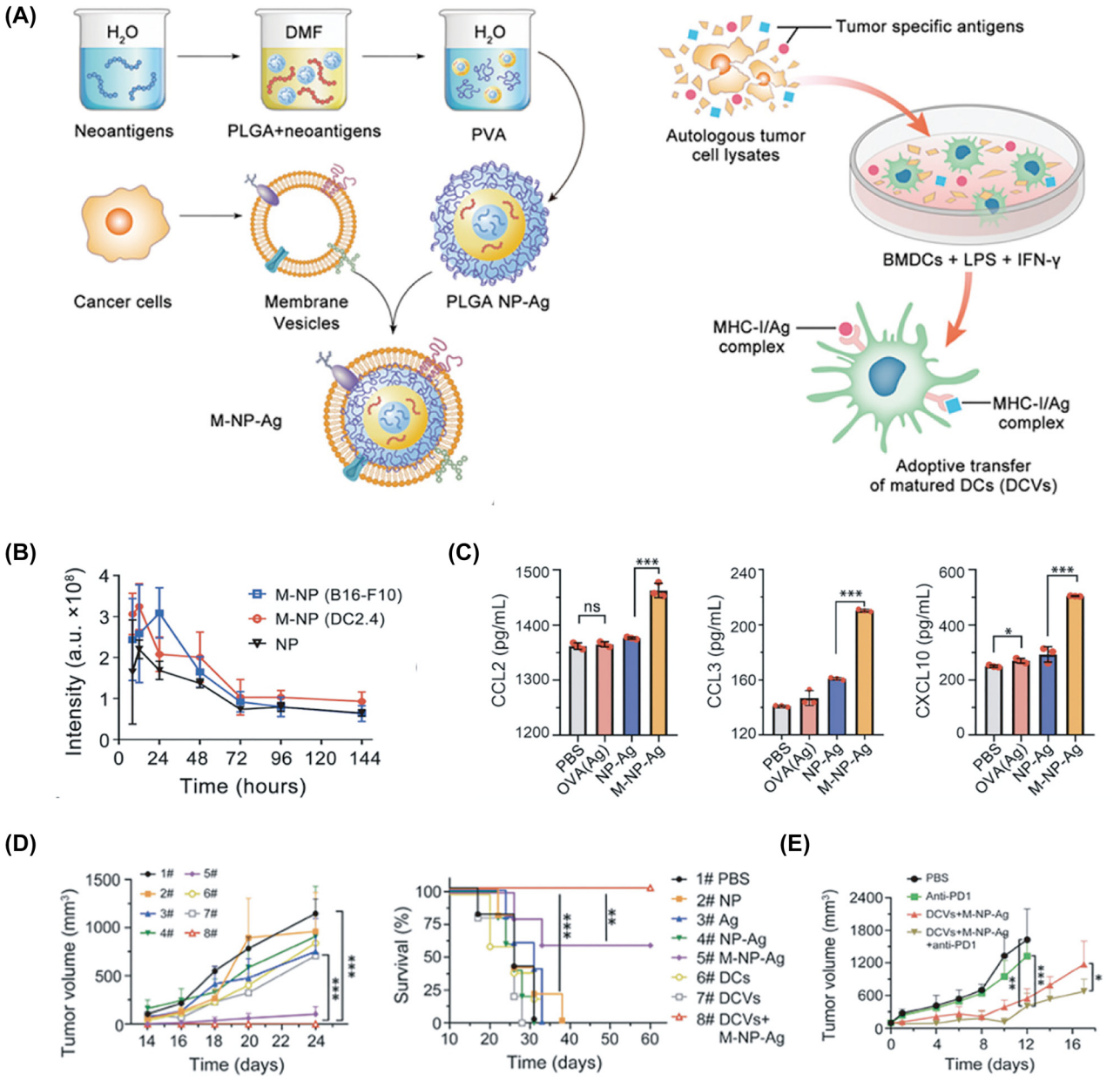

Figure 3: Cancer cell membrane-coated nanovaccines combined with adoptive dendritic cell transfer for personalized immunization. (A) Schematic illustration of nanovaccines design and adoptive DC transfer. (B) Time course quantification of DiR fluorescence intensity in the lymphatic regions after various injections (n = 3). (C) Levels of CCL2, CCL3, and CXCL10 in supernatant of macrophage culture medium *in vitro* after treated (n = 3). (D) Tumor growth profiles and survival curves of C57BL/6 mice in control and treated groups (n = 5). (E) Tumor growth profiles of all groups treated on days 0 and 7 (n = 5). (Image source: Xiao et al. [32])

and significantly regressed tumor growth in prophylactic melanoma and breast cancer models (Figure 3D and E).

Cell-hitchhiking NDDSs

Cellular hitchhiking leverages diverse cells to enhance the biological capability of nano drug delivery systems. Using the intrinsic abilities of cells, cell-hitchhiking NDDSs could avoid immune system clearance from the circulation and perform multiple functions, including pathogens elimination, tumor eradication as well as immune system surveillance [70]. Erythrocytes, T cells, macrophages, and even inactivated cancer cells can deliver a myriad of payloads, including proteins, therapeutics, and nanoparticles by simply adsorption, ligand-receptor interaction, chemical conjugation, and internalization [71]. Both adsorption and ligand-receptor methods do not

require cell modification but might damage cell membranes and cell functions. In contrast, chemical conjugation provides the strongest binding but needs permanent cell surface modification. Besides, internalization also leaves the cell unmodified but might result in the degradation of internalized biodegradable payloads.

Typically, because cell surfaces are composed of negatively charged biomolecules which provide hydroxyl, carboxyl, or phosphate functional groups, surfaces of cells are negatively charged. As a result, these innate and physical properties make it possible for positively charged nanoparticles readily adhere to cells by electrostatic interactions, hydrogen bonds, and van der Waals forces [72]. For example, Zhao and his coworkers encapsulated chemotherapeutic drugs into biodegradable polymeric poly (lactic-co-glycolic acid) (PLGA) nanoparticles and subsequently attached nanoparticles onto erythrocytes via electrostatic interactions, constructing an erythrocyte leveraged chemotherapy platform. Nanoparticles can easily dissociate from erythrocytes in a shear-dependent way due to the high shear stress produced by the narrow lung capillaries and then be deposited in the target site to release drugs. The circulation time of the drug nanoparticles was elongated, and also the efficiency of drug delivery highly improved. *In vivo* study showed that this platform significantly slow down lung metastasis progression and improved the survival rate [33].

Erythrocytes have an innate immune function, capturing bacterial pathogens during circulation and handing them to APCs in the spleen [73]. Based on this intrinsic ability, Ukidve et al. [74] conjugated ovalbumin (OVA), a model antigen, onto the polystyrene carboxylate nanoparticles. The protein-coated nanoparticles were efficiently attached to erythrocytes through incubation, and the number of nanoparticles was anchored up to 24 per cell. Nevertheless, it is necessary to figure out how to make the antigen firmly adhere to the red blood cells, which is enough to resist the shear stress of the blood vessels and reach the spleen. In this case, sufficient loading maintained to escape lung uptake because of the decreased expression of phosphatidylserine on erythrocyte membranes. Compared with control groups, the delivery of nanoparticles to the spleen could enhance adaptive immune response and inhibit tumor progression. This versatile nanosystem served as an option for adjuvant-free vaccine.

In addition to general therapeutics delivery, cells could load photosensitizers for synergistic therapy. Fang et al. [75] synthesized polyethyleneimine-conjugated chlorin e6 (PEI-Ce6) by an amide condensation reaction, and the PEI-Ce6 cationic polymers easily coated on oxidized autologous tumor cells through electrostatic adsorption. Cell-hitchhiking nanosystems were then dispersed in 9-fluorenyl methoxycarbonyl (Fmoc)-KCRGDK-phenylboronic acid (FK-PBA) hydrogels to activate the vaccine. Through the recognition of overexpressed sialic acid on tumor cells by PBA, FK-PBA can specifically target the residue tumor areas and trigger continuous immune activation. Combined with photodynamic therapy (PDT), the vaccine maintaining adequate antigens can effectively mature DCs, lower regulatory T cells, higher neoepitope-specific $CD8^+$ T cells, and inhibit tumor relapse for personalized immunity.

In addition to physical adsorption, utilizing ligand-receptor interactions carried out by receptors that are naturally present on the surface of cells is another strategy for constructing cell-hitchhiking NDDSs that do not need cell modification [76]. For instance, cell surface adhesion receptor CD44 which is widely expressed in normal and tumor cells could bind with a variety of ligands especially hyaluronic acid [77]. In this case, CD44-HA interaction has been investigated to attach nanoparticles to different types of white blood cells, including T cells, B cells, and macrophages [78, 79].

T cells also present various cell receptors such as internalizing receptors CD90 and noninternalizing receptors CD45. Hence, Zheng et al. [80] evaluated the effects of targeting these drug-loaded nanoparticles to T-cells through the internalizing receptor CD90 vs. the noninternalizing receptor CD45. PEGylated immunoliposomes were used to assess the possibility of targeting adoptive cell therapy (ACT) T-cells with a TGF-β inhibitor, which maintained the release of TGF-β inhibitor over three days *in vitro*. Compared to free drug dosage, both CD45 and CD90 targeted liposomes increased T-cell granzyme expression *in vitro*, but only CD45 targeted liposomes recruited more donor T-cells in tumors, which could boost T-cell antitumor activity. In contrast, vehicles targeting CD90 enhanced tumor regression and survival *in vitro*. Thus, maximal therapeutic efficacy might be achieved by optimal targeting of T-cells via unique receptors [80]. Later, Tang et al. [81] also found that anchoring the nanogel particles to CD45 on the surface of T cells with anti-CD45 ligands ensured that the nanoparticles would not be engulfed by the cells. Since the nanogel backpack itself was crosslinked by cytokines interleukin-15 (IL15), they developed a carrier-free drug delivery. Compared with traditional encapsulation drug delivery, nanogel backpacks could achieve nearly 100% drug loading and avoid potential problems such as carrier-drug interactions and carrier safety. Therefore, this technology can greatly improve the actual effects of drugs. In addition, the drug was delivered only to the tumor and was not released in normal tissue, so T cells equipped with cytokine nanogel backpacks did not exhibit toxicity in normal tissue.

Another approach to bind nanoparticles stably to cell surfaces is chemical conjugation, which is stronger than physical adsorption or ligand-receptor binding. Proteins found abundantly on cell surfaces provide functional groups

like amines and thiols for covalent binding. For example, Xie et al. [34] expanded the T cell backpack strategy for delivery of interleukin-2 (IL-2) to address IL-2 release syndrome and non-specific tissue damages. A redox-responsive bis-N-hydroxy succinimide crosslinker was used to create a nanogel out of repetitive IL-2/Fc units that was then attached to the amine groups on the T cell membrane. The study showed that T-cell surface-anchored nanogels improved the expansion of transferred T-cells 80-fold compared with free IL-2 administration and promoted the differentiation of the $CD8^+$ memory precursor with less T-cell exhaustion. With no overt toxicity and better efficiency against melanoma metastases in a mouse model, the controlled responsive delivery of IL-2/Fc made it possible to safely provide the stimulating cytokine in repeated doses.

In addition, free thiols on the plasma membrane of T cell possess the capacity to link nanoparticles through chemical coupling. Based on this, Wangs group constructed multilamellar liposomal vesicles (cMLV) to encapsulate SCH-58261 (an A2aR-specific small molecule antagonist). The maleimide-functionalized cMLV were then chemically conjugated with chimeric antigen receptor (CAR)-T cell without affecting cells functions, named as SCH. The increased accumulation of SCH in tumor areas resulted in the highest engraftment of T cells and the highest expression of intracellular interferon (IFN)-γ relative to other groups. Herein, this strategy enabled the effective administration of SCH to the tumor microenvironment, which may suppress hypofunctional CAR-T and reverse the tumor-residing T cells hypofunction [82]. Besides, Zhao et al. [35] used TNBC cell corpses as inactive chaperones to deliver anti-PD-1 and doxorubicin (DOX)-loaded liposomes by chemical conjugation (Figure 4A). Biological traits of inactivated tumor cells and physical properties of lung capillaries synergistically facilitated the accumulation and retention of drugs in lung metastases. DOX-induced immunogenic cell death (ICD) and PD-1 blockade boosted the antitumor immune response, reversed immunosuppression, and reprogrammed the immune microenvironment in the lung (Figure 4B). In lung metastasis mouse models, Cell-PD-1/liposomes significantly elicited the antitumor and antimetastatic effects, induced tumor regression, and decreased metastatic foci in lungs without loss of body weight.

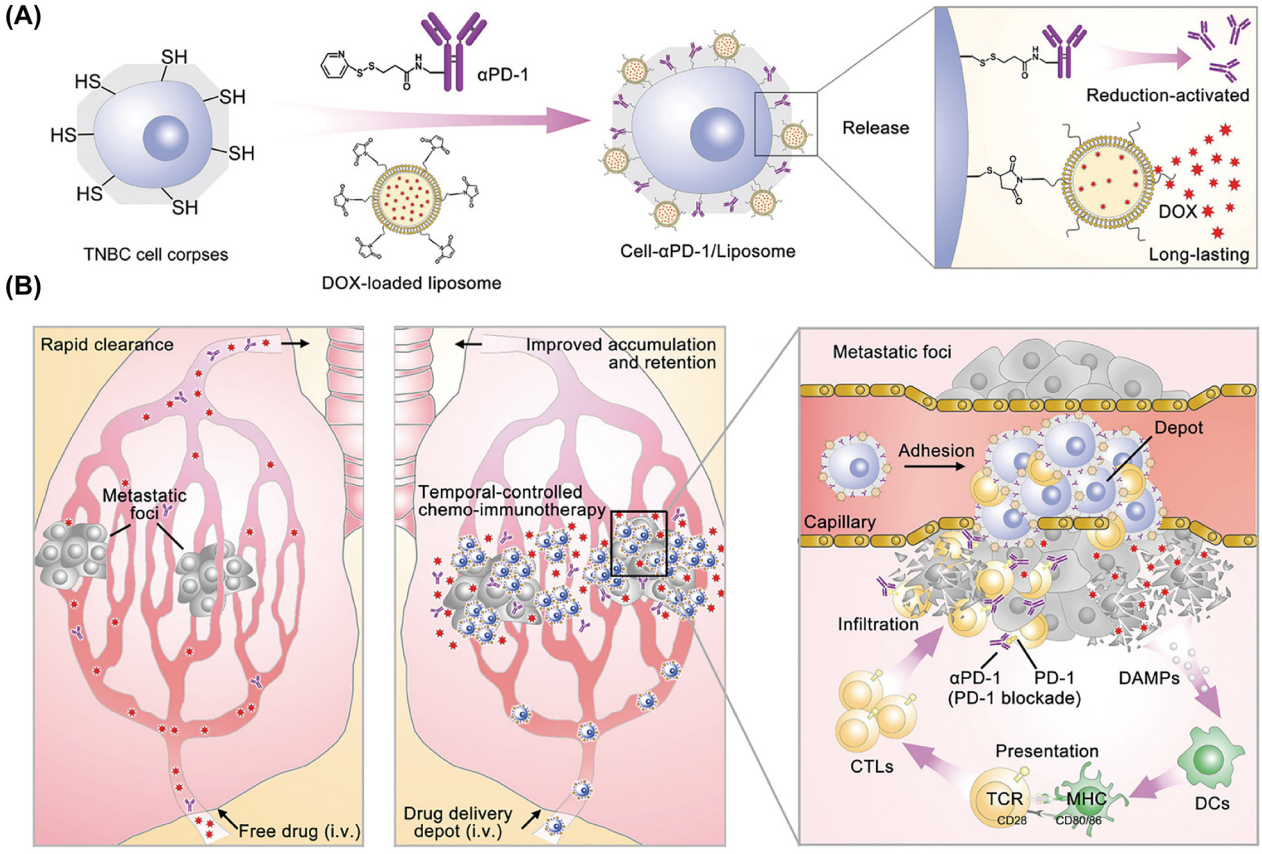

Figure 4: Dead tumor cells-leveraged biomimetic nanomedicine for targeted drug delivery against lung metastasis of triple-negative breast cancer. (A) Schematic illustration of the design of walking dead triple-negative breast cancer cells. (B) Schematic illustration of mechanisms for suppressing lung metastasis with temporal chemo-immunotherapy (Image source: Zhao et al. [35]).

Moreover, monocytes like neutrophils and macrophages are capable of phagocytosis, making an internalization method feasible for delivering therapeutic nanoparticles. For example, paclitaxel-loaded liposomes can be internalized by neutrophils. Since neutrophils are capable of identifying the postoperative inflammatory signals, this new nanosystem exhibited superior inhibitory effects on the recurrence of mice glioma [83]. In addition, it has been shown that Ly6C highly-expressed monocytes (MC) increased as the tumor developed with enhanced recruitment to tumor sites. Ly6C^{hi} MC could internalize nanoparticles which was used as the drug delivery platform to enhance the drug accumulation in tumors. Based on this, Lang et al. [36] developed a ternary heparanase-sensitive micelle-loaded monocyte delivery system (HDNH@MC) for metastatic breast cancer chemo-immunotherapy. They conjugated HS with the chemotherapeutic drug DTX and an indoleamine 2,3-dioxygenase (IDO) inhibitor NLG respectively, to create amphiphilic copolymers, then mixed two copolymers to obtain the PD-1/PD-L1 inhibitor HY19991 (HY)-loaded Hpa-sensitive micelle (HDNH). Then, the Ly6C^{hi} monocyte loaded HDNH through phagocytosis (Figure 5A). Leveraging the targeting capacity of Ly6C^{hi} monocytes to tumor sites and the high expression of Hpa in tumors, HDNH@MC efficiently released DTX, NLG, and HY in tumor to augment the anti-tumor immune response. Thus, in the 4T1 breast carcinomas mice model, HDNH@MC boosted tumor-inhibition effects in contrast with free drugs, inhibited lung metastasis, and prolonged the survival of mice (Figure 5B and C).

Since the exogenous formulation of nanoparticle-loaded monocytes was time-consuming, less than 5% of the reinjected monocytes preserved their viability and ability to migrate naturally, severely limiting their efficacy. In light of this, Zheng et al. [84] developed a strategy to form NP-loaded macrophages *in vivo* by direct injection of apoptotic bodies encapsulating NPs. Apoptotic bodies were used as carriers to package CpG-modified gold-silver nanorods (AuNRs). After intravenous administration, the apoptotic bodies were first selectively phagocytosed by inflammatory Ly-6C^{+} monocytes and formed AuNR-loaded macrophages (MAs). Due to the tumor-homing ability of MAs, nanodrugs efficiently transported to the internal regions of tumors and enhanced PTT efficacy. Combined with the photothermal effect induced by nanorod and immunostimulation promoted by CpG, this cell-based biomimetic

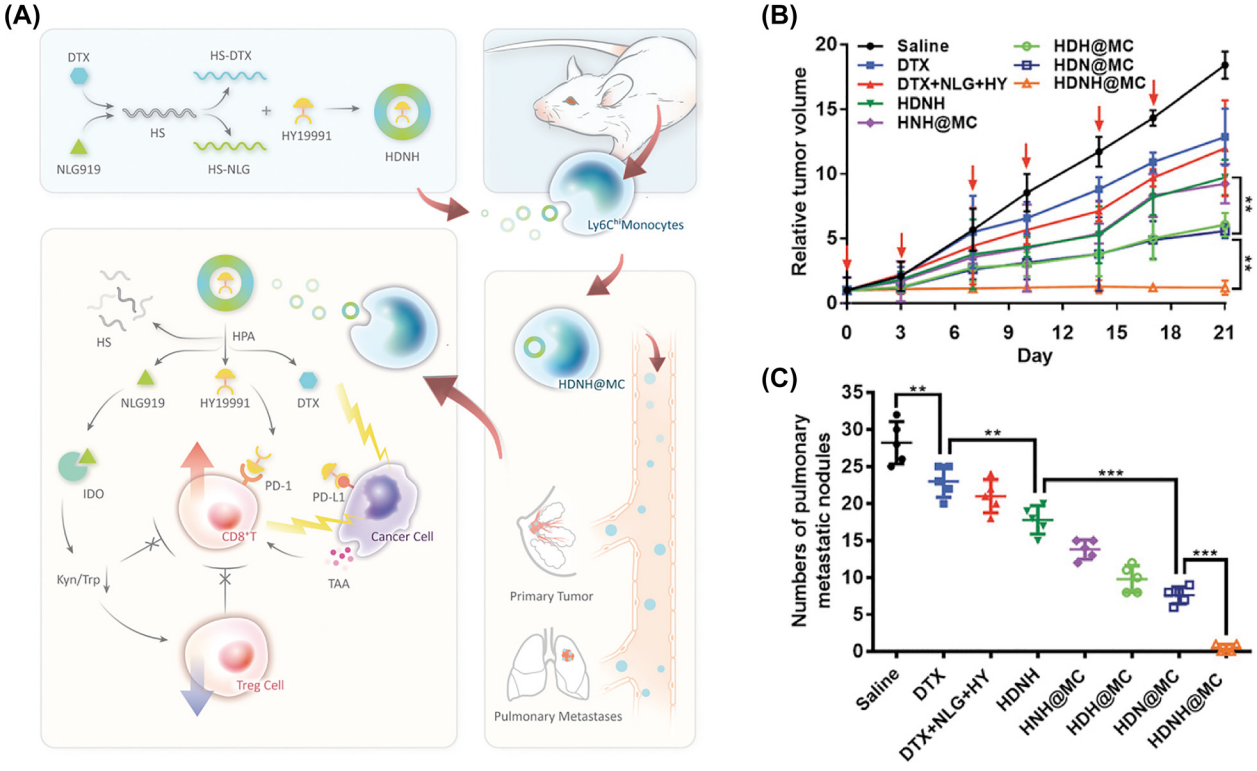

Figure 5: Hpa-sensitive micelles-loaded monocytes improves chemo-immunotherapy of metastatic breast cancer. (A) Chemo-immunotherapy of metastatic breast cancer by the Hpa-sensitive micelles@monocytes system. (B) The variation curves of tumor volumes during the therapy period (n = 6). (C) Numbers of the lung metastatic nodules (n = 5) (Image source: Lang et al. [36]).

system not only eradicated tumors and inhibited tumor metastasis but also established long-term immune protection and prevented tumor recurrence.

Bioidentical molecules-constructed NDDSs

Endogenous protein-like NDDSs

Endogenous proteins have emerged as nanocarriers for their potential use in drug delivery. For instance, Nab-paclitaxel (Abraxane) used albumin in its formulation approved by FDA in 2004, which has been extensively used for treating metastatic breast cancer, non-small cell lung adenocarcinoma, and pancreatic cancer [85]. As an endogenous component, albumin not only comprises a variety of binding sites for small molecule drugs and biomolecules but can also be protected against systemic degradation and clearance through intrinsic physiological mechanisms [86]. Cen et al. [37] constructed ZnS@BSA (bovine serum albumin) nanoclusters through a self-assembly method for cancer immunotherapy. Due to specific binding between BSA with metal ions, BSA loaded zinc and sulfur by an ion diffusion method. Once targeted to the tumor, zinc and sulfur ions were released in an acidic tumor microenvironment (TME) which significantly improved cyclic guanosine monophosphate-adenosine monophosphate synthase/interferon gene stimulator (cGAS/STING) signals. In hepatocellular carcinoma-bearing mouse models, the nanoclusters promoted the infiltration of immune cells into the tumor site, exerting an enhanced therapeutic effect.

Apart from albumin-based NDDSs, a cage-like nanostructure formed by endogenous ferritin has potential in drug delivery. Ferritin is a ubiquitous iron storage protein with the external diameter of 12 nm and internal cavity of 8 nm which can be developed as NDDSs for cancer imaging and therapy [87]. Ferritin can be used to target tumors and penetrate deeply into tumor tissues since it can adhere to cancer cells' overexpressed transferrin receptor 1 (TfR1) and scavenger receptor class A membrane 5 (Scara5). Accordingly, Tan and his coworkers developed a bionic apoferritin nanocage (AFN) encapsulating cytotoxic mertansine (M-AFN) by a disassembly-assembly procedure for anticancer therapy. In cancer stem cells-enriched 3D tumorspheres, M-AFN can be largely internalized by tumorsphere cells and induce significant eradication of CSCs. Besides, compared to mertansine alone, M-AFN drastically hindered the development of secondary tumorspheres as well as the pre-existing tumorspheres [38]. Later, the same group proposed a ferritin nanocage system comprising the photothermal therapeutic agent 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide (DiR) and chemotherapeutic epirubicin to enhance their accessibility to CSCs. The DiR-loaded nanocages (DBN) could be selectively taken up by cancer cells and preferentially accessed to CSCs fractions. The DiR-mediated PTT effects induced by DBN disrupted the abominable barriers formed by tumor-related macrophages and fibroblasts. To this end, epirubicin-loaded nanocages (EBN) could penetrate tumor tissues deeply to elicit superior therapeutic effects. Simultaneous delivery of ferritin-based biomimetic system effectively suppressed lung metastasis of breast cancer. This work described a novel strategy for anti-tumor metastasis by exploiting natural proteins as nanocarriers to target CSCs in tumor tissues [88].

Lipoprotein-like NDDSs

Lipoproteins are endogenous occurring nanostructured particles comprising proteins (e.g., apolipoprotein A1, ApoA1) and lipids (e.g., phospholipids and cholesterol esters), playing a critical role in the transportation of fatty acids and biomolecules. Inspired by their unique targeting abilities and natural functions, these endogenous lipoprotein-like systems have become attractive candidates for the delivery of diverse imaging or therapeutic agents [89]. Tan et al. [39] fabricated a bioinspired lipoprotein (bLP) to load photosensitizer DiOC18(7) (DiR) (D-bLP) and chemotherapy drug mertansine (M-bLP) respectively. They found that D-bLP could effectively target and penetrate the tumor tissue after intravenous injection but hijacked by stromal cells such as cancer-associated fibroblasts (CAF) or tumor-associated macrophages (TAM) in the tumor and could not access tumor cells. Upon 808 nm laser, the photothermal effects of D-bLP can kill tumor stromal cells and destroy the extracellular matrix, thereby breaking through the tumor stromal delivery barrier. Based on this, the accumulation and penetration of M-bLP in tumor tissues significantly improved, and the distribution of M-bLP to tumor cells was increased by 27-fold. This strategy significantly inhibited the recurrence and metastasis of breast cancer, exhibiting superior therapeutic effects compared with the liposome control group.

Besides, high-density lipoprotein (HDL) could directly transport payloads through scavenger receptor class B type I (SR-BI) that abundantly overexpressed on hepatocellular carcinoma (HCC) cell membranes [90]. Therefore, Wang et al. [40] designed a biomimetic synthetic high-density lipoprotein (sHDL) for the simultaneous delivery of photothermal agent DiR and immune primers, enabling imaging-guided synergistic therapy for HCC (Figure 6A). The self-assembled sHDL delivered cargos into the cytosol of HCC cells by an SR-BI dependent pathway (Figure 6B). Under laser irradiation, sHDL triggered robust ICD in Hepa1-6 cells proved by the increased release of high-mobility group box-1 (HMGB1) and ATP (Figure 6C). Combined with Mertansine, sHDL improved

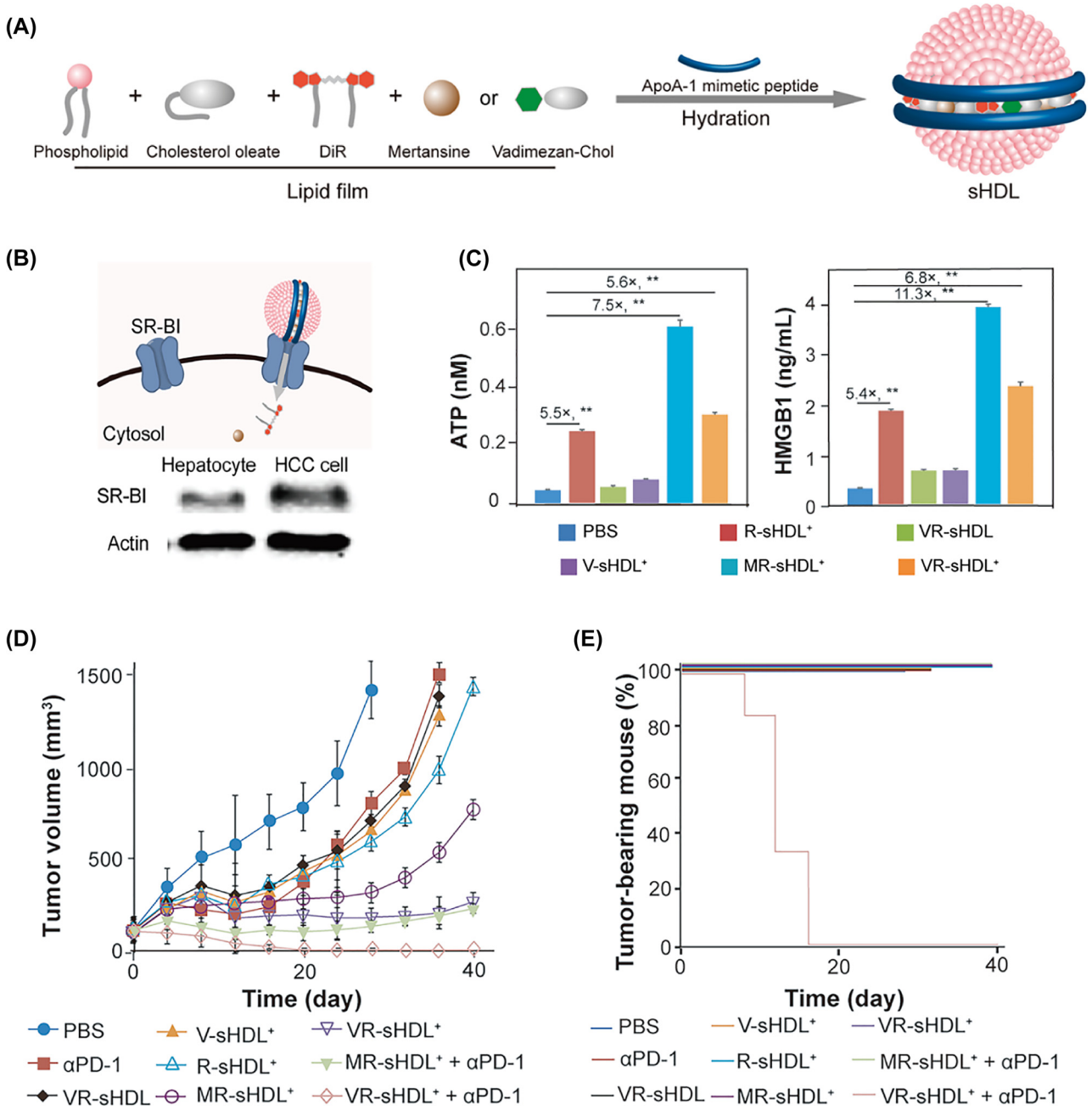

Figure 6: Synthetic high-density lipoprotein (sHDL) for hepatocellular carcinoma therapy. (A) Schematic illustration of construction of sHDL. (B) Mechanisms of SR-BI-mediated cellular uptake and expression of SR-BI in hepatocellular carcinoma cells (HCC) and normal hepatocytes. (C) Treatment-induced extracellular release of ATP and HMGB1 from Hepa1-6 cells treated with different sHDLs. (D) Tumor growth kinetics of Hepa1-6 tumors in C57BL/6 mice, (E) the percentage of tumor-bearing mice after different treatments (n = 6) (Image source: Wang et al. [40]). $^{**}P < 0.01$.

ICD effects while was less effective in initiating DC maturation than the vadimezan combination due to mertansine-induced cytotoxicity against DCs. Hence, the sHDL-based combinatorial approach suppressed tumor growth and triggered anti-tumor immunity after being combined with anti PD-1 therapy (Figure 6D and E). In their subsequent work, they found that sHDLs selectively delivered payloads into alternatively activated macrophage (M2) and Hepa1-6 HCC cells. To this end, they proposed a strategy to regulate the target cells with functional sHDLs encapsulating esterase-responsive prodrugs of vadimezan and gemcitabine (VG-sHDLs). Gemcitabine boosted DC maturation and classically activated macrophages (M1) differentiation while preferentially killing M2 and HCC cells. Meanwhile, the myeloid-derived cells

(MDC) mobilization and differentiation into DCs were improved by the vadimezan with no toxicity. Accordingly, VG-sHDLs effectively improved tumor filtration of $CD8^+$ T cells and reverted M2-mediated immune suppression, and induced tumor growth retardation [91].

Exosome-like NDDSs

Exosomes develop naturally when successive invaginations of the plasma membrane occur with a size range of 30–150 nm (average 100 nm). These nanosized vesicles horizontally transfer their bioactive contents from parental cells into recipient cells enabling intercellular communication [92]. The intrinsic biocompatible and non-cytotoxic properties of exosomes confer them as ideal nanocarriers for drug delivery. Autologous cancer-derived exosomes have merged as promising delivery systems for cancer treatment because they can target the tumor microenvironment. Li et al. [41] formulated ExoGEM by loading gemcitabine into pancreatic cancer cell-derived exosomes via sonication for targeted chemotherapy. The study found that the cellular uptake of gemcitabine increased and resulted in a significantly stronger cytotoxic effect of gemcitabine, but heterologous cellular uptake was less effective. In the biodistribution study, autologous exosomes could target pancreatic cancer, and the concentration of gemcitabine in the tumor site was enhanced via ExoGEM delivery. ExoGEM treatment significantly inhibited tumor growth in tumor-bearing mice with prolonged survival, while showing no toxicity to normal tissues. Notably, ExoGEM treatment resulted in the complete inhibition of tumor regrowth in several mice.

In addition to small drug molecules, exogenous formulation involved nucleic acid encapsulation into an exosome-based nanosystem. For instance, researchers engineered exosomes (iExosome) obtained from normal fibroblast-like mesenchymal cells containing siRNA or short hairpin RNA (shRNA) to target $Kras^{G12D}$, a typical pancreatic cancer mutation. In pancreatic cancer models treated with iExosome, $Kras^{G12D}$ orthotopic tumor growth was significantly inhibited, while iExosome did not affect the growth of BxPc-3 $KRAS^{WT}$ tumors *in situ*. Compared with traditional RNA drug carrier liposomes, iExosome shown better efficacy in different pancreatic cancer models depending on the CD47 on the surface of exosomes and macropinocytosis facilitated by oncogenic KRAS [42]. Furthermore, Yang et al. [93] proposed a cellular-nanoporation method (CNP) that could produce large amounts of exosomes carrying therapeutic mRNAs and targeting peptides for disease treatment, overcoming the limitation of low yields. To prepare exosomes containing transcribed mRNA and peptides, the researchers transfected various cells with plasmid DNAs by focal and transient electrical stimulation. Compared with traditional bulk electroporation, CNP greatly increases exosome production by 50-fold and increases mRNA transcripts in it by more than 103-fold. *In vivo* studies showed that mRNA-containing exosomes produced by CNP had a better ability to penetrate the blood-brain barrier, achieve tumor enrichment, and significantly lower accumulation in other organs such as the liver and spleen. The median survival of mice in the experimental group was 49 days, which was much longer than that of the control group 37 days.

Bacteria-like NDDSs

Bacteria-based vectors have become popular as therapeutic agents or as drug delivery systems for immune system regulation. Bacterium are perfect candidates for targeted cancer therapy because they are preferentially home to necrotic/hypoxic tumor regions [94]. Hence, Yi et al. [95] proposed a bacteria-inspired photoimmunotherapy based on intact microbes without any modification. They found that attenuated Salmonella can proliferate in many types of solid tumors but be rapidly cleared in normal organs after intravenous injection. More importantly, inflammation caused by bacteria can destroy tumor blood vessels, which in turn lead to thrombosis inside the tumor, making the color of the tumor tissue darker. *In vivo* photoacoustic imaging studies have found that intravenous injection of bacteria can contribute to a significant increase of near-infrared absorbance due to the formation of thrombus in six types of mouse tumors. Under near-infrared laser irradiation, the local temperature of these tumors rose rapidly, and the bacterial-infected tumors were ablated. In addition, bacteria can function like immune adjuvants due to the stimulation of systemic immunity. Such photoimmunotherapy will further boost an anti-tumor immune response, especially combined with immune checkpoint blockade therapy, which can achieve effective suppression of distant tumors and inhibit tumor recurrence through immune memory effects [95].

Additionally, bacteria outer membrane vesicles (OMVs) produced by bacteria maintain plenty of intrinsic adjuvant components inherited from original bacteria, which can stimulate immune maturation and trigger inflammation in a controllable fashion [96]. OMVs possess a stiff bi-layered membrane structure enabling nanoplatform stability which can be easily prepared through fermentation and purification processes [97]. Based on these, Huang et al. [43] developed antibiotic-loaded OMVs based on *Acinetobacter baumannii*. According to their research, a high amount of antibiotics in OMVs entered the pathogenic bacteria efficiently and were excreted by OMVs

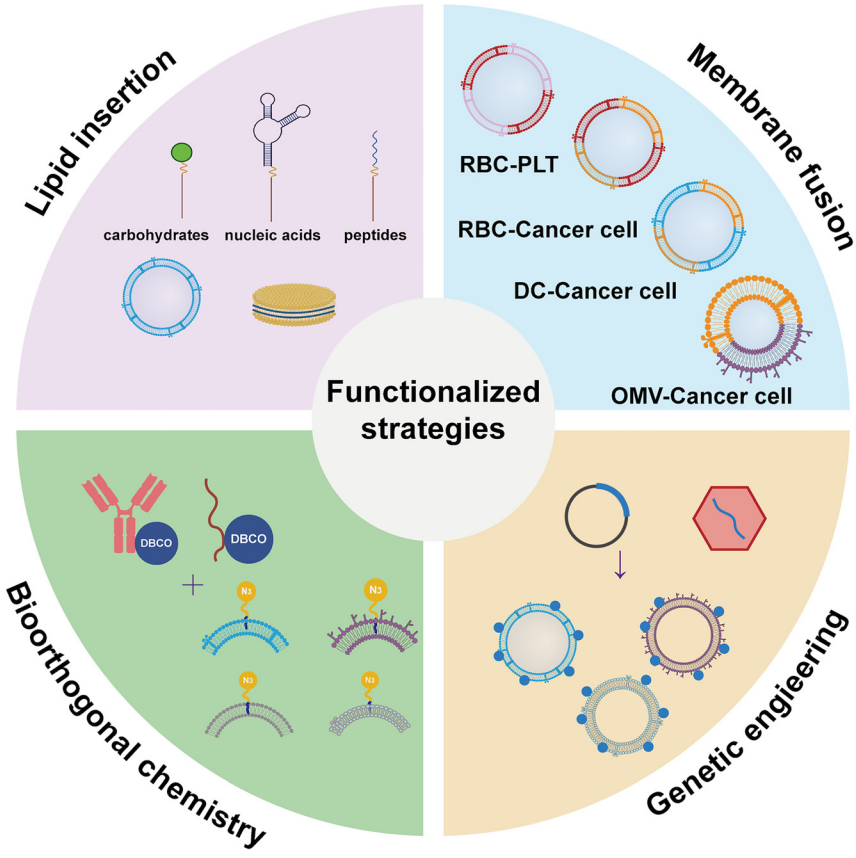

Figure 7: Schematic illustration of different strategies for functionalizing biomimetic nanomedicine including lipid insertion, membrane fusion, bioorthogonal chemistry, and genetic engineering. Insertion of lipid-conjugated molecules into cell membranes/lipoproteins. Membrane fusion by different source cells. Modification of azido groups on cell membranes or liposomes followed by linkage with molecules through bioorthogonal chemistry. Genetic modification to introduce transgene protein expression on membrane surfaces. RBC, red blood cell; PLT, platelet; DC, dendritic cell; OMV, outer membrane vesicles.

through mechanisms of enhancing the expression of high efflux pump and secretion of OMVs. This innovative antibiotic delivery system exhibit a long-lasting bactericidal effect in the intestine with superior biocompatibility. Ye's group prepared doxorubicin-loaded OMVs (DOX-OMVs) from attenuated *Klebsiella pneumonia* for cancer chemo-immunotherapy. *In vivo* study revealed that doxorubicin was transported into cancer cells efficiently by OMVs. In A549 tumor-bearing BALB/c nude mice, DOX-OMV could inhibit tumor growth and induce the apoptosis and necrosis of cancer cells with favorable tolerability and safety profile. Moreover, the increasing immunogenicity of the tumor microenvironment induced by DOX-OMVs allowed for the mobilization of macrophages, which might work synergistically with their cargo DOX [44].

Strategies for further functionalization of biomimetic NDDSs

Although biomimetic NDDSs are compelling for cancer and inflammation treatment, they still need improvement for implementation. One of the main factors is the unavoidable difficulty of future efficient and accurate functionalization. Thus, to further endow the biomimetic delivery systems with functionality and expandability, they can be modified by several methods. Here are four promising strategies to functionalize biomimetic NDDSs. The easiest way is to insert lipid-based conjugates into the membrane or lipoproteins by simply incubation. The second facile strategy is fusing different cell membranes by stirring, extrusion, or sonication. The third method involves introducing biorthogonal reactive groups to the surface of cells or liposomes and coupling with ligands, proteins, or NPs through click chemistry. The fourth method is to engineer cells through genetic modification. Besides, combination of these strategies could further confer biomimetic NDDSs with more functions (Figure 7, Table 2).

Lipid insertion

Lipid insertion is a strategy that introduces lipid-conjugated functional moieties automatically onto natural cell membranes or lipoproteins. The insertion process depends on physical forces rather than chemical

Table 2: Summary of representative work of further functionalized biomimetic nanomedicine.

Functionalized strategy	Biomimetic nanomedicine	Additional components	Disease	Refs.
Lipid insertion	Cancer cell membrane-coated PLGA nanoparticles	Mannose	Melanoma	[98]
	Exosomes derived from dendritic cells	Aptamer sgc8	Acute lymphoblastic leukemia	[99]
	Synthetic high-density lipoprotein	CpG	Gliomas	[100]
	RBC membrane-coated drug nanocrystals	c(RGDyK)	Gliomas	[101]
	RBC membrane-coated miR155 nanogel	M2pep peptides, HA2 peptides	Glioblastoma	[102]
	Macrophage containing soravtansine prodrug	legM	Metastasis breast cancer	[103]
	Lipoprotein containing oxaliplatin	legM	Breast cancer	[104]
Membrane fusion	RBC membrane-coated ultrasound-propelled nanorobots	Platelet membrane	Bacterial infection	[105]
	RBC membrane-coated copper sulfide nanoparticles loading doxorubicin	Cancer cell membrane	Melanoma	[106]
	Cancer cell membrane-coated metal organic framework	Dendritic cell membrane	Breast cancer, colon cancer	[107]
	Cancer cell membrane-coated PLGA nanoparticles containing ICG	Outer membrane vesicles	Melanoma, breast cancer	[108]
Bioorthogonal chemistry	Macrophage membrane-coated magnetic nanocluster loading short interfering RNA	RGD	Breast cancer	[109]
	THP-1 membrane-coated PLGA nanoparticles	Heparin	SARS-CoV-2 infection	[110]
	Leucocyte membrane-coated magnetic nanoclusters	pMHC-I, anti-CD28	Lymphoma	[111]
	Dendritic cell membrane-coated PLGA nanoparticles containing imiquimod	Anti-αCD3ε	Melanoma, colon cancer	[112]
	Exosomes derived from M1 macrophages	Anti-CD47, anti-SIRPα	Breast cancer	[113]
Genetic engineering	Cell membrane coated-nanoparticles loading dexamethasone	VLA-4	Lung inflammation	[114]
	T cell membrane coated-protein nanoparticles containing ORY-1001	PD-1	Melanoma, breast, colon cancer	[115]
	Exosomes	Anti-CD3, anti-HER2	HER2-expressing breast cancer	[116]
	Exosomes derived from T cells	PD-1	Melanoma	[117]
	Outer membrane vesicles	Tumor antigen peptides	Melanoma, colon cancer	[118]
Multiple engineering	Hybrid M1, platelet, and cancer cell membranes nanovesicles	SIRPα	Melanoma, breast cancer	[119]
	Hybrid 293T and THP1 cell membrane nanovesicles	ACE2	SARS-CoV-2 infection	[120]

PLGA, poly (lactic-co-glycolic acid); CpG, 5′-C-phosphate-G-3'; RBC, red blood cell; legM, legumain-specific propeptide of melittin; pMHC-I, peptide-loaded major histocompatibility complex class-I; SIRPα, signal regulatory protein alpha; VLA-4, very late antigen-4; PD-1, programmed cell death protein 1; HER2, human epidermal growth factor receptor 2; ACE2, angiotensin-converting enzyme 2.

interactions by taking advantage of the fluidity of lipid layers. Besides, for preparation and formulation optimization, this approach provides a precise and efficient way to alter ligand density by regulating its initial input [121]. Lipid insertion is appealing as a powerful method for enhancing the targeting abilities and biological functions of biomimetic NDDSs due to its benefits.

Lipid insertion of carbohydrates

Mannose, a crucial molecule in antigen recognition, has been utilized to modify the cell membrane for targeting APCs to trigger immune responses [122]. For example, researchers fabricated a cancer cell membrane-coated PLGA nanoparticles loading a Toll-like receptor-7 (TLR-7) agonist R837. They then incorporated mannose-conjugated 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy-(polyethylene glycol) (DSPE-PEG-Man) onto cancer cell-coated nanoparticles (NP-R@M-M). Because of the strong affinity with abundant mannose receptors on dendritic cells, such nanosystems improved cellular uptake by APCs and facilitated DC maturation. After intradermal injection, NP-R@M-M could effectively accumulate in draining LNs with prolonged retention and active tumor-specific immune responses [98].

Lipid insertion of nucleic acids

Aptamers have also been investigated as function moieties to modify into cell membranes. As short single-stranded nucleic acids, aptamers are synthetic affinity molecules that recognize varieties of targets, including single molecules, biomolecules, and cells, through their unique three-dimensional

structures. Zou et al. [99] reported a direct functionalization of exosomes with diacyl lipid-PEG-(DNA) aptamer sgc8 conjugates. With the modification of sgc8, the uptake of exosomes in overexpressed protein tyrosine kinase 7 (PTK7) cells was higher than in control cells. They found that such modified exosomes increased cellular uptake by a different endocytosis pathway compared with free exosomes, proving to be an attractive platform for effective targeting delivery of therapeutic agents as well as diagnostic agents.

Furthermore, to enhance cancer immunotherapy, an oligonucleotide containing the 5′-C-phosphate-G-3′ (CpG) motif triggers TLR-expressed cells to produce an innate immune response which could also be inserted into lipoprotein-like NDDSs [90]. Moon's group reported the use of cholesterol-modified CpG (Cho-CpG) for sHDL functionalization. Cho-CpG was incorporated into neoantigen antigen-loaded nanodiscs through simple mixing. They proved that vaccination with peptide and CpG-loaded sHDL combined with anti-PD-1 treatment induced significant neoantigen-specific T-cell immune responses against glioma cells, and 33% of mice with established orthotopic GL261 glioma had their tumors eradicated. Such a nanosystem provided a promising strategy for synergistic immunotherapy of gliomas and other cancer [100].

Lipid insertion of targeted peptides

It has been effective to surface modify cells and lipoproteins with tumor-homing peptides utilizing a variety of targeted peptide sequences. For instance, Chai et al. [101] established a biomimetic drug delivery system composed of a drug nanocrystal and peptide-modified cell membrane for tumor targeting and therapy. RBC membrane-coated drug nanocrystals were prepared and functionalized with c(RGDyK), a specific targeting ligand with an affinity for integrins overexpressed on cancer cells. They first incorporated streptavidin into the RBC membrane through lipid insertion and then interacted with biotin-linked c(RGDyK). The peptide-modified group showed significantly higher drug enrichment in the tumor than non-decorated groups at 2 and 24 h after administration due to its active-targeting ability. This nanosystem enhanced therapeutic effects both in subcutaneous and orthotropic glioma models. Similar strategies were used to modify bacterial outer membrane vesicles. Chen et al. reported a tumor-targeted platform consisting of an OMV-coated polymeric nanoparticle and RGD peptides. Decorated with RGD peptides, nanomedicine improved its tumor-targeting capacity, exerted its chemotherapeutic efficacy in tumor tissues, and improved immune response, leading to the prevention of tumor metastasis [123].

Moreover, Gao et al. [102] proposed a virus-mimicking nano-therapeutic platform for glioblastoma therapy by constructing membrane-coated nanogel modified with two functional peptides, M2pep peptides, and hemagglutinin (HA2) peptides. The researchers first crosslinked miR155 with a DNA-grafted polymer brush to obtain the nucleic acid hydrogel, and they subsequently used erythrocyte membranes to encapsulate miR155 nanogel (Mem-Gel). They conjugated M2pep peptides and HA2 peptides with DSPE-PEG, which were incorporated into the erythrocyte membranes to produce the Vir-Gel. M2pep peptide could specifically bind surface receptors on M2-microglial and macrophage cells to enhance the Vir-Gel's targeted delivery. At the same time, the HA2 peptide facilitated the fusion with the endosomal membrane, which accelerated the release of nanogel. In this way, miR155 could promote M2 anti-inflammatory phenotype to M1 pro-inflammatory phenotype repolarization in microglia and macrophages. In glioma-bearing mice, Vir-Gel could rapidly accumulate in the brain and showed 1.92-fold higher enrichment than that of miR155 nanogel at 8 h-post injection. This nanoplatforms exhibited long circulatory lifetime, specific targeting ability as well as superior antitumor effects [102].

By modifying the surface of macrophages with enzyme-responsive peptides, it is possible to improve their tumor-targeting capabilities. Cao et al. [103] leveraged a legumain-response macrophage-based delivery system (LD-MDS) by inserting legumain-specific propeptide of melittin (legM) and soravtansine (DM4) prodrug. When activated by legumain protease in the tumor, LD-MDS can be converted into exosome-like nanovesicles that contain DM4, which 4T1 cancer cells can efficiently internalize, inhibiting tumor metastasis (Figure 8A). Compared with control groups, LD-MDS significantly enhanced the accumulation in all metastatic foci areas, including inner sides and external surfaces. Lipid-conjugated legM was also used to be incorporated in bioinspired lipoprotein systems. Li et al. [104] designed a tumor-activated transformable lipoprotein of oxaliplatin (TA-OBL) (Figure 8B). *In vivo* imaging system showed that the signals of TA-OBL were much higher at the tumor site than in the group without legM modification, and could be detected even at 60 h after injection. Due to the overexpression of legumain in tumor sites, TA-OBL would be stimulated particularly to restore melittin, allowing for intratumoral penetration of stromal barriers and access into cancer cells in the tumor. Therefore, the ICD-inducing oxaliplatin was delivered to the cancer cells by TA-OBL, which elicited antitumor immune responses for cancer immunotherapy.

Membrane fusion

Since different cell types possess their own special inherent properties, they have been investigated as sources of

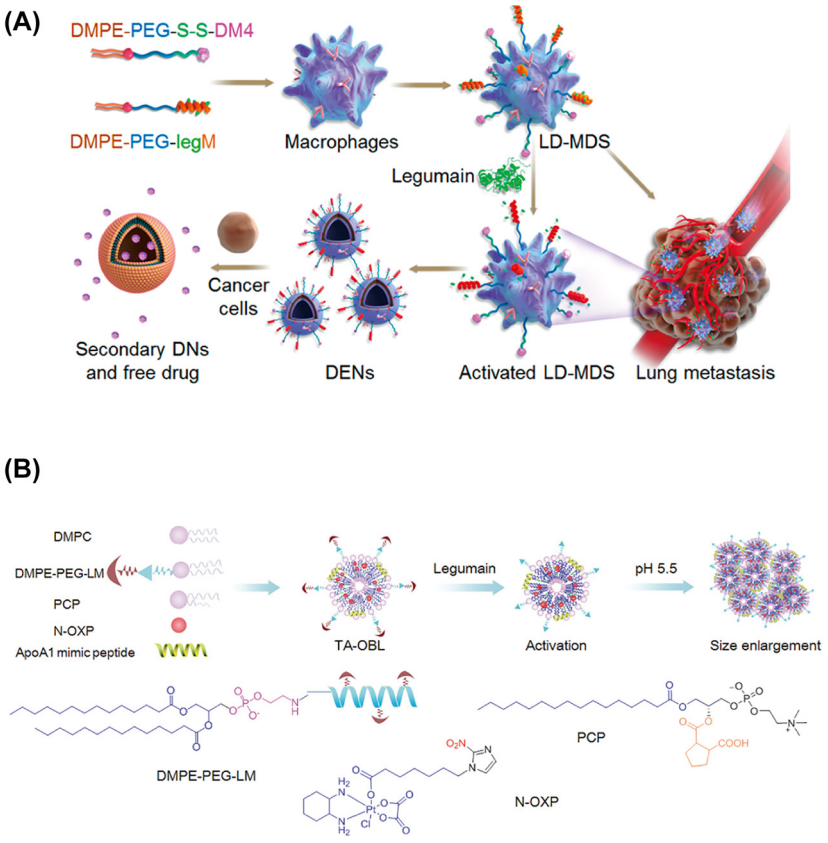

Figure 8: Biomimetic nanodrug delivery systems engineered by lipid insertion. (A) Schematic illustration of the bioengineered macrophage delivery system (LD-MDS) for specific targeting of lung metastasis. Image source: Cao et al. [103]. (B) Schematic illustration of construction of cancer-accessing TA-OBL to boost antitumor immune responses. (Image source: Li et al. [104])

biomimetic NDDSs materials. The criteria for selecting a cell membrane depend mainly on the unique characteristics of different cells and the need for disease treatment [124]. Based on this, the developed technology of cell-inspired biomimetic NDDSs has been extended to fuse cellular membranes from diverse types of cells, providing an elaborate method for NDDSs with enhanced functionalities [125, 126].

RBC-platelet hybrid membrane NDDSs

Due to their biocompatibility and capacity for immune clearance escape, RBCs were initially utilized in the preparation of hybrid membranes. Zhang's group reported red blood cell-platelet membrane-coated nanoparticles, which retained surface membrane proteins from both cells. They used the förster resonance energy transfer (FRET) strategy to demonstrate successful membrane fusion, as the recovery of fluorescence emission (543 nm) from the donor on the platelet membrane was observed when two membranes incubated together. In consequence, dual-membrane-coated nanoparticles exhibited long circulation and good biodistribution in mouse models. Compared with erythrocyte-coated nanoparticles and platelet-coated nanoparticles, hybrid membrane-coated nanoparticles exhibited both physicochemical properties of two single-membrane-coated nanoparticles [127].

RBC can also absorb pore-forming toxins released by gram-positive bacteria, and at the same time platelets can interact and bind with bacterial pathogens by specific membrane proteins [55]. Thus, researchers used RBC membranes and platelet membranes to fabricate ultrasound-propelled nanorobots. Because of inheriting the attractive biological abilities from the parental components, nanorobots simultaneous remove pathogenic bacteria (such as *Staphylococcus aureus*) and toxins from the bloodstream. Meanwhile, nanorobots could exhibit rapid acoustic propulsion and move in the blood much like a natural motile cell, reaching speeds of up to 35 μm per second. This biomimetic nanosystem promoted their effective binding to pathogens and enhanced neutralized abilities. Combining these multiple biological functions of hybrid cell membranes with the fuel-free propulsion nanorobots will provide a new vision for a broad-spectrum detoxification treatment [105].

RBC-cancer cell hybrid membrane NDDSs

Cancer cell membrane-coated NDDSs display excellent self-recognition and internalization by the parental cancer cell types. However, the formation of cancer cell membrane vesicles could lead to a loss of membrane protein integrity and incomplete immune surveillance avoidance [128]. Hence, researchers

have explored RBC-cancer cell-coated NDDSs as effective cancer therapeutic strategies. For example, membrane materials of red blood cells and melanoma tumor cells were fused to construct hybrid biomimetic membranes (RBC-B16), and the hybrid membranes were coated with DOX-containing copper sulfide nanoparticles (DCuS@[RBC-B16]NPs) for combination photothermal/chemotherapy of melanoma. DCuS@[RBC-B16]NPs showed intrinsic properties of two source cells. Compared with nanoparticles alone, DCuS@[RBC-B16]NPs exhibited highly specific self-identification by source cell lines *in vitro* and significantly prolonged the circulation time. Thus, the novel platform demonstrated excellent synergistic PTT/chemotherapy with nearly 100% inhibition of melanoma tumor growth. In conclusion, the fusion of membrane-coated biomimetic nanoparticles from multiple cell types will facilitate the personalized treatment of different tumors [106].

Similarly, Han et al. [129] also used cancer cell membranes and RBC membranes to construct an intravenous nanovaccine. Nanoerythrosome uses the RBC membrane to accumulate into the spleen and specifically deliver antigens to the APCs therein, eliciting anti-tumor immunity. An individualized tumor vaccine can be rapidly constructed by fusing two membranes and surgically removing tumors in model animals. The postoperative recurrence and metastasis of melanoma can be significantly inhibited with the combination of ICB therapy.

DC-cancer cell hybrid membrane NDDSs

Dendritic cells contribute to taking up, processing, and presenting tumor antigens because of the antigen peptide-major histocompatibility complex (pMHC) on the cytomembrane [130]. Therefore, Liu et al. [107] engineered a tumor-specific vaccine depending on DC and 4T1 cell membranes. Such hybrid cell membranes maintained functional proteins associated with DCs and cancer cells like pMHC and co-stimulatory molecules, which gave nanoparticles multiple biological capabilities, including lymph node-homing capacity and antigen-presenting ability. Hence, nanovaccines could not only directly activate T cells, but also stimulate the maturation of DCs followed by T cell immune response. Based on these two pathways, *in vitro* and *in vivo* studies confirmed that NDDS has the potential to be used as a vaccine to resist tumor growth.

In addition, Xu et al. [131] constructed a biomimetic multicellular nanoengager consisting of a second-near-infrared-window (NIR-II) absorbing polymer cloaked with a hybrid of DC and tumor cell membranes for synergistic photothermal immunotherapy (Figure 9A). The level of damage-associated molecule patterns (DAMPs) and T cell-stimulating factors enhanced as a consequence of the fusion of immunologically interrelated two cell lines. Upon NIR-II photoirradiation, the primary tumors in mice gradually ablated and further promoted anti-tumor T cell immunity. In addition, this combination therapy also showed its ability to generate immune memory for long-term immune surveillance.

Bacteria-cancer cell hybrid membrane NDDSs

Bacteria could be investigated as vaccine candidates owing to their immunological function to enhance the immunogenicity of autologous tumor antigens. For instance, by fusing melanoma cell membrane vesicles and attenuated *Salmonella* outer membrane vesicles, a combination therapy nanoplatform based on eukaryotic-prokaryotic vesicles (EPV) was designed and constructed (Figure 9B). Melanoma cell membrane vesicles were used to provide tumor antigens, and attenuated Salmonella outer membrane vesicles seemed as natural adjuvants. Both vesicles were used as shell carriers to coat a photothermal core, which assembled from the photothermal agent indocyanine green (ICG) and PLGA. In the group treated with nanovaccine and laser, it can be observed that the mature proportion of bone marrow-derived DCs reached 96.9%, the secretion levels of TNF-α and interleukin 12 (IL-12) significantly improved by 18–56% with a higher T cell proliferation rate (80.7%) [132].

Similarly, Nie's group developed a codelivery nanoparticle vaccine cloaked with tumor cell membranes and bacteria *E. coli* cytoplasmic membranes to display antigen and adjuvant. As an exogenous adjuvant, the bacterial membrane fragments can be rapidly recognized by the immune systems resulting in DC maturation and T cell priming. In multiple mouse cancer models, the vaccine can induce a robust tumor-specific immune response, effectively inhibit tumor recurrence, induce tumor regression and prolong postoperative survival [108].

Bioorthogonal chemistry

Recently, bioorthogonal chemistry has provided an effective tool for selectively modifying biomolecules both *in vitro* and *in vivo*. Coupling a pair of biologically rare reactive groups specifically and efficiently with each other, biorthogonal reactions occur under mild physiological conditions without interactions with other internal biomolecules and interference with the biosystem [133, 134]. In addition, utilizing cellular biosynthesis and metabolic engineering, the reactive groups can be delivered to cells, specifically on the cell membrane in a site-specific manner [135]. Hence, bioorthogonal chemistry is regarded as a novel technique for developing biomimetic NDDSs [136, 137].

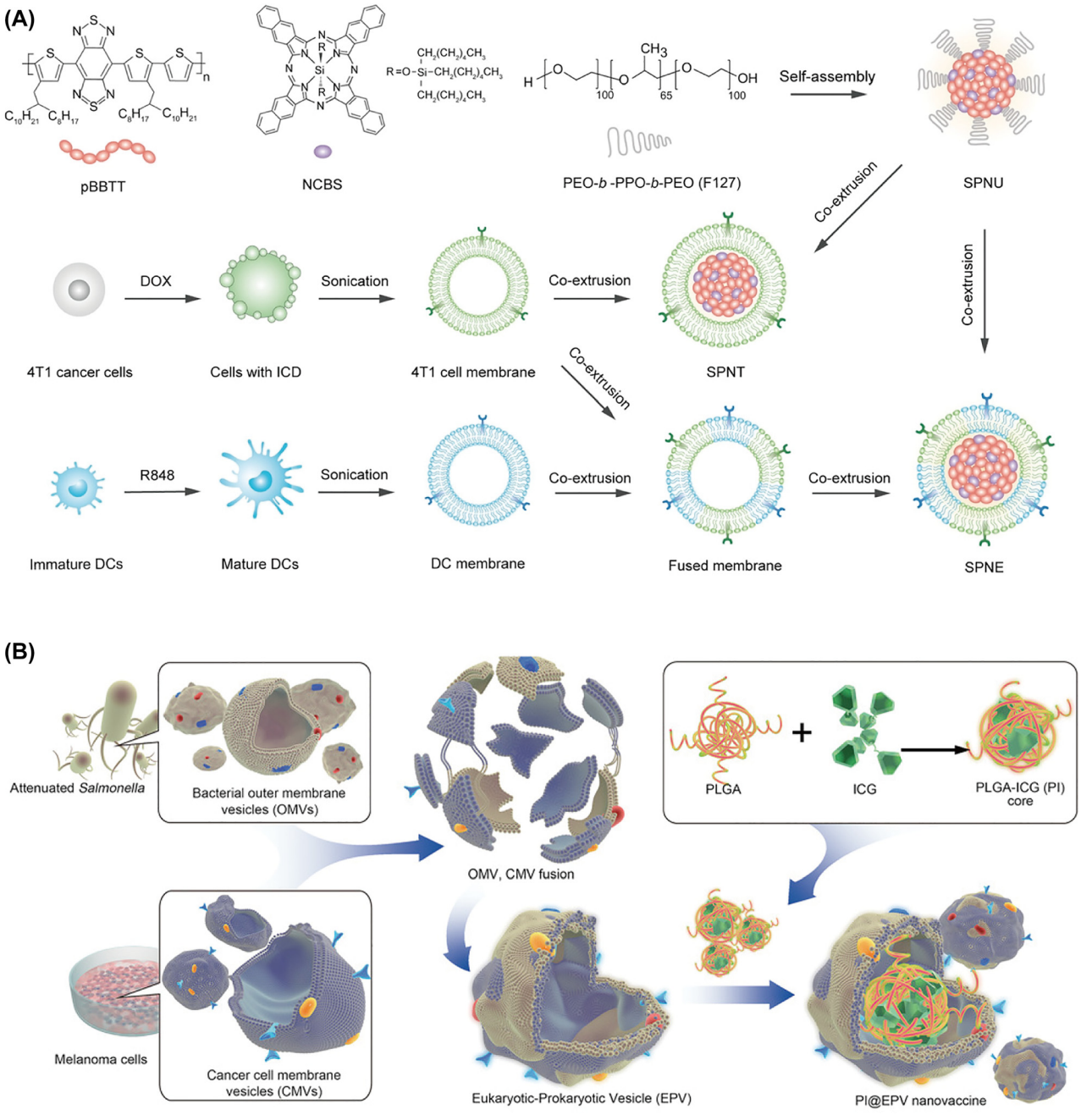

Figure 9: Biomimetic nanodrug delivery systems engineered by membrane fusion. (A) Schematic illustration of preparation of DC-cancer cell membrane coated nanoengager. Image source: Zhang et al. [131]. (B) Schematic illustration of construction of eukaryotic-prokaryotic vesicles coated nanovaccine (Image source: Tang et al. [132]).

Bioorthogonal chemistry for biomolecule-coated NDDSs

Bioorthogonal chemistry could be used to conjugated antibodies with nanoparticles. For example, protein-conjugated liposomes were constructed through click chemistry methods, in which dibenzocyclooctyne (DBCO) was conjugated to IgG and the modified IgG was linked with azide-liposomes. Compared to bare liposomes, DBCO-IgG liposomes based on hydrophobic interactions showed enhanced tropism for neutrophils of inflamed lungs, mimicking the tropism of nanoparticles with agglutinated protein (NAPs) for pulmonary neutrophils. Moreover, DBCO-IgG liposomes had anti-inflammation abilities because they could decrease the retention of neutrophils in the pulmonary vasculature and inhibit the extravasation of neutrophils [138].

Bioorthogonal chemistry for cell membrane-coated NDDSs

Several studies have functionalized specific moieties on the cell membrane by bioorthogonal reactions to improve the targeting ability of biomimetic NDDSs. Zhang et al. synthesized a biomimetic magnetosome based on magnetic nanoclusters camouflaged with macrophage membranes for siRNA delivery. As a tumor-targeting peptide, DBCO-RGD was decorated onto azide-labeled macrophage via click chemistry. Studies demonstrated the high enrichment in tumors of NDDSs and efficient tumor-targeted delivery of siRNA [109]. In addition, biomimetic NDDSs have been exploited for viral targeting and inhibition [64]. Studies suggested that interactions occur between viral S protein and the glycocalyx molecules of the membranes like heparin, which further enhance the binding affinity between S protein and angiotensin-converting enzyme 2 (ACE2). Thus, Zhang's group developed heparin-functionalized cellular nanosponges (HP-NS). Azido groups (N_3) were introduced onto the host cell membrane, and obtained membranes then wrapped PLGA nanoparticles as polymeric cores. By conjugating DBCO-heparin on THP-1 membranes through bioorthogonal reactions, nanosponges with higher heparin density revealed better binding capacity with S proteins and higher prevention of viral infectivity [110].

Bioorthogonal reactions can also enhance immunity properties of biomimetic NDDSs by modification of antibodies on the cell membrane. For example, Zhang et al. [111] constructed biomimetic magnetosomes as artificial antigen-presenting cells (aAPCs), which were fabricated by combing magnetic nanoclusters (MNC) with a leucocyte membrane coating. Peptide (SIINFEKL)-loaded pMHC-I and co-stimulatory ligand anti-CD28 were conjugated to the N_3-engineered leukocyte membrane through mild and rapid click chemistry. *In vitro* studies indicated that aAPCs could have good affinity with T cells leading to a high increase in T cell expansion and activation due to stimulatory signals. Besides, the reinfused aAPC-T cell complexes could target tumor tissues through magnetic control and be monitored visually through magnetic resonance imaging.

However, anti-CD28 and MHC I-Ag decorated aAPCs only activate antigen-specific T cells, while polyclonal T cells should also be activated and expanded to enhance anticancer immunity. Therefore, Xiao et al. [112] developed nanoscale aAPC to augment T cell-based immunotherapy. They constructed imiquimod-loaded PLGA nanoparticles camouflaged with azido-labeled DC membrane and then modified with anti-CD3ε antibody by click chemistry (Figure 10A). Through αCD3ε antibodies modification, nanoscale aAPCs enhanced accumulation in LNs which was 7.6-fold higher than the unmodified group. Moreover, in combination with anti-PD-1 treatment, aAPCs dramatically increase the activation and proliferation of both polyclonal and antigen-specific $CD8^+$ T cells and trigger antitumor immune responses (Figure 10B). In the prophylactic B16-F10 tumor model, aAPCs suppressed tumor growth and prolonged survival time.

Bioorthogonal chemistry for cell-hitchhiking NDDSs

Recent studies have employed bioorthogonal chemistry for attaching nanoparticles to different cells or living creatures and provided a new vision for hitchhiking-based delivery systems. For example, Zhang et al. [139] functionalized neutrophil-derived exosomes with ultrasmall Prussian blue nanoparticles (uPB-Exo) by click chemistry for Rheumatoid arthritis therapy. uPB-Exo could selectively enhance enrichment in activated fibroblast-like synoviocytes, wherein they neutralized pro-inflammatory cytokines and alleviated oxidative inflammatory stress. In addition, targeted to inflammatory synovitis, uPB-Exo enhanced deep penetration into the cartilage. Using an MRI system, accurate diagnosis of RA *in vivo* might achieve sensitively and specifically by real-time monitoring of inflamed joint.

Zheng et al. [140] developed bioorthogonal phage-based NDDSs for chronic colon cancer treatment. They first obtained an N_3-modified phage (A-phage) that can specifically inhibit the growth of *Fusobacterium nucleatum*. Subsequently, they synthesized dextran nanoparticles (IDNPs) containing the chemotherapeutic drug irinotecan (IRT) and then modified nanoparticles to obtain D-IDNPs. Through copper-free click chemistry, A-phage and D-IDNPs can be covalently linked to form phage-mediated nanomedicines (A-phage-D-IDNPs) under physiological conditions. Phages can specifically target tumors colonized with *Fusobacterium nucleatum* and further mediate the enrichment of nanodrugs in tumor tissues. By inhibiting the proliferation of *Fusobacterium nucleatum*, it can effectively inhibit the chemotherapy resistance of colorectal tumors, improving therapeutic effects.

Bioorthogonal chemistry for exosome-like NDDSs

Bioorthogonal chemistry offers a facile and precise method for functionalizing exosomes with specific antibodies or immunostimulatory molecules. Nie et al. [113] developed a pH-sensitive exosome for cancer treatment. They obtained exosomes derived from M1 macrophages (M1-exos) and engineered them with two different antibodies of CD47 and SIRPα by click chemistry. Relying on the specific

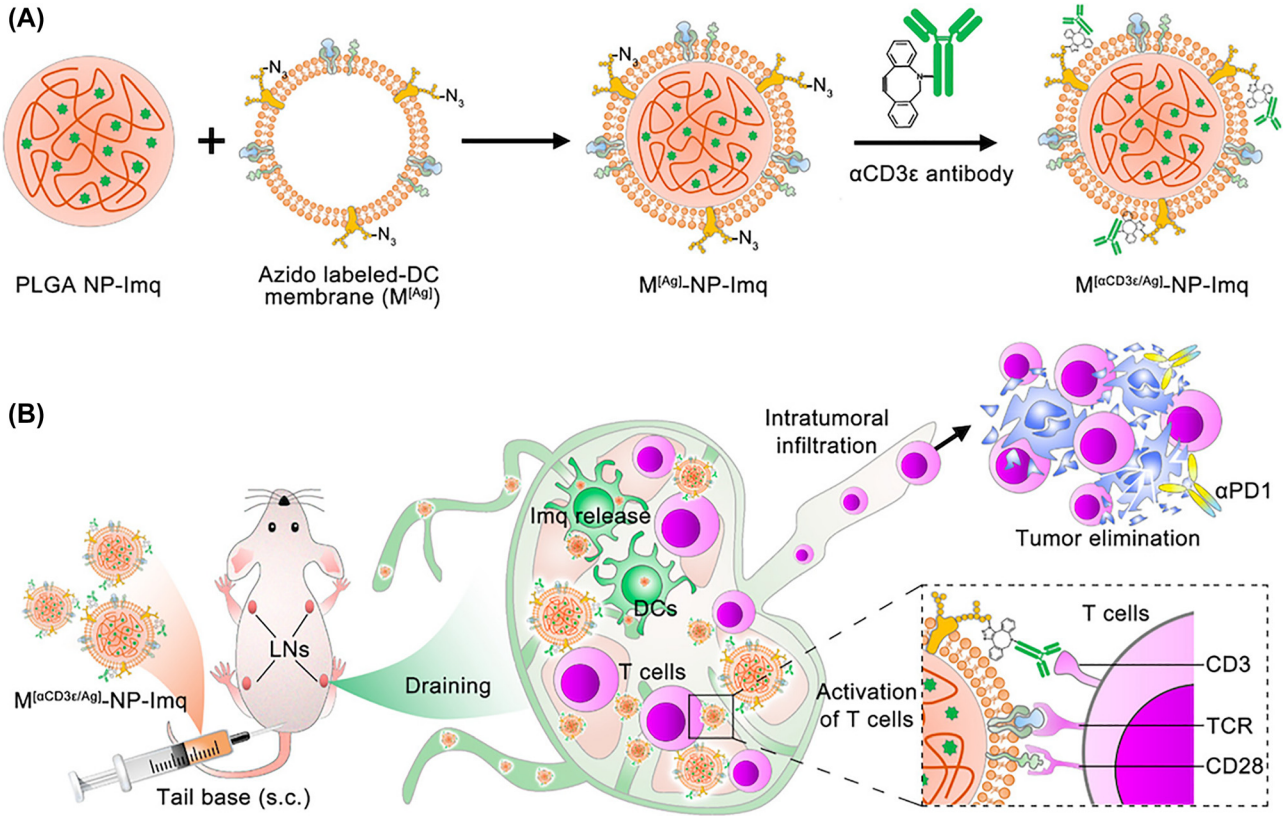

Figure 10: Engineering nanoscale artificial antigen-presenting cells (aAPCs) by bioorthogonal chemistry for cancer immunotherapy. (A) Schematic illustration of the fabrication of aAPCs nanovaccine. (B) Schematic illustration of the mechanisms of aAPCs to potentiate antitumor immunity (Image source: Xiao et al. [112]).

recognition between CD47 antibodies and CD47 on the tumor surface, M1-exos can target tumors. Cleavage of the benzoic-imine bonds in the acidic tumor microenvironment enables M1-exos to release SIRPa and CD47 antibodies. SIRPa antibodies blocked SIRPa on macrophages, and CD47 blockade resulted in the eradication of "don't eat me" signals and enhanced phagocytosis of macrophages. Meanwhile, M1-exos effectively repolarized the M2 macrophages to M1 phenotypes.

Genetic engineering

Genetic modification has created precise and facile methods for cell engineering, which could result in novel and crafted functions by altering the complex proteins expressed on the cell surface. To obtain genetic engineering cells, it could utilize viral vehicles such as adenovirus, lentivirus, and adenovirus to transfect gene-containing plasmids into cells with excellent efficiency [141]. Liposome transfection, electroporation, and gene gun have also been developed for intracellular gene delivery [142].

Genetic engineering cell membrane-coated NDDSs

Cell membrane-coated nanoparticles could be modified genetically to express highly specialized affinity ligands, enabling targeted delivery of the nanoparticles. For instance, Inflamed endothelial cells have been shown to increase vascular cell adhesion molecule-1 (VCAM-1) expression to attract immune cells such as leukocytes through binding with very late antigen-4 (VLA-4) ligands expressed on cell membranes [143]. In light of this, Park et al. [114] transfected the integrin α4 gene into C1498 cells, a cell line with high levels expression of integrin β1 but lack integrin α4 expression, to display both VLA-4 components. They harvested the resulting engineering membranes to coat dexamethasone (DEX)-loaded nanoparticles for inflammation treatment. *In vitro* experiments demonstrated the targeting ability of this nanoformulation to inflamed cells with no hamper on DEX activity. Moreover, in a endotoxin-induced lung inflammation model, nanoformulation exhibited significant therapeutic effects. In their subsequent work, they transfected B16F10 cells to express high levels of hemagglutinin protein. Locating on the Influenza A virus surface,

HA is highly involved in the fusion of the viral envelope and endosomal membrane. They then covered isolated membranes with PLGA nanoparticles containing miRNA. It is demonstrated that the virus-mimicking nanoformulation could achieve endosomal escape and enhance the delivery of mRNA to the cytosol of target cells, increasing the expression of model reporter genes. Through the administration of miRNA-loaded nanoparticles *in vivo*, local and systemic administration can trigger significant increases in encoded protein expression levels [144].

In addition, Zhai et al. [115] genetically engineered a cytotoxic T lymphocytes (CTL) cell line PD-1-CTLL-2 that overexpressed PD-1 through retrovirus transduction. The protein nanoparticles containing ORY-1001 were wrapped with the PD-1-CTLL-2 cell membrane to generate an epigenetic nanoinducer (OPEN). Through the recognition of ligands, OPEN can actively target PD-L1-overexpressing tumor cells to deliver ORY-1001, rapidly releasing ORY-1001 under the action of intracellular glutathione (GSH). Since ORY-1001 is a histone lysine-specific demethylase 1 (LSD1) inhibitor, it can increase the expression of type I interferons (IFNs). *In vivo* studies showed that OPEN upregulated IFN-β levels by 23-fold and tumor cell MHC-I expression and antigen presentation by nearly 2-fold, which promoted the activation and proliferation of tumor-specific CTLs within tumors. Since PD-1 on OPEN also blocked the feedback upregulation of PD-L1 on tumor cells, OPEN significantly inhibited tumor growth and prolonged survival in various murine models with TNBC, melanoma, or colorectal cancer.

Genetic engineering exosome-like NDDSs

It is popular to modify exosomes with functional ligands to enhance targeting capacity by a genetic method. Shi et al. genetically engineered exosomes with two distinct monoclonal antibodies. Because human epidermal growth factor receptor 2 (HER2) is commonly overexpressed in human breast cancers, they suggested that engineered exosomes dually target CD3 on the T cell membrane and HER2, enabling robust immune responses against HER2-positive breast cancer. To this end, they display both anti-human CD3 and anti-human HER2 antibodies on the surface of the exosome by genetic encoding. It showed that the resulting exosomes could redirect and activate CTL to attack HER2-expressing breast cancer cells, which exhibited significantly robust and specific anti-tumor activity. This research proved that endogenous exosomes were feasible for targeted breast cancer immunotherapy. Thus they provided a potential platform technology for broad genetic engineering to develop a new generation of immuno-nanomedicines [116].

Additionally, Li et al. constructed PD-1-expressed CTLL-2 cells by lentivirus transduction. They then harvested the secreted PD-1-displaying microvesicles and exosomes by differential centrifugation. In contrast with microvesicles, PD-1-overexpressing exosomes increased the protein expression associated with cytotoxicity, cell binding function of T cells, as well as T cell receptor signaling pathway. PD-1-expressing exosomes effectively enhance the activation and proliferation ability of $CD8^+$ effector T cells by blocking the PD-1/PD-L1 pathway. Besides, PD-1 exosomes might also directly eliminate tumor cells by FasL and granzyme B (GzmB) [117].

Genetic engineering bacteria-like NDDSs

Bacteria can be genetically engineered to treat diverse diseases, such as inflammatory bowel disease, hepatocellular carcinoma or metastatic breast cancer [145, 146]. Additionally, exogenous moieties from different pathogens and other sources can be retained in OMVs to enhance their immune modulation ability through genetic engineering.

Cheng et al. [118] developed a plug-and-display multifunctional OMVs vaccine platform by introducing SpyCatcher or SnoopCatcher to modify cytolysin A (ClyA) on OMVs. Tumor antigen peptides was functioned with SpyTag and SnoopTag tags. Through isopeptide bond formation, the protein catcher can spontaneously conjugate with the protein tag. A variety of tumor antigen peptides can be specifically displayed to the surface of OMVs, triggering specific and synergistic antitumor immune responses. Due to their small size and bacterial inherent features, OMVs efficiently accumulated in the draining LNs after local injection and were captured by DCs, stimulating DCs maturation. OMVs-based vaccine eliminated melanoma lung metastases and inhibited the growth of subcutaneous colorectal cancer. Based on this, Yue et al. [147] use a similar strategy to modify *E. coli* to produce OMVs. Under the control of arabinose-induced promoters, engineered OMVs exhibited the tumor antigen and Fc fragment of mouse immunoglobulin G through ClyA on the surfaces. Through oral administration, these OMVs can cross the intestinal epithelium into the lamina propria, stimulate DCs maturation, significantly inhibit tumor growth and induce immune memory in mouse models of melanoma lung metastatic and subcutaneous colon cancer.

Multiple engineering

Combining the above engineering strategies has been investigated to expand the function of biomimetic NDDSs. For instance, Rao et al. [119] used both genetic engineering

methods and membrane fusion. They constructed hybrid cell membrane nanovesicles (hNVs) using M1 cell membranes, platelet membranes, and cancer cell membranes. Cancer cells exhibited SIRPα receptor variants by genetic engineering. Due to the high affinity of platelet membranes and SIRPα mutants for the tumor microenvironment, hNVs highly accumulated at the tumor site and blocked CD47 on tumor cells. Nanovesicles promoted M1 polarization by delivering TAMs reprogramming signals and stimulators of interferon genes (STING) agonists. In a TNBC model, hNVs significantly increased the proportion of M1/M2 and activated CTLs compared to the control group treated with M1 membrane-coated nanoparticles or CD47 monoclonal antibody alone. It demonstrated that CD47 blockade and repolarization of M2 to M1 effectively enhanced anti-tumor immunity.

Similar strategies were used to treat SARS-CoV-2 infection. Rao et al. [120] designed decoy nanoparticles for COVID-19 and engineered them through two steps. Genetic modification is the first step. They transfected genes into 293T cells to highly expressed ACE2 receptors, which are highly involved in SARS-CoV-2 infection. The second step is membrane fusion of ACE2-293T and THP1 cells, which display abundant cytokine receptors. The coronavirus was interrupted by the nanodecoys and lack of capacity to infect pulmonary epithelial cells by competing for virus binding. Moreover, in an acute pneumonia mouse model, the nanovesicles efficiently neutralized and depleted extensive cytokines such as interleukin 6 (IL-6) and granulocyte–macrophage colony-stimulating factor (GM-CSF) depending on cytokine receptors, and exerted amelioration effects of lung injury and immune disorder.

In addition, by combining lipid insertion and genetic engineering strategies, Jiang's group constructed a co-delivery system of paclitaxel (PTX) and response 1 (Redd1)-siRNA through OMVs for tumor metabolism microenvironment regulation. The clustered regularly interspaced short palindromic repeats (CRISPR)-mediated approach was used to genetically engineer bacteria *E. coli* BL21 (ΔmsbB), the source of OMVs. Since ΔmsbB mutant can decrease the acyl chains of lipopolysaccharide (LPS), the endotoxicity of OMVs was reduced, resulting in the inhibition of side effects induced by intravenous injection of OMVs, such as systemic cytokine release. They loaded Redd1 siRNA into OMVs via electroporation and then anchored DSPE-PEG-CA-PTX and DSPE-PEG-mannose onto membranes through incubation. The mannose-modified OMVs specifically target M2 macrophages by the mannose receptor. Once targeting the tumor site, the nanosystem released PTX by pH responsiveness. Then, M2 macrophages internalized Redd1 siRNA to increase their level of glycolysis, which potentiating in macrophage repolarization, tumor inhibition and TME remolding proved by *in vitro* and *in vivo* studies [148].

Conclusion and outlook

NDDSs have emerged as increasingly attractive candidates for various biomedical applications such as cancer and inflammation. However, they struggle with insufficient circulation time, unsatisfactory biodistribution profiles, and off-target therapeutic outcomes. Hence, approaches to further develop biomimetic NDDSs are emerging to address the above problems. Due to the unique intrinsic properties and extraordinary biological ability of natural molecules, biomimetic NDDSs with biocompatibility and hybrid functionalities could enhance their targeting and therapeutic potential. In this review, we summarized versatile biomimetic NDDSs based on two concepts. One is camouflaged by a biomimetic exterior, and the other is constructed from bioidentical molecules. We detailed research in each category of biomimetic NDDSs with an emphasis on how these strategies define the biological identity of drug delivery systems and mimic the host biology.

Then, we highlighted unique functionalized strategies, including lipid insertion, membrane fusion, bioorthogonal engineering, and genetic engineering. Each strategy can be used on its own or in combination with others as preferred to achieve multiple engineering. Although based on distinct fundamental concepts, these techniques all have nondisruptive functionalization steps consistent with the construction and preparation processes of current biomimetic delivery systems. As a result, compared with traditional chemical conjugation methods, it will minimize the damage to susceptible biomolecules, and maintain the integrity of natural structures, offering a wide range of ligand choices and precise controlling of ligand density. Versatile engineering strategies break the limit on cells, cell-derived vesicles, cell-derived membranes, or biological molecules by introducing the function of different exogenous moieties, enlarging the possibilities for the application of biomimetic systems. We discussed the applications of each strategy, with a focus on how the approach enhances the functionality of biomimetic NDDSs.

However, the successful translation of biomimetic NDDSs into the clinic is still challenging. First, studies presented in this review were undertaken mostly in small animal models, mainly with mice rather than in humans. Given the complexity, diversity, and heterogeneity of patient-specific cancer or inflammatory network in humans, current studies of biomimetic nanomedicine are scattershot and restricted. For example, in many cases, experimental nanomedicine doses might be neither impossible to achieve nor irrelevant to human physiology [149]. Meanwhile, many non-commercial biomimetic NDDSs were presumably not synthesized under standardized circumstances. As a result, study findings might only apply to the very specific formulation of the biomimetic

NDDSs employed. Moreover, evaluating the toxicity profiles of biomimetic nanomedicine is also rather difficult for their complexity compared with traditional nanoparticles. Both biological and synthetic components should be considered in nano-bio interactions study, but appropriate models have not been used [150]. In addition, it would be difficult to control the purity and quality of the candidate biomolecules and cells. Also, realizing automated production of rapid, accurate, and reproducible customized biomimetic NDDSs is challenging [20]. Therefore, industrial production and quality control of biomimetic NDDSs for clinical application is restricted.

Thus, it is necessary to combine analytical approaches with effective and standardized manufacturing to break regulatory barriers and promote the approval of biomimetic nanomedicine. First, immunotoxicity and haematotoxicity of biomimetic NDDSs are required to test by *in vitro* and *in vivo* experiments, especially in humans. The impact of the immune system on nanoparticles' ability to deliver targeted drugs could be better understood [151]. The immunological side effects and possible effectiveness of the intended nanoformulations would be better studied using spontaneous tumor models and humanized mice models using patient-derived xenografts. Moreover, it is also critical to reduce batch-to-batch variance in manufacturing. The biomimetic NDDSs should be improved by standardized protocols to prohibit introducing excessive components, which will enable scale-up manufacturing. The contaminants and infectious agents must be regulated under an acceptable standard, whether biological molecules, living cells, or cell membranes are used [149]. Furthermore, new technology and exploration of disease could develop biomimetic NDDSs. For example, using the CRISPR Cas-9 system, electro-transformation, and transposon-mediated transfection will significantly increase the safety and efficiency of genetic engineering. Therefore, engineering strategies will enlarge the landscape of biomimetic NDDSs in light of the new methodologies and discoveries. The interdisciplinary research of nanotechnology, biotechnology, medicine, and pharmaceutics can reduce development costs, bridge the gap between preclinical studies and clinical practice, and eventually provide more effective biomimetic nanomedicine to patients.

Research funding: Financial supports from National Key R&D Program of China (2022YFC3401404), National Natural Science Foundation of China (32170935 and 31930066), the Youth Innovation Promotion Association of CAS (2019283) are gratefully acknowledged.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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